SPECIAL ISSUE

ABSTRACTS OF THE XX INTERNATIONAL CONGRESS ON SCHIZOPHRENIA RESEARCH

April 2–April 6, 2005, Savannah, Georgia

Contents

Introduction

INTERNATIONAL CONGRESS ON SCHIZOPHRENIA RESEARCH

The International Congress on Schizophrenia Research began meeting in April 1987, as part of the National Plan for Schizophrenia. It developed as the U.S. sister meeting of the Winter Workshop on Schizophrenia held in Europe every other year, organized by Steven Hirsch and Tim Crow. At the time of its inception, there was no scientific group in the U.S. which was organized around the discovery of mechanisms and treatments for schizophrenia. The meeting's goals were to allow scientists to exchange ideas, plan research projects, and see new treatment developments. The first meeting was small, numbering only 187, and each subsequent Congress has grown in attendance, to more than 1,500.

The goals of the meetings are to provide a forum for active investigators from around the world from academia, government, and industry to exchange information, be exposed to new ideas in neuroscience, and socialize. Ultimately we want the Congress to promote research activity and provide a scientific base and technical breadth to the field of schizophrenia research. Several practical goals are of utmost importance in this pursuit, first among which is to foster growth and interest among young scientists so they will invest their careers in this field. To this end, we began the Young Investigator Award Program in 1987, and have to date, including those awardees for our 2003 meeting, sponsored more than 281 young scientists to attend the Congress. Many of these scientists and clinicians are now established investigators in the field and devoted Congress participants. Another goal is to have a mixed group of basic and applied scientists, so that a true opportunity for informed translational research can transpire. At each of the recent meetings, approximately one third of the scientists are bench experimentalists and two thirds are clinical scientists. A third goal is to have scientists attend from around the world, since schizophrenia is an illness of worldwide incidence and concern. That goal is gradually being met, with 45 countries being represented at our last Congress and greater than 50% of attendees being outside the U.S. The Congress has facilitated collaborations across countries and continents and helped increase the scientific stature of research around the world.

To facilitate all of these goals, the setting for the International Congress is a matter of serious consideration for the Organizers. Characteristics of natural beauty, recreational possibilities, and cultural interest are important to complement the scientific goals. The Organizers recognize the capable and hard work of the Congress staff, without which this meeting could never occur. Over the lifetime of the Congress, the National Institute of Mental Health, the William K. Warren Foundation, several very faithful pharmaceutical companies, the University of Maryland's MPRC (serving as the operating institution), Case Western Reserve University through 1999, and now the University of Minnesota have all made the entire project feasible. But the most valuable resources of the Congress are the schizophrenia investigators from around the world, whose abstracts are represented in this volume, and whose science has drawn the attention of investigators, schizophrenia voluntaries, foundations, governments, newspapers, and politicians in all countries to this very needy area of medical research.

Carol A Tamminga, M.D.
University of Maryland School of Medicine
Maryland Psychiatric Research Center

S. Charles Schulz, M.D.
Chairman, Department of Psychiatry
University of Minnesota Medical School

1. Diagnosis

BASIC SYMPTOMS IN FIRST-EPISODE PSYCHIATRIC DISORDERS: DIAGNOSTIC VALIDITY OF THE SCHIZOPHRENIA PREDICTION INSTRUMENT

B. Bailey,* G. Berger, P. Conus, A. Chanen, M. Berk, A. Yung, L. Phillips, P. D. McGorry
ORYGEN Research Centre, University of Melbourne, Parkville, VIC, Australia

Our aim is to examine the diagnostic validity of basic symptoms using the Schizophrenia Prediction Instrument (SPI-A) comparing first-episode psychosis with bipolar and major depressive disorders. Basic symptoms are early self-reported symptoms often preceding the onset of a psychotic episode. Previous research on basic symptoms in different patient groups indicated good diagnostic validity for at least a subgroup of basic symptoms (i.e. cognitive symptoms), when adolescent patients with first-episode psychosis were compared with i) adolescent patients with affective disorders, ii) patients with other psychiatric diagnoses and iii) healthy controls. Some subgroups of basic symptoms (e.g. bodily sensations, attenuated negative symptoms) did not, however, differentiate the psychotic adolescent group from the affective disorders group (Meng, Bailey, submitted). Recently, Klosterkoetter & Schultze-Lutter developed the SPI-A, based on the Bonn Scale for the Assessment of Basic Symptoms (BSABS). The SPI-A assesses the symptoms on a quantitative 7-point rating scale, as opposed to the BSABS, which rated the symptoms qualitatively for their presence or absence only. The quantitative assessment of basic symptoms with the SPI-A may prove to have better diagnostic validity than the BSABS across different patient groups. In this paper patients with first-episode schizophrenia or schizophreniform disorder will be compared with patients with first presentation bipolar or major depressive disorder using the aforementioned quantitative interview SPI-A. As previous research by the first author has shown, significant differences on at least a subset of basic symptoms can be expected between the different diagnostic groups. It is also likely with the new quantitative assessment, that the intensity ratings of the basic symptoms (or at least certain subgroups) will differentiate the patient groups. Specifically, we would expect that less intense cognitive but more marked affect and bodily sensations symptoms will differentiate the diagnostic groups regarding remains to be seen. By comparing the qualitative (BSABS) and quantitative (SPI-A) approaches we will be able to provide additional information on the concurrent validity of the SPI-A. B. Bailey was supported by the Fellowship grant of the Swiss National Science Foundation (grant no. PBBS1-104680).

IMPULSIVITY AND SCHIZOPHRENIA: COULD PSYCHOMETRICS BE USED?

F. J. Bayle,* A. Dervaux, M. O. Krebs, J. P. Olie, H. Caci
SHU, CH Sainte-Anne, Paris, France

Impulsivity has been implicated in a wide range of behavioural disorders including, antisocial and borderline personality disorders, substance abuse, ADHD, aggression and schizophrenia. Although impulsivity appears to be an important behavioral trait, the wide range of self report, behavioural, social, and biological techniques for measuring impulsivity has led to confusion and lack general agreement in defining it. The search for well-based clinical constructs is increasing since the progress in biological psychiatry and genetics give new tools for understanding the process underlying behaviors. Apart potential endophenotypes, reliable measurements can be give by psychometrics. The BIS10 is the latest version of the Barratt Impulsivity Scale and it is one of the most widely used. The BIS11 measures three subtraits (second order factors): (1) motor (2) non-planing and (3) cognitive impulsivity. The three subscales have moderate correlations with each other and very significant correlations with the BIS total score. Assess impulsivity by self-questionnaire could be difficult. Barratt had suggested that it is difficult to assess one's own thought processes and more than assess a feeling dimension as anxiety. For schizophrenics this difficulty can be enhanced by the cognitive impairment and the deficiency into insight. Therefore we conducted a study to compare the BIS10 between schizophrenics and general population. We include 281 subjects from general population and 193 schizophrenic patients as assessed by structured interview (DSMIV criteria). The scale reliability was estimated by using the alpha Cronbach coefficient. The polychorics correlations were factor analysed following the PROMAX and the retained factors rotated obliquely. The factor solutions were compared between population and by referring to former analysis of the BIS. The solutions were then compared using Tucker s Congruence coefficient (CC), the Root Mean Square measure (RMS) and Cattell s salient variable similarity index (S). A psychologically acceptable solution was found for each population. The number of factor after rotation was similar in each population but the item loaded in the factors were slightly distinct. The similarity coefficients give results that need to be confirmed in complementary studies. The item analysis and the factor solution is discussed at the highlights of the schizophrenics particularities (insight, cognition, behavioural disturbances).

REDUCED IDEA DENSITY IN SPEECH AS AN INDICATOR OF SCHIZOPHRENIA AND KETAMINE INTOXICATION

C. Brown,* M. Covington, J. Semple, J. Brown
Artificial Intelligence, University of Georgia, Athens, GA, USA

Idea density is the number of propositions expressed per 100 words. Snowdon et al. (JAMA 1996) found low idea density in written prose to be a strong predictor of Alzheimer's disease in later life. In this study, we automate the measurement of idea density and show that low idea density is weakly correlated with schizophrenia and with subanesthetic doses of ketamine, which is thought to produce a cognitive impairment similar to schizophrenia. An idea or proposition is anything that can be true or false. Thus 'The brown dog barked in the garden' contains three propositions (dog was brown, dog barked, it happened in the garden). Kintsch (1974) introduced propositional density (idea density) as a measure of text complexity. Idea density corresponds closely to the ratio of verbs, adjectives, adverbs, prepositions, and conjunctions to the total number of words in a speech sample. Exploiting this fact, we developed a Computerized Idea Density Rater (CIDR), which estimates idea density through part-of-speech tagging. We used CIDR to analyze two sets of volunteers' descriptions of pictures from the Thematic Apperception Test. A between-groups comparison of schizophrenics and healthy controls, revealed that patients' speech tended to contain lower idea density. In a placebo-controlled, double-blind, cross-over study of healthy volunteers given subanesthetic doses of ketamine, idea density was somewhat lower in the ketamine condition, even though disordered speech was not, in general, evident to the listener. While not conclusive, these results suggest that the automated measurement of idea

density is potentially useful for psychiatric diagnosis. This research was supported by GlaxoSmithKline Research & Development Ltd.

IDENTIFYING AN EMPIRICALLY VALID DURATION OF ILLNESS CRITERION FOR SCHIZOPHRENIA

P. Dudgeon,* A. J. Mackinnon, P. D. McGorry
Department of Psychology, University of Melbourne, Parkville, VIC, Australia

Objective: Use of the 6 month duration of illness criterion for schizophrenia in all editions of the DSM from version III onwards, and also in the Feighner system, appears to have been arbitrarily chosen. This paper investigates whether there is any empirical validity for the 6 month criterion that primarily differentiates schizophrenia from schizophreniform disorder in DSM-IV and DSM-III-R. Method: The duration of illness of 453 people diagnosed in their initial episode with schizophrenia or schizophreniform disorder under DSM-IV or DSM-III-R criteria was subjected to truncated normal mixture model analysis. Results: Two overlapping component distributions were identified for duration of illness under either set of DSM criteria, thereby indicating two discrete latent groupings of duration of illness were feasible in DSM-III-R and DSM-IV. The duration at which there was equal probability of predicted membership to either grouping was used as a potential cut point to differentiate cases in the two component distributions. This heuristic identified about 6 months as being appropriate for DSM-IV, and about 14 months for DSM-III-R. Conclusions: This is the first study to provide strong empirical support for duration of illness criterion for schizophrenia in DSM-IV, but not the equivalent criterion in DSM-III-R. This is despite about 87% of cases being common to both DSM cohorts used in teh analyses. Reasons for this difference in findings are discussed, together with consideration of the benefits from using alternative cutpoints that may give a stronger probability of correct allocation to the schizophrenia group. The effect of choosing different cutpoints for improving the differential prediction of both short and long term outcomes for schizophrenia will also be considered.

DIVERGENT HPA AXIS RESPONSES TO STRESS IN SCHIZOPHRENIA ATTRIBUTABLE TO PRESENCE OR ABSENCE OF HIPPOCAMPAL PATHOLOGY

M. Goldman,* N. N. Hussain, E. Van Cauter
Psychiatry, University of Chicago, Chicago, IL, USA

Dexamethasone suppression is impaired, hippocampal adrenal hormone receptors are diminished, and hippocampal pathology is prevalent in schizophrenia. The relationship of these findings to patients' increased vulnerability to stress has been challenged however because many patients' HPA axis responses are blunted. Hippocampal pathology impairs stress tolerance, and enhances both the peak and duration of HPA axis responses to stress in animal models of schizophrenia. No study, however, has assessed whether differences in patients' pathology account for divergent clinical findings. Hyponatremic polydipsic schizophrenics (HPS) have relatively marked loss of anterior hippocampal volumes (the portion which regulates neuroendocrine responses) relative to normonatremic polydipsics (NPS), whose volumes in turn are smaller than normonatremic nonpolydipsic (NPS) and healthy controls (HC). We assessed HPA axis responses to cold pressor (60 sec hand immersion in iced water) in 7 HPS, 6 NPS, 9 NNS and 11 HC. Hippocampal influences were accentuated by conducting the study in the evening and examining the 'braking' of the adrenocorticotropin (ACTH) and cortisol (CORT) responses for 105 min following stress. Power was enhanced by utilizing apriori Helmert contrasts, comparing (H1) HC to the three schizophrenic groups, (H2) NNS to NPS and HPS, and (H3) NPS to HPS. Time courses were broken down into linear and quadratic trends and the interactions with Helmert contrasts used to compare patterns of the responses. Baseline ACTH levels were similar across the three schizophrenic groups, but the peak change was significantly greater in HPS (6.5±5.6 pg/dl) and NPS (5.8±10.5) than NNS who exhibited essentially no response (0.6±2.6) (H2 P<.03). Peak change in HC was 2.3 ±5.1 pg/ml. Baseline and peak CORT responses showed a parallel pattern. ACTH levels in NPS transiently rose and fell similar to HC, but remained elevated throughout the sampling period in HPS (H3Xlinear trend P<.003). HPS, but not NPS, exhibited a marked delay in the CORT return to baseline (H3Xquadratic trend P<.01). Thus imagable hippocampal pathology may account for divergent HPA axis responses in schizophrenia. The findings provide further evidence that schizophrenic patients with water imbalance represent a distinct subtype characterized by marked hippocampal pathology which underlies both their life-threatening water imbalance and mental illness by disrupting their ability to regulate stress responses.

CURRENT DSM-IV DISORDERS AND COMORBIDITIES IN POTENTIALLY PRODROMAL PATIENTS

H. Graf von Reventlow,* F. Schultze-Lutter, S. Ruhrmann, A. Wieneke, H. Picker, I. Becker, J. Klosterkoetter
Department of Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany

Comorbid disorders are frequently described in first-episode psychosis. Thus, the aim of the study was to evaluate the prevalence of DSM-IV disorders and comorbidities in subjects meeting criteria for a putatively initial prodrome of psychosis, which should help to optimize correct identification and adequate treatment. A sample (n=146) of potentially prodromal subjects was assessed with the Structural Clinical Interview for DSM-IV disorders, Axis I (SCID I). All subjects met basic symptoms (BS), and/or attenuated psychotic symptoms (APS), and/or brief limited intermittent symptoms (BLIPS), and/or recent functional deterioration and risk factor (trait/state) criteria of a potential initial prodrome of first-episode psychosis. Exclusion citeria were an organic disorder or substance misuse/abuse possibly accounting for the mental problems, an IQ equal or below 70, an age below 16 or above 40 years, and a past or present psychotic episode other than psychosis n.o.s. The results showed that almost 70% of the potentially prodromal subject already suffered from at least one current psychiatric disorder, mainly affective disorders (48%) and/or anxiety disorders (31%). Highest rates of individual DSM-IV disorders were found for major depression (21%), brief depressive disorder (22%), and social phobia (22%). 16 of 146 (12%) potentially prodromal subjects already met criteria for psychosis n.o.s., all except 3 (19%) also meeting criteria for at least one additional disorder. Most subjects meeting criteria for an initial prodrome of first episode psychosis met categorical DSM-IV criteria for a psychiatric disorder. This should significantly add to the distress, suffering, and decline in functioning experienced by these help seeking subjects, and is thus a possible target for complementary treatments in early psychosis. In fulfilling the criteria for a current psychiatric disorder, these problems may also be regarded worthwile for a treat-

ment in its own respect, and the results should trigger further research on specialised treatment for subgroups of potentially prodromal subjects.

IMPROVING THE RELIABILITY OF DIAGNOSING SCHIZOPHRENIA BY USE OF A BAYESIAN BELIEF NETWORK

M. Hastie,* P. Dudgeon, S. Tipping, K. Elkins, A. Mackinnon, P. D. McGorry
ORYGEN Youth Health, Parkville, VIC, Australia

Objective: A principal source of unreliability in diagnosing schizophrenia and other functional psychotic disorders is uncertainty about the presence of symptom and course of illness. Bayesian belief networks (BBNs) are a computerised method of formally incorporating quantified estimates of uncertainty about diagnostic criteria into a diagnostic assessment so that researchers may obtain the conditional probability of a diagnosis of schizophrenia (or any other functional psychotic disorder) given the profile of criteria being met or not met. Method: An inter-rater reliability trial was carried out on 4 different belief network structures using a sample of 32 people with early functional psychosis. Results: Intraclass correlations were well above 0.90 for the diagnosis of schizophrenia and most other psychotic disorder from using the best performing BBN. These reliability values were well above those obtained using conventional diagnostic decision tree methods and also those typically reported in the literature for the diagnosis of schizophrenia. Conclusions: The initial findings suggest that BBNs can significantly improve diagnostic reliability and may represent an important advance over current diagnostic methods. The talk will conclude with demonstrations of the broad application of BBNs, including the facility to provide diagnoses with incomplete diagnostic ratings.

PRELIMINARY EVALUATION AND DEMONSTRATION OF A BAYESIAN BELIEF NETWORK FOR ASSISTING DIAGNOSIS OF PSYCHOSIS

M. K. Hasty,* P. Dudgeon, S. Tipping, K. Elkins, A. MacKinnon, P. McGorry
EPPIC, ORYGEN Youth Health, Parkville, VIC, Australia

Uncertainty about course of illness and expression of symptomatology commonly occurs in the early stages of psychosis and may reduce the reliability of diagnosis. Bayesian belief networks (BBNs) offer a novel method of directly incorporating such uncertainty into the diagnostic process. The current study examined the interrater reliability and procedural validity of four BBNs developed specifically for DSM-IV differential diagnosis in early psychosis. Thirty-two young people with a recent onset of psychotic illness were assessed using a joint interview interrater design. Almost two thirds of the intraclass correlations for interrater reliability exceeded 0.90, with the lowest being 0.70. The level of agreement between diagnoses derived using the best performing BBN and those obtained using a conventional decision tree approach was also good (96.1% agreement). Our results show higher levels of interrater reliability than typically reported and provide evidence for the procedural validity of this method. These results verify the potential value of BBNs and support further development as an aid to diagnosis as well as other areas of decision making in psychiatry. Demonstrations of one of the BBNs will be provided to highlight some of the advantages of this technology.

PREDICTIVE FACTORS OF RESPONSE TO CLOZAPINE IN SCHIZOPHRENIA: A 6-MONTH COHORT STUDY

J. Henna
Psychiatry, USP, Sao Paulo, Sao Paulo, Brazil

Background: It is known that at least 30% of patients with Refractory Schizophrenia (RS) do not respond completely to clozapine, particularly in terms of positive symptoms. These patients are defined as incomplete responders or as having Super-Refractory Schizophrenia (SRS). The aim of the present study was to characterize such patients in terms of demographic and psychopathological variables as compared with patients with RS or those who respond to antipsychotics (Non Refractory Schizophrenia, NRS) Methods: One hundred and two outpatients diagnosed with schizophrenia by the DSM-IV criteria were studied during a 6 months follow-up trial. Psychopathology was assessed by the BPRS and the PANSS, the Schedule for Deficit Syndrome (SDS), the Calgary Depression Scale for Schizophrenia (CGS) and the Quality of Life Scale (QoL). Patients were rated at 2-month intervals. Patients were classified as RS or NRS based on Kane et al criteria at the beginning of the study. Patients who, at the end of the study, failed to reduce in 20% of the total BPRS scored at baseline and maintained a degree of severity of 4 in two of the positive items of the scale were defined as SRS. Results: At the end of the study there were 25 NRS, 43 RS and 34 SRS patients. Groups showed no differences in terms of demographic variables. Patients with SRS could be distinguished from RS by having a higher severity in positive symptoms (SRS: mean=22,18 sd=6,4 RS: mean=16,85 sd=7,8 NRS mean=12,52, sd=4,1- ANOVA 0,001) and negative symptoms (SRS: mean=24,67, sd=9,8 RS mean=23,98, sd=8,9 NRS: mean=16,84, sd=9,1 ANOVA= 0,004) as well as in Quality of Life (SRS; mean= 48,73, sd=8,7 RS, mean= 53,5 sd= 8,6 NRS mean= 66,58 sd= 8,1-ANOVA 0,03) There were no differences in terms of Deficit Syndrome and Depression between SRS and RS. Conclusions: Baseline severity of illness and the presence high scores of positive symptoms may be considered to be predictive factor of partial response (super refractoriness) in patients taking clozapine.

STABILITY OF THE DIAGNOSIS OF DEFICIT SYNDROME IN SCHIZOPHRENIA: A 5-YEAR FOLLOW-UP STUDY

K. Hong,* D. Park, K. Choi, D. Lee
Psychiatry, Sungkyunkwan University School of, Seoul, South Korea

Objectives: Primary, enduring negative symptoms have been used to define the deficit syndrome of schizophrenia and the diagnostic validity of the deficit syndrome has been demonstrated by clinical, biological and neuropsychological studies. This study aims at evaluating the long-term stability of the diagnostic category of the deficit syndrome using direct patient assessments. Methods: The subjects were thirty-two patients with schizophrenia who were categorized into deficit or non-deficit subgroup using the Schedule for the Deficit Syndrome(SDS) in their remission or partial remission state and maintained long-term treatments with antipsychotics (mostly atypical drugs). These patients were re-assessed based on the same deficit syndrome criteria an average of 5.6 years after having been previously categorized. Lifetime presence of clinical symptoms were evaluated using Krawiecka Scale. Results: The majority(87.5%) of the

patients who were classified as non-deficit at the initial assessment continued to remain non-deficit during the follow-through period. However, only 37.5% of the patients classified as deficit at the initial assessment remain classified as showing deficit syndrome. Compared to the non-deficit group, patients of the deficit group at the final assessment showed significantly higher scores of positive symptoms at their previous psychotic states. Among the individual items of SDS, 'poverty of speech' was the most highly predictable for the long-lasting deficit syndrome. Conclusions: This study showed low long-term stability of the deficit syndrome categorized by SDS criteria. It might suggest that deficit symptoms could be improved by the optimal long-term treatment with atypical antipsychotics. The insufficient stability might also be originated from the limitation of the SDS criteria for the identification of the state-independent deficit syndrome.

ANXIETY AND DEPRESSION SYMPTOMS IN PSYCHOMETRICALLY IDENTIFIED SCHIZOTYPY

K. E. Lewandowski,* N. Barrantes-Vidal, T. R. Kwapil
Psycholgy, University of North Carolina Greensboro, Greensboro, NC, USA

The neurodevelopmental vulnerability for schizophrenia appears to be expressed across a dynamic multidimensional continuum of adjustment referred to as schizotypy. This model suggests that nonpsychotic schizotypic individuals should exhibit mild and transient forms of symptoms seen in full-blown schizophrenia. Given that depression and anxiety are reported to be comorbid with schizophrenia, especially the positive symptom dimension of the disorder, the present study examined the relationship of psychometrically defined schizotypy with symptoms of depression and anxiety in a college student sample (n = 1,254). Confirmatory factor analysis indicated that a three-factor solution of positive schizotypy, negative schizotypy, and neurosis provided the best solution for self-report measures of schizotypy, anxiety, and depression. The model indicated that symptoms of depression and anxiety are more strongly associated with the positive-symptom dimension of schizotypy than with the negative-symptom dimension. This is consistent with studies of schizophrenic patients and longitudinal findings that positive-symptom schizotypes are at risk for both mood and non-mood psychoses, while negative-symptom schizotypes appear more specifically at risk for schizophrenia-spectrum disorders.

PRODROMAL SYMPTOMS OF PSYCHOSIS AMONG UNDERGRADUATE STUDENTS

R. L. Loewy,* J. K. Johnson, T. D. Cannon
Psychology, UCLA, Los Angeles, CA, USA

In order to examine the base rates of prodromal psychotic symptoms in a non-clinical population, we asked a large sample of undergraduate students to report the presence and frequency of prodromal symptoms, along with related distress, by completing the Prodromal Questionnaire (PQ). Undergraduate students enrolled in Introductory Psychology classes at UCLA received course credit for their participation. Compared to the preliminary PQ validation sample (Loewy, Bearden, Johnson, Raine, & Cannon, 2004), students' reports of positive symptoms were almost indistinguishable from the reports of outpatients without psychotic-spectrum diagnoses. The majority of students reported experiencing several positive symptoms in the past month, with 43% exceeding the suggested screening cutoff for treatment-seeking individuals of 8 or more positive symptom items. Fewer participants reported symptoms at higher frequencies or with related distress. For symptoms that occurred at least weekly, which is the threshold set for diagnosis of an Attenuated Prodromal Syndrome on the Structured Interview for Prodromal Syndromes (SIPS; Miller, et al., 2002), twenty-five percent of participants scored above the cutoff of 8 or more positive symptoms, and 2% reported distress from at least eight symptoms. The present study suggests that the PQ may perform similarly across different populations, and with the use of different ascertainment strategies. These results also indicate that prodromal symptoms are commonly reported by college students; therefore, in non-treatment-seeking samples, selection for interview may not be feasible unless other qualifying factors are utilized, such as symptom frequency and distress. The results of this study support further examination of the predictive validity of prodromal screening in non-clinical populations.

SUBSTANCE USE IN FIRST-EPISODE PSYCHOSIS: PREVALENCE AND RELATIONSHIP TO PSYCHOPATHOLOGY

M. McConchie,* L. Hides, D. I. Lubman, T. M. Proffitt, P. D. McGorry, G. E. Berger
Unit for Neuroprotection in Young People (UNYP), ORYGEN Research Centre, University of Melbourne, Melbourne, VIC, Australia

Aim: To explore the relationship between substance-use and severity of psychotic symptoms from index admission until a 12-week follow-up. Introduction: There is evidence to suggest that patients experiencing a first-episode psychosis (FEP) with co-morbid substance use display more severe positive and general psychopathology symptoms and less severe negative symptoms than non-substance users. In particular Linzen and colleagues (1994) and Van Os and colleagues (2002) both reported increased positive symptoms in patients with co-morbid psychotic disorders and cannabis abuse or dependence. However, these findings have not consistently been identified across studies and few studies have used standardised measures of substance use or symptomatology. Method: One hundred and twenty-nine (M=97, F=32, mean age=19.35) FEP patients were recruited into a 12-week longitudinal study of phospholipid metabolism in FEP. Symptom severity and substance use was assessed at baseline and at a 12-week follow-up. Axis I diagnostic information, including substance use disorders was confirmed using the Structured Clinical Interview for DSM-IV. Psychopathology was assessed using the Brief Psychiatric Rating Scale, Scale for the Assessment of Negative Symptoms, Positive and Negative Syndrome Scale and the Global Assessment of Functioning. Results: 47.7% of participants met DSM-IV criteria for a current substance use disorder. 38.5% met criteria for a current cannabis use disorder, and 46.9% for a lifetime cannabis use disorder. 16.2% of patients had lifetime amphetamine abuse or dependence, 11.5% had lifetime alcohol abuse or dependence and 4.6% had lifetime opioid abuse or dependence. A between-groups ANOVA at baseline and week-12 showed that current cannabis users had significantly more severe PANSS positive symptoms and PANSS general psychopathology symptoms than non-substance users ($p<0.05$). Interestingly, current cannabis abuse or dependence showed a significant relationship with poorer insight ($p = 0.018$) and increased hostility ($p = 0.006$) at index admission, yet only a lifetime substance use disorder was significantly correlated with poor insight at the week-12 follow-up ($p =0.025$). Conclusions: FEP patients with cannabis and other substance use disorders at baseline had more severe positive psychotic symptoms at admission and

at 12-week follow-up. Patients who had continued to use substances at the 12-week time point had worse global, social and occupational functioning.

STRESS, HPA AXIS FUNCTIONING AND ONSET OF ILLNESS IN PATIENTS AT HIGH RISK FOR PSYCHOSIS

P. McGorry,* K. Thompson, L. Phillips, P. Komesaroff, H. Yuen, S. Wood, C. Pantelis, A. Yung
ORYGEN Research Centre, ORYGEN Youth Health, Parkville, VIC, Australia

The aim of this study was to investigate the relationship between stress, both perceived and biological, and the onset of illness in a sample of patients at ultra high risk of developing psychosis. It was hypothesised that psychological stressors would combine to effect endogenous plasma cortisol levels. These cortisol levels would in turn cause an increase in the severity of symptoms, and a change in MRI indices and glucocorticoid receptor numbers. A total of 29 young people were recruited for this study from the PACE Clinic over a 12-month period. Six of these patients were later excluded from the study for various reasons, resulting in a final sample of 23 patients. At baseline, patients were interviewed using a number of psychopathological interviews and questionnaires, and a blood and saliva sample and MRI scan were taken as soon as practicable after the initial interview was conducted. A total of five (21.7%) subjects made the transition to psychosis within the two year study period. There was a significantly lower plasma cortisol level found in the patients who made transition to psychosis compared to those who did not ($p<.0005$). A regression showed that hassles accounted for 65% of the variance in plasma cortisol level ($p=.019$), but the number of reported life events did not contribute significantly ($p=.94$). A second series of regressions showed that plasma cortisol accounted for 31% of the variance in Hamilton Depression score ($p=.017$), 31% of the Hamilton Anxiety score ($p=.017$), and 23.4% of the BPRS severity rating ($p=.042$). Patients with high ratings of symptom severity on the BPRS had significantly lower right hippocampal volume to whole brain ratio ($p=.018$), and smaller intracranial volumes ($p=.010$), whole brain volumes ($p=.007$), a smaller number of glucocorticoid receptor numbers ($p=.044$), and a lower level of global functioning according to the GAF ($p=.001$). Taken together these results suggest that the number of perceived hassles experienced by young people at high risk of psychosis can be an important factor in raising their cortisol levels. These raised cortisol levels in turn effect the severity of depression, anxiety and psychotic symptoms that are experienced, thereby lending some support to the diathesis-stress model of schizophrenia.

THE 4PAS: A NEW SELF-REPORT QUESTIONNAIRE TO ASSESS THERAPEUTIC ALLIANCE IN SCHIZOPHRENIC PATIENTS

D. Misdrahi,* H. Verdoux, F. Bayle
Service Hospitalo-Universitaire, CH Charles Perrens, Bordeaux, France

Medication compliance is one of the foremost problems affecting neuroleptic efficacy in schizophrenic patients. Almost 50% of all prescriptions are associated with poor compliance with treatment, which constitutes a poor prognostic factor for schizophrenia. Among factors influencing compliance, the communication attitude of the clinician and therapeutic relation are main points of compliance. Patients who formed good alliances with their therapists were more likely to remain in psychotherapy, comply with their treatment than patients who did not (1). Commonly, alliance scales have been constructed to assess psychotherapy efficacy. Therefore, the objective was to defined validations criteria for a new self-report easy to use in clinical psychiatric practice to assess therapeutic alliance. This study was performed in a population of consenting inpatients who fulfilled criteria for schizophrenia and schizoaffective disorders (DSM IV). Assessments of the alliance were obtained by a 4-point ordinal alliance self report (4PAS) and a 8-cm visual analog scale (VAS) completed by the patient after the acute phase and one week before discharge. Self-report is a 11 item questionnaire. All items are answered on a 4 points scale. This original tool has been constructed on the basis of the Helping Alliance questionnaire of Luborsky (2). Higher is the final score higher is the quality of alliance. 86 inpatients were included. The scale reliability was estimated by using the alpha Cronbach coefficient. A factor analysis was performed on the tetra/polychoric correlation matrix. The item analysis and the factor solution is discussed. The therapeutic relation with the clinician could be considering as a prerequisite for a good treatment course and outcome. Detection of subpopulations characterized by determinants of poor alliance could be the first step for clinicians in enhancing schizophrenia prognosis linked to poor compliance. Information and tools for practitioners are needed. References 1 Frank, A.F. and J.G. Gunderson, The role of the therapeutic alliance in the treatment of schizophrenia. Relationship to course and outcome. *Archives Of General Psychiatry*, 1990. 47(3):p. 228-36. 2 Luborsky, L., et al., Two helping alliance methods for predicting outcomes of psychotherapy. A counting signs vs. a global rating method. *J Nerv Ment Dis*, 1983. 171(8):p. 480-91.

PSYCHOPATHOLOGY IN GENETICALLY VULNERABLE YOUNG RELATIVES OF SCHIZOPHRENIA PATIENTS

D. M. Montrose,* D. Dworakowski, J. Miewald, V. A. Diwadkar, M. S. Keshavan
Western Psychiatric Institute and Clinic, Pittsburgh, PA, USA

Background: Children with a biological relative with schizophrenia are at greater risk for developing psychopathology, the patterns of which have not been adequately characterized in the literature. Methods: This study was carried out through the Pittsburgh Risk Evaluation Program at the Western Psychiatric Institute and Clinic. We examined the frequency, patterns and clinical correlates of non-psychotic psychopathology in individuals at an increased genetic risk for developing schizophrenia (HR). Seventy-seven children and adolescents, aged 6 to 24 years, were evaluated. Diagnoses were obtained by using the SCID and K-SADS. HR relatives (first- and second-degree) were highly more likely to have a diagnosable disorder. Results: In order of frequency, the observed Axis I disorders (37 males 14.57±3.1 years; 40 females 15.85±4.3 years) included ADHD (n=20), depression (n=12), oppositional defiant disorder (n=11), conduct disorder (n=7), anxiety disorder (n=9) and bipolar disorder (n=5). Approximately 40% of the subjects (n=32) did not have any Axis I disorder. (Please note: the total adds up to more than 77 because of co-morbid disorders.) Less frequent diagnoses included adjustment and substance use disorders and uncomplicated bereavement. Subjects with Axis I disorders had higher scores on measures of schizotypy, social dysfunction, soft neurological signs, and perseverative errors on the WCST. A subgroup of subjects with "externalizing" Axis I disorders (ADHD, Conduct and ODD) had

the greatest association with psychopathological measures. Conclusions: Psychopathology is common in child and adolescent relatives of schizophrenia patients (approximately 60%). Relatives with already manifest psychopathology as a group appear to have more prominent abnormalities in schizotypy, neurological function and executive abilities compared to those without psychopathology. Interestingly, subjects with externalizing disorders had the most prominent association with the above measures known to be associated with susceptibility to schizophrenia. Longitudinal follow up is needed to determine whether non-psychotic psychopathology would predict schizophrenia spectrum disorders, and eventually schizophrenia or other related psychotic disorders in genetically vulnerable individuals.

ALEXITHYMIA FUNCTION ON PERSONALITY DISORDERS ASSESSMENT IN FIRST-ONSET PSYCHOSIS

R. Ouellet,* L. Diguer, V. Jomphe, C. Merette, M. A. Roy
Centre de Recherche Universite Laval Robert-Giffard, Quebec, QC, Canada

Assessment of personality disorders among people suffering from schizophrenia and schizophrenia-like psychosis provides precious information on the etiology, the outcome and the treatment of psychotic disorders. None of the existing methods to assess personality disorders has been designed to address the specificities of this clinical population. The aim of this study is to assess the convergence between two widely used methods, the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) and the Millon Clinical Multiaxial Inventory Third Edition (MCMI-III) in a sample of 20 first-episode patients. As predicted, Spearman correlations show little agreement between the clinical scales of both instruments. Alexithymia was assessed in order to explain the low diagnostic agreement. The hypothesis that the lower agreement correlates with the higher alexithymia score is strongly supported in our sample ($r = 0.52$, $p = 0.01$). These results show the importance of developing a method to assess personality disorders that could combine the benefits of the questionnaire and the interview. Moreover, results emphases the relevance of alexithymia as a confounding variable when assessing personality disorders and suggest that alexithymia could be systematically assessed among psychotic individuals.

DEFINING THE STEPS TOWARDS RECOVERY IN SCHIZOPHRENIA: A PROPOSED INITIATIVE

S. Rodriguez,* C. Kosik-Gonzalez, G. Gharabawi, C. Bossie, J. Docherty
Clinical Operations, Janssen Medical Affairs, L.L.C., Titusville, NJ, USA

Although diagnostic criteria that define schizophrenia have been rigorously established, a need still exists for effectively communicating the course and outcomes of the disorder to patients. In other areas of medicine, this communication is facilitated by well-established definitions for remission and recovery. While it is questionable whether recovery is a realistic goal in schizophrenia, defining the path to remission may have important advantages for advancing care by: (1) assessing the progress of the current treatment paradigm, (2) identifying the barriers to remission, and (3) improving communication and setting expectations with patients, families, and caregivers. Recently, an expert group convened and developed consensus-based remission criteria for schizophrenia.[1] For this project, we will build on this previous work by defining the course of remission. We hypothesize that there are specific and measurable changes in patient status that precede the remitted state. We propose to involve a core panel of representatives from treatment teams, caregivers, patients, and advocacy groups in order to: (1) identify the stages of schizophrenia from an acute episode through sustained remission (2) develop a simple tool for patient assessment through these stages, and (3) pilot a program for educating patients, families, and caregivers regarding this concept. Progress on this initiative will be presented. Supported by Janssen Medial Affairs, L.L.C. 1. Andreasen NC, Carpenter W, Kane JM et al. Remission in Schizophrenia: Proposed Criteria and Rationale for Consensus. *American Journal of Psychiatry*. In press.

ANXIETY DISORDERS IN RECENT-ONSET PSYCHOSES: PRELIMINARY RESULTS

M. Roy,* E. Raymond, C. Vallieres, M. H. Gobeil, R. H. Bouchard, C. Merette, M. Maziade
Centre de recherche universite Laval Robert Giffard, Universite Laval, Beauport, QC, Canada

Background: Recent studies have reported an elevated frequency of AD in SZ and the probable association of AD with various indicators of severity of psychotic illness. Moreover, genetic epidemiological data suggest a genetic link between AD and SZ. The goals of the current pilot study were: i) to develop a new instrument to assess comorbidity in psychotic subjects; ii) to gather preliminary data on the prevalence of AD in subjects with recent onset psychosis. Methods: Subjects were assessed using a novel instrument, the Evaluation diagnostique et dimensionnelle des psychoses et de leur comorbidite (EDDPC), which combines several instruments to assess psychoses diagnoses and various other dimensions of illness including comorbidity. We developed standardized rules to interpret criteria related to diagnostic hierarchies. Fifteen recent-onset and clinically stable psychotic subjects were interviewed by a research assistant using the EDDPC. All were recruited at the Clinique Notre-Dame-des-Victoires which is a service devoted to the treatment of people an early stage of treatment of their psychotic disorder. Results: We observed high rates of AD: i) Obsessive-Compulsive Disorder (OCD): 20% (n=3); ii) Social phobia (SP): 53.3% (n=8); iii) Panic Disorder (PD): 33.3% (n=5); iv) PTSD: 20% (n=3); v) generalized anxiety disorder: 6.7% (n=1). Sixty percent (n=9) of the subjects had at least one AD, among whom two thirds (n=6) presented at least one AD prior to the onset of psychosis. We also observed a very high rate of co-occurrence of AD since there were a total of 20 AD diagnoses obtained in a total of only 9 individuals. The EDDPC also allows to assess the impact of using supplemental instruments (e.g., YBOCS) on the detection of co-morbid anxiety disorders. We obtained some evidence that using AD scales increases diagnostic sensitivity since they allowed detecting 3 SP, 1 OCD and 1 PD that were not detected using only the SCID probes. Conclusions: This pilot study confirms that high rates of AD are found in recent-onset SZ subjects. It suggests that these various AD frequently co-occur and provides leads about the sources of heterogeneity in rates of AD in psychotic subjects reported in the literature.

EARLY PSYCHOPATHOLOGY AMONG AFFECTIVE VS. NONAFFECTIVE FIRST-EPISODE PSYCHOTIC DISORDERS IN THE MCLEAN-HARVARD FIRST EPISODE PROJECT

P. Salvatore,* H. M. Kaur Khalsa, J. Hennen, D. A. Yurgelun-Todd, R. J. Baldessarini, M. Tohen
Cognitive Neuroimaging, McLean Hospital/Harvard Medical School, Belmont, MA, USA

Modern psychiatric nosology conceives of primary psychotic disorders as discrete syndromes with distinct symptom structures, courses,and outcomes,despite considerable overlap of specific psychopathological features. Few studies have considered the prevalence and evolution of specific psychotic and other features from the start of psychotic illnesses. The study objective was to identify psychopathological structures capable of differentiating patients with affective vs. nonaffective psychotic disorders from their earlier presentations. We hypothesized that early psychotic features would be similar in form and prevalence across diagnostic groups, but that other dimensions of psychopathology would associate with eventual DSM-IV categorizations. In this study 450 patients hospitalized for first-lifetime primary psychotic illness of any type were retrospectively evaluated to correlate early symptomatic and prodromal presentations with later DSM-IV diagnoses. Data were obtained by baseline and follow-up SCID assessments, family interviews, and review of medical records, applying the Bonn Scale for Assessment of Basic Symptoms. We used multivariate regression modeling to identify factors associated with outcome defined as categorization by consensus DSM-IV diagnoses, based on at least 2 years of follow-up that included baseline and later SCID assessments, as affective (bipolar or major depressive disorders with psychotic features) or nonaffective disorders (schizophrenia or other nonaffective psychoses). It was found that psychotic features, including Schneiderian first-rank symptoms, Capgras and other misidentification phenomena, were similarly prevalent in prodromes and index episodes among persons meeting DSM-IV criteria for affective (N=250) and nonaffective (N=200) psychotic disorders. However, the subgroups were clearly distinguished by initial presentations of mood, sleep, and psychomotor disturbances in the affective subgroup vs. social and cognitive impairment in nonaffective subjects. These findings add to the view that patients later meeting diagnostic criteria for major affective disorders with psychotic features or schizophrenia-like psychotic disorders share similar specific psychotic features from their earliest clinical presentations, though follow distinct paths of development in other dimensions of psychopathology. Support: NARSAD(PS), Eli Lilly(DY-T), Bruce J. Anderson Foundation, Bipolar Disorders and Psychopharmacology Research Fund(RJB).

COMPARISON OF NEUROLOGICAL SOFT SIGNS IN SCHIZOPHRENIA AND OTHER NON-AFFECTIVE PSYCHOSES: A CLINICAL STUDY

S. Saraf,* B. N. Manjula Devi, T. Jagadisha, B. N. Gangadhar
Psychiatry, National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore, Karnataka, India

Aim: Patients with schizophrenia have neurological soft signs (NSS) suggestive of a non-specific brain dysfunction. This study examined if NSS are specific to schizophrenia. Methods: Never-treated patients suffering from schizophrenia (n=40) and unspecified nonorganic psychosis (n=19) meeting ICD-10 Diagnostic Criteria for Research (ICD-10 DCR) were recruited into the study. NSS was assessed using the Neurological Evaluation Scale (NES) and cerebellar signs was assessed using the The International Cooperative Ataxia Rating Scale for Pharmacological Assessment of the Cerebellar Syndrome (ICARS). The Abnormal Involuntary Movement Scale (AIMS) was used to evaluate abnormal movements and Simpson Angus Extrapyramidal Side Effects Scale (SAEPS) to evaluate extrapyramidal symptoms, which might interfere with NSS and cerebellar signs assessment. The Positive and Negative Syndrome Scale (PANSS) was used to measure psychopathology. There was good inter-rater reliability for all these measures. The NES score in schizophrenia patients in the present study was compared with the earlier studies done at our institute. Results: Patients with schizophrenia and the unspecified nonorganic psychosis did not differ on the total score or any of the subscale scores for neurological soft signs and cerebellar functions. The two groups did not differ in any other socio-demographic or clinical variables. Patients with unspecified psychosis had less severe positive syndrome score. The NES score of schizophrenia patients in this study was comparable with the earlier studies done at our institute. In these studies schizophrenia patients, had significantly higher NES score as compared to healthy controls. Conclusions: The findings suggest that neurological soft signs are not specific to schizophrenia and they occur with similar severity in patients with unspecified psychoses as well. The alternative explanation is that both schizophrenia and unspecified psychoses are nosologically similar entities, with the latter having less severe positive psychopathology, which cause them not to be diagnosed as schizophrenia according to the strict criteria of ICD-10 DCR.

IMPROVING OUTCOMES FOR CHILD AND ADOLESCENT ONSET SCHIZOPHRENIA IN RURAL AND REMOTE COMMUNITIES OF AUSTRALIA

H. J. Stain,* G. Sartore, S. Blinkhorn, B. Kelly
Centre for Rural and Remote Mental Health, University of Newcastle, Orange, NSW, Australia

Many researchers agree with the need to develop a neurocognitive profile for the identification of children at risk for schizophrenia. While numerous intervention programs have been trialed for first episode schizophrenia (FES), there has been a lack of research directed towards FES service delivery for rural and remote communities (RARC). Pathways to care analyses for urban communities indicate both an extensive period of symptomatic behaviour and multiple primary health care consults prior to accessing mental health services (Stain et al,2003). This paper presents an analysis of routine clinical mental health service data for first presentation 10-25 year old patients (N=1445) in the Mid Western rural region of New South Wales. Demographic, clinical and service features, including rate of identification of FES in this sample, will be reported against characteristics specific to RARC. Symptomatology was measured by a number of instruments including K10, HoNOSCA and HONOS. Implications for delivery of appropriate early intervention services for child and adolescent onset schizophrenia in RARC are discussed. Stain, H.J., Kisely, S., Miller, K., Tait, A. & Bostwick, R. (2003). Pathways to care for psychological problems in primary care. *Australian Family Physician*, *32*, 955-960.

CORTIOCOTROPIN RELEASING HORMONE TEST IN PATIENTS AT HIGH RISK OF PSYCHOSIS

K. Thompson,* G. Berger, P. Komesaroff, L. Phillips, P. D. McGorry
ORYGEN Research Centre, ORYGEN Youth Health, Parkville, VIC, Australia

Stress has long been thought to be one of the factors associated with the onset of psychosis. The diathesis-stress model of schizophrenia hypothesises that there are a number of factors, including environmental factors such as stress, that combine to effect the abnormal substrate thought to be underlying schizophrenia. The combined dexamethasone/corticotropin-releasing hormone test provides a sensitive test of the hypothalamic-pituitary-adrenal axis. We applied this test in a specialised sample of patients at ultra high risk of developing psychosis. These patients were referred to the Personal Assessment and Crisis Evaluation Clinic, a specialised Clinic for young people between the ages of 15 and 25 years who are at high risk of developing psychosis. A total of 12 patients gave informed consent to participate in this study. Over a two year period 3 (25%) of the 12 patients made the transition to psychosis. The results suggested that patients who made the transition to psychosis had significantly lower levels of anxiety and depression, and reported experiencing fewer life events over the month preceding intake to the Clinic. The transition group began the DEX/CRH test with a higher baseline cortisol level, and showed a steady rise in cortisol level over the course of the test. In comparison, those who did not make transition had lower levels of cortisol, with some decline with the last sample ($p>.05$). In terms of ACTH, patients who made the transition to psychosis show a blunted response to DEX/CRH compared to the control group ($p>.05$). Even though only tentative conclusions can be drawn from the DEX/CRH responses in our PACE sample due to the small sample size, they show a blunted response in both cortisol and ACTH for patients who later make the transition to psychosis, suggesting a less responsive HPA axis.

2. Phenomenology

NEUROLOGICAL ABNORMALITIES IN CHILDREN WITH LEARNING AND/OR BEHAVIORAL PROBLEMS ARE NOT ASSOCIATED WITH LATER PSYCHOTIC DISORDER: A TWENTY-YEAR FOLLOW-UP STUDY

G. P. Amminger,* S. Ohmann, M. Voracek, G. Tatzber, B. Schuch, M. Feucht, M. Friedrich
Adolescent Psychiatry, Medical University Vienna, Vienna, Austria

PURPOSE: We investigated the relationship between neurological abnormalities in childhood and the development of a psychotic disorder in adulthood. METHODS: Longitudinal follow-up study of 82 children (mean age 8.63, SD 2.07 years) who presented to a child psychiatric service with learning and/or behavioral problems between 1980 and 1981. Neurological soft and hard signs were evaluated using the standardized assessment tool of Touwen & Prechtl (1970) which includes tests for the sensomotoric system, body posture, vestibular sense reactions, coordination of extremities, fine motor functions, dyskinesias, gross motor functions, quality of movement, associative movements, and visual system. In 2001 diagnostic follow-up was conducted employing computerized information of psychiatric hospital admissions and a semi-structured telephone interview yielding four major outcome categories of self-experienced psychiatric problems: psychotic symptoms, depressive symptoms, anxiety, substance abuse problems. RESULTS: At follow-up 27.7% of the sample reported depressive symptoms, 21.4% anxiety symptoms, 13.3% substance abuse problems. Nobody was found with psychosis. Deviant performance in diadochokinesis and associative movements on both right and left was associated with depressive symptoms in adulthood. CONCLUSIONS: The findings are not consistent with reports of increased levels of neurological abnormalities during childhood in individuals who later develop schizophrenia or affective psychosis. In the present sample neurological signs were generally a rather weak indicator of an unspecific psychiatric vulnerability.

THE MODIFIED VERSION OF THE QUALITY OF LIFE SCALE: CORRELATION WITH NEGATIVE SYMPTOMS IN REFRACTORY SCHIZOPHRENIA

B. S. Avrichir,* H. Elkis
Psychiatry, Institute of Psychiatry of University of Sao Paulo Medical School, Sao Paulo, SP, Brazil

Background: there has been a growing awareness of the problem of the negative symptoms over the last few decades and speculations on specific etiopathogenesis of such symptoms have been made by some authors especially due to the finding of a correlation between negative symptoms and neuroimaging and neurochemical parameters. However, there is no consensus among authors regarding the definition of negative symptoms. Negative symptoms are commonly considered a dimension which represents what is called the schizophrenia. They have also been considered an important feature associated with refractoriness, although most definitions of treatment resistance focused on the persistence of positive symptoms. It is known that 30% of patients with schizophrenia do not respond to conventional antipsychotics and 30% of those patients (Refractory Schizophrenia -RS) do not respond completely to clozapine. (incomplete responders or Super-Refractory). The aim of the present study was to evaluate the correlation between negative symptoms and quality of life in refractory and super refractory schizophrenia. Methods: patients diagnosed with schizophrenia by the DSM-IV criteria were studied during a 6 months follow-up. Psychopathology was assessed by the PANSS, the Schedule for Deficit Syndrome, the CGI, the Calgary Depression Scale for Schizophrenia and the Heinrich Quality of Life Scale. They were diagnosed into refractory, super-refractory and non-refractory and, in a second moment, into deficit and non-deficit patients. To avoid a tautological conclusion in the correlation between negative symptoms and quality of life (repeated analysis of variance), the intrapsychic functions were subtracted from the original QoL scale, as it closely relate to the deficit symptoms. The construct validity and consistency of the modified QoL scale were analyzed. The influence of factors other than negative symptoms on quality of life, was evaluated. Results: Cronbach value for the MQoL scale was 0.94. Mean MQoL scores of refractory, super refractory schizophrenic patients were significantly different from non refractory patients. MQoL scores were lower among patients with deficit syndrome. There was a negative correlation between negative symptoms and QoL (Pearson r =-0.64). Conclusions: Negative symptoms strongly correlate to quality of life in schizophrenia. The modified Heinrich QoL Scale seems to be a valid and reliable tool to assess quality of life in schizophrenic patients.

DURATION OF UNTREATED PSYCHOSIS AS A PREDICTOR OF ONE-YEAR OUTCOME: THE WEST LONDON FIRST-EPISODE SCHIZOPHRENIA STUDY

T. R. Barnes,* S. B. Hutton, S. H. Mutsatsa, E. M. Joyce
Department of Psychological Medicine, Imperial College, London, United Kingdom

First-episode studies of schizophrenia have consistently suggested that the longer psychosis proceeds before treatment, the poorer the clinical and social outcomes. This association was examined in the context of the West London First Episode Schizophrenia Study. Relevant data at initial assessment and one-year follow-up were available for 96 patients (72 males, 24 females) with DSM-IV schizophrenia. The median period between assessments was 387.5 days. The median value for duration of untreated psychosis (DUP) was 16 weeks while for duration of untreated illness (DUI: DUP plus prodrome) the figure was 130 weeks. For analysis, the DUP and DUI were log transformed due to positive data skewness. The assessments included mental state (SAPS, SANS), and social function (SFS). IQ was calculated from 4 WAIS subtests, and the Cambridge Automated Neuropsychological Test Battery was administered, which includes tests of planning, spatial working memory and attentional set-shifting. Data analysis revealed significant positive correlations between DUP and scores for symptom-derived syndromes of both positive psychotic symptoms (delusions and hallucinations) and negative symptoms at follow-up, but not a sum score for core negative symptoms (SANS items for affective flattening and alogia). Longer DUP was significantly associated with lower total scores on the SFS at follow-up, as well as SFS subscales reflecting employment/occupation, engagement in social activities, and independence of activities of daily living. These associations remained significant with partial correlations taking account of age at the onset of illness and baseline scores. There were no significant associations between DUP

and the cognitive measures except a significant negative correlation with IQ at follow-up. DUI showed none of the significant associations found with DUP. The sample was divided into those with a DUP of 12 weeks or less (n=46) and the remainder, with a longer DUP. There was no significant difference in baseline IQ, but the latter group had a significantly lower mean IQ score at follow-up, as well as poorer social function and more severe negative symptoms. The findings suggest that longer DUP may have some predictive value for poorer outcome in respect of persistent symptoms, social re-integration and global intellectual function. A possible confound is the overlap between the scales rating negative symptoms and social function.

FIRST-EPISODE PSYCHOSIS IN A HIGH-IQ GROUP: EVIDENCE FROM THE CAMEO EARLY INTERVENTION SERVICE

J. Barnett,* U. E. Werners, K. E. Hill, R. Brazil, O. Gallagher, B. J. Sahakian, E. T. Bullmore, P. B. Jones
Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom

Widespread cognitive impairments are intrinsic to schizophrenia and are also reported in first-episode psychosis. The existence of patients with schizophrenia who show no cognitive impairment remains controversial and may depend on the sensitivity of tasks used to assess cognitive function. Children who will later develop schizophrenia show, on average, lower IQ than healthy controls and those who will later develop affective psychoses. At least two studies have reported increased risk for schizophrenia in very high-IQ individuals, but little is known about the manifestation and effects of psychotic disorders in people with very high IQ. This study aimed to assess the cognitive and clinical effects of first-episode psychosis in high-IQ individuals. The CAMEO early intervention service based in Cambridge provides clinical assessment and care co-ordination for young people with first-episode psychosis or who are thought at risk of psychosis. All referrals to the service receive a one-hour neuropsychological assessment, and premorbid IQ is estimated using the National Adult Reading Test (NART; Nelson 1982). NART-estimated IQ in CAMEO ranges from 92-125 with a mean of 110. Severe cognitive deficits (at least two SDs below manufacturer's norms) are found in three-quarters of CAMEO cases, with 95% of cases performing more than 1 SD below the norm on at least one test. High-IQ patients experience lower negative symptoms and have higher global functioning than average-IQ patients despite experiencing equal levels of psychotic symptoms. We conclude that high IQ does not protect against positive symptoms of psychosis nor against specific cognitive impairments, which are present in almost every case of first-episode psychosis. Implications for neurodevelopmental theories of schizophrenia and other psychotic disorders are discussed.

FACTOR ANALYSIS OF SCHIZOTYPAL SYMPTOMS IN FIRST-DEGREE RELATIVES OF PSYCHOTIC PATIENTS

M. Beperet,* I. Mata, J. M. Lopez-Ilundain, F. Perez-Nievas
Fundacion Argibide, Pamplona, Navarra, Spain

The Schizotypal Personality Questionnaire (SPQ; Raine, 1991) is a 74-item self-rating questionnaire with a dichotomous response format (yes/no), developed to cover the nine schizotypal features, based on DSM-III-R criteria. Several independent factor analytic studies have reported a three-factor structure of the SPQ in community and clinical samples. Furthermore, a recent factor analysis of the SPQ in 124 relatives of schizophrenic patients has reported the same factor structure. The aim of this study was to carry out a factor analysis of the SPQ in a large sample of relatives of psychosis patients, as well as to study the influence of age and sex on SPQ scores. A sample of 280 first-degree relatives of 107 psychosis patients completed the SPQ. A three-factor solution consisting in cognitive-perceptual, interpersonal, and disorganized symptoms, explaining 24% of the variance, was obtained. Correlation analyses between the factor loadings for each component and the SPQ original three factors indicated a strong and factor-specific correspondence between the three largest components obtained in this study and the established three SPQ factors. Internal consistency of the SPQ total scale and each of its three factors was found to be at least acceptable. No gender differences were obtained for the SPQ total scale or any of the three factors. Among siblings, age was negatively correlated with the cognitive-perceptual factor score. However, among parents, no significant correlations between age and SPQ scores were found. This study confirms that schizotypal symptoms among relatives of psychosis patients, as measured with the SPQ, show a three-factor structure. While gender does not appear to have much influence on SPQ scores among relatives of psychosis patients, younger siblings of psychosis patients have significantly higher scores on the SPQ cognitive-perceptual factor.

EMOTIONAL OVER-INVOLVEMENT, SELF-EFFICACY, AND RECOVERY FROM SCHIZOPHRENIA: AN UNDERSTANDING OF AN INDEX OF EXPRESSED EMOTION THROUGH NARRATIVE

N. J. Breitborde,* S. R. Lopez, E. Ochs, K. H. Nuechterlein
Psychology, University of California, Los Angeles, Los Angeles, CA, USA

This study explores the mechanisms underlying the association between the expressed emotion index of emotional over-involvement (EOI) and schizophrenic relapse. We tested the hypothesis that relative to low EOI caregivers, high EOI caregivers may lead their ill relatives to believe that they lack the necessary efficacy to recover on their own from their illness. To test this hypothesis, we carried out two studies based on narratives of 20 caregiving relatives of individuals with schizophrenia. In the first study, we applied a qualitative analysis to a subset of 8 narratives and found that the narratives of high EOI caregivers contain a "logic of limited efficacy" that is not observed among low EOI caregivers. More specifically, within the narratives, high EOI caregivers described the control of their ill relatives' symptoms as dependent on the presence of the caregiver, whereas low EOI caregivers did not. To test the generalizability of this finding, coders rated the narratives for all caregiving relatives. These ratings revealed similar differences between high and low EOI caregivers. Moreover, when EOI was treated as a dimension (0-5) rather than as a dichotomous (high/low) variable, the prevalence of the "logic of limited efficacy" within caregivers' narratives was found to increase as EOI increased. Together, the results from the qualitative and quantitative analyses indicate that high EOI caregivers perceive their ill relatives' ability to recover as dependent on the presence of the caregiver. The presence of this "logic of limited efficacy" within the familial environment might have a deleterious effect on ill individuals' self-efficacy of recovery, thereby increasing their risk of schizophrenic relapse.

MALADAPTIVE PSYCHOTIC-LIKE EXPERIENCES IN A NON-PSYCHOTIC POPULATION OF YOUNG PEOPLE II: STABILITY AND EFFECTS OF TREATMENT

J. Buckby,* A. R. Yung, S. M. Cotton, C. Stanford, K. A. Godfrey, E. J. Killackey, E. M. Cosgrave, P. D. McGorry
Psychiatry, ORYGEN Youth Health, University of Melbourne, Parkville, Melbourne, VIC, Australia

Background: Psychotic-like experiences (PLEs) have been found to be a risk factor for development of full blown psychotic disorder. However, they are also common in the general population. Previously research has identified 3 distinct types of PLE in a help seeking cohort of young people aged 15-24. These were: bizarre experiences, persecutory ideation and magical thinking. Bizarre experiences and persecutory ideation were associated with depression and poor functioning but magical ideation was not, unless associated with distress. However, the association between PLEs and functioning was no longer significant after adjusting for depression. Hence an important issue was to determine whether PLEs decreased in conjunction with improvement in level of depression. We investigated this by longitudinal follow up of the original sample over 6 months. Method: Young people aged 15-24 presenting to a mental health service with non-psychotic complaints were assessed at baseline and 6 months for presence of PLEs, level of depression and functioning. 3 methods for defining depression were used: categorical threshold DSMIV diagnosis, unidimensional cut-off score of a self report measure and a continuous self report measure. Results: Levels of change in depressive symptomatology and PLEs were examined. Bizarre experiences and persecutory ideation changed with change in functioning. However magical ideation did not. Further analyses to clarify the relationship with depression are underway.

THE PSYCHOSIS OBSERVATIONAL RATING SYSTEM© (PORS): DEVELOPMENT OF THE BEHAVIORAL ITEMS

S. V. Catts,* S. Andrews, K. Bird, P. B. Ward, N. McConaghy
Psychiatry, University of Queensland, Herston, QLD, Australia

Background: There are excellent diagnostic instruments for schizophrenia, however the design of dimensional symptom-focused rating scales has been slower. We are designing a rating scale which aims to comprehensively capture the structure of the symptoms and signs of schizophrenia, called the Psychosis Observational Rating System (PORS). Methods: One hundred subjects with psychotic symptoms were rated on 68 behavioural items. A series of focused exploratory factor analyses were carried out on the item ratings. Results: Ten "fields of observation" (behavioural domains) were identified and named: Neglect, Excited Behaviour, Depressed Behaviour, Psychomotor Oddity, Confusional Affect, Affective Oddity, Affective Flattening, Thought Disorder, Impoverished Thinking, and Preoccupation-related Behaviour. Each of these behavioural domains is reflected in a number of component behaviours. For example, in the domain of Thought Disorder, there are three components, namely: Disorganised Thinking, Confused Thinking, and Odd Verbalisation. Each behavioural component has several forms contributing to the rating of the respective behavioural component. For instance, there are three forms of Disorganised Thinking, namely: Derailment, Tangentiality, and Circumstantiality. Using the PORS, Disorganised Thinking is rated dimensionally according to the degree that any one of these three forms is present. Conclusion: It is feasible to construct a system to rate assessment domains identified statistically by factor analysis.

MISINTERPRETED FACIAL EMOTIONS, SYMPTOMS AND SOCIAL FUNCTIONING IN SCHIZOPHRENIA

A. S. Cohen,* T. M. Nienow, T. J. Dinzeo, N. M. Docherty
Psychology, Kent State University, Kent, OH, USA

Patients with schizophrenia exhibit impairment in their ability to correctly recognize other peoples emotions, and the severity of this emotion recognition deficit has been associated with poorer levels of social functioning. However, the mechanisms underlying emotion recognition deficits and social functioning impairments are poorly understood. There is some evidence to suggest that patients, as a group, tend to incorrectly misinterpret other peoples facial expressions as having an overly negative valence. Thus, it seems a reasonable supposition that patients poor social functioning may reflect, in part, a perceptual bias. Moreover, given the considerable heterogeneity across patients in presenting symptoms and emotional states, there may be differences across patients in the types of emotions that they mistakenly assign to others. The present study examined the relationship between misinterpreted facial emotions, symptom severity and social functioning. The error profiles of 67 state hospital patients and 22 nonpsychiatric controls on the Facial Emotion Identification Test were analyzed. A misinterpretation index score, which reflected the number of incorrect emotion responses taking into account the total number of errors, was separately computed for each of six types of emotion (happy, sad, fearful, angry, surprised and shame). Results suggest that the error profiles were remarkably similar for patients and controls. However, in contrast to prior findings, a significantly greater percentage of the patients (13%) vs. controls (6%) erroneous responses had a positive valence. Within the patient group, individuals who erroneously reported seeing anger emotions tended to have poorer social functioning and more severe positive and disorganization symptoms. Patients who erroneously reported seeing shame, tended to have better overall functioning, less severe positive symptoms and a trend for more severe negative symptoms. The implications of these results are discussed.

FIRST EPISODE AND NEUROLEPTIC FREE PATIENTS WITH SCHIZOPHRENIA HAVE REDUCED INSULIN SENSITIVITY: A MINIMAL MODEL ANALYSIS

T. A. Cohn,* T. Wolever, D. Bois, R. B. Zipursky, G. Remington
Psychiatry, University of Toronto, Toronto, ON, Canada

Patients with schizophrenia have an increased prevalence of diabetes (1). While much research attention is being paid to the effects of atypical antipsychotic medication on glucose homeostasis, an equally important area of investigation is whether patients with schizophrenia are prone to diabetes independent of antipsychotic treatment. There is limited evidence in this regard (2). We are not aware of published studies using rigorous and validated measures of insulin sensitivity and pancreatic beta cell function in neuroleptic free patients with schizophrenia. To investigate this issue, we studied 8 male and 1 female patient with schizophrenia prior to antipsychotic treatment

(7 neuroleptic naive, 2 neuroleptic free for > 3 months) and 9 healthy controls matched by age, BMI, ethnicity, gender and smoking status. Insulin sensitivity (Si), glucose effectiveness (Sg), acute insulin response to glucose (AIRG) and disposition index (Di) was determined using Bergman's Minimal Model Analysis of the Frequently Sampled Intravenous Glucose Tolerance Test. In addition, Homa IR was calculated from the fasting glucose and fasting insulin. Compared with controls, subjects (age 26.5 ± 8.8) had significantly reduced Si (0.498 ± 0.234 versus 0.934 ± 0.399, p=0.014), a tendency for reduction in Sg (0.022 ± .009 versus 0.032 ± 0.005, p= 0.137) and DI (1370 ± 872 versus 2300 ± 1356, p= 0.103) whereas AIRG was similar. The reduced insulin sensitivity in the subjects was also reflected in a tendency for increased fasting insulin (34.81 ± 11.30 versus 28.41 ± 6.44, p= 0.159) and Homa IR (0.95 ± .44 versus 0.18 ± 0.06, p=0.089). These data suggest that, independent of antipsychotic treatment, schizophrenia is associated with insulin resistance. In addition, compensation in insulin secretion is incomplete. The findings are consistent with an increased prevalence of diabetes in schizophrenia and should be taken into account in evaluating the effect of antipsychotic medication on glucose regulation.
1. Dixon L, Weiden P, Delahanty J, Goldberg R, Postrado L, Lucksted A and others. Prevalence and correlates of diabetes in national schizophrenia samples. *Schizophr Bull* 2000;26(4):903-12. 2. Thakore JH. Metabolic disturbance in first-episode schizophrenia. *Br J Psychiatry Suppl* 2004;47:S76-9.

BEHAVIORAL INDICATORS OF SCHIZOTYPY IN THE BIOLOGICAL PARENTS OF SOCIAL ANHEDONICS: A PRELIMINARY EXAMINATION OF THE FAMILIALITY OF SCHIZOPHRENIA-SPECTRUM BEHAVIOR

L. M. Collins,* S. Miller, C. Chamberlin, K. Biondo, C. Noone, W. W. Leung, J. J. Blanchard
Psychology, University of Maryland at College Park, College Park, MD, USA

This study provides an initial examination of behavioral signs characteristic of schizoid and schizotypal personality disorders in social anhedonics and their biological parents to examine the familiality of atypical interpersonal behavior in a group of putative schizotypes. A community sample of psychometrically identified 18 to 19 year-old social anhedonics (N=48) and controls (N=40), as well as their biological mothers (N=79) and biological fathers (N=44) were rated using a coding system for schizophrenia-spectrum behaviors based on videotaped clinical interactions. Schizoid signs (e.g., constricted facial affect, lack of non-verbal expression) differentiated the social anhedonia proband group from the control proband group, but schizotypal signs (e.g., inappropriate affect, odd behavior) did not. The incremental validity of proband schizoid sign ratings over traditional clinical interview ratings of schizophrenia-spectrum symptomatology was examined. Results generally replicated our previous reports using a larger sample of the utility of schizoid sign ratings beyond traditional clinical symptom ratings in the identification of social anhedonics. Interestingly, mothers of social anhedonics exhibited significantly more schizotypal signs than mothers of controls, but the mothers of these groups did not differ on schizoid signs. However, traditional clinical interview ratings of schizophrenia-spectrum symptomatology did not contribute to the identification of mothers of social anhedonics. Neither schizoid nor schizotypal signs or symptoms differentiated fathers of social ahedonics from fathers of controls. Correlational analyses showed significant correlations between proband and mother schizophrenia-spectrum behaviors as well as between proband and father schizophrenia-spectrum behaviors, but no significant relationship between mother and father schizophrenia-spectrum behaviors was observed. These findings generally support previous reports of atypical behavior characteristic of schizoid personality disorder in social anhedonics and provide preliminary support for the familiality of atypical interpersonal behavior in the biological parents of social anhedonics, as putative schizotypes. This study was supported by NIMH grant 5-21640.

RECENT ONSET PSYCHOSIS

F. Dickerson,* J. Boronow, C. Stallings, A. Origoni, S. Cole, R. Yolken
Stanley Research Center, Sheppard Pratt, Baltimore, MD, USA

Studies of persons with psychosis close to the time of illness onset are important to determine the role of environmental factors in disease etiology and to establish a baseline for early therapeutic interventions. We sought a sample of individuals with an onset of psychosis within the past two years. Inclusion/exclusion criteria also included age between 13 and 45 inclusive and the absence of drug induced psychosis. We identified eligible persons by screening consecutive inpatient and partial hospital admissions to Sheppard Pratt Hospital. Participants' cognitive functioning, symptom severity, social functioning, and illness beliefs were assessed. Participants also provided a blood sample from which common genetic polymorphisms and antibodies to human herpes viruses were evaluated. To date, we have enrolled n=45 individuals, n=31 inpatients and n=14 outpatients. All participants were diagnosed with the SCID; n=18 met criteria for a schizophrenia spectrum disorder (schizophrenia, schizoaffective disorder, or schizophreniform disorder); n=23 for an affective disorder (bipolar disorder or major depression); and n=4 met criteria for another psychotic diagnosis (brief psychotic disorder, delusional disorder, or psychotic disorder NOS). The individuals with a schizophrenia spectrum diagnosis differed from individuals with other diagnoses in being younger (21.7 vs. 29.7 yrs., p<.002); having less education (11.9 vs. 14.9 yrs., p<.0005); having a higher proportion of males (94.4 vs. 22.2%, p<.0001). The individuals with a schizophrenia spectrum disorder also had greater cognitive impairment (mean cognitive RBANS total score 66.7 vs. 82.6, p<.0002) particularly in the domain of immediate verbal memory (mean score of 68.8 vs. 86.1, p<.0005) and WRAT Reading (43.4 vs. 48.9, p<.02) as well as increased negative symptoms (mean PANSS Negative score of 20.6 vs. 16.4, p<.02). The diagnostic groups did not differ in their length of illness, race, maternal education, or paternal education. They also did not differ significantly in PANSS positive symptom score, PANSS general symptom score, PANSS total symptom score, Wisconsin Card Sort performance, or parameters of social functioning. Our studies indicate that individuals with schizophrenia differ from individuals with other psychotic disorders at the onset of their psychotic illness. This work was supported by the Stanley Medical Research Institute.

CORRELATION BETWEEN DISABILITY AND PSYCHOPATHOLOGY IN SCHIZOPHRENIA

A. Elias,* R. S. Murthy
Psychiatry, National Institute of Mental Health and Neuro Sciences, Bangalore, Karnataka, India

Existing literature suggests that disability in schizophrenia is related to its symptoms. Aim of the present study is to look for any cor-

relation between disability and psychopathology as well as illness duration in schizophrenia in the absence of other disabling conditions. 30 patients who were admitted in National Institute of Mental Health And Neuro Sciences (NIMHANS),India, with ICD-10 diagnosis of schizophrenia participated in the study after giving informed consent. Patients with any other psychiatric or medical diagnosis, tardive dyskinesia and other serious side effects due to drug treatment were excluded. All patients were assessed with Positive And Negative Syndrome Scale (PANSS) and Disability Assessment Schedule (DAS-II). Pearson correlation test and multiple linear regression analysis were done using disability score as dependent variable and positive syndrome subscale score, negative syndrome subscale score and general psychopathology subscale score as well as illness duration and age as independent variables. Pearson correlation test showed significant positive correlation of total PANSS score and negative syndrome score with DAS score (r=0.629 and 0.510 respectively). There was no significant correlation between illness duration or age and disability. Multiple linear regression analysis with DAS score as dependent variable and negative syndrome subscale score, positive syndrome subscale score and general psychopathology subscale score as well as age and duration of the illness as independent variables yielded adjusted R square value of 0.487. 48.7% of the variance on disability scores can be explained with psychopathology, age and duration of illness. The total PANSS score and negative syndrome subscale score showed maximum correlation with disability. This is consistent with previous reports. The measured disability was contributed neither by any other illness nor by serious side effect of drug like tardive dyskinesia. The implication of the findings is that even though the overall psychopathology correlates with the disability scores, negative syndrome, as opposed to positive syndrome and illness duration, would maximally contribute towards the extent of disability in schizophrenia.

BELIEFS ABOUT CAUSES OF SCHIZOPHRENIA REPORTED BY RELATIVES OF URBAN AFRICAN AMERICAN INPATIENTS WITH FIRST-EPISODE OR CHRONIC SCHIZOPHRENIA

M. L. Esterberg,* M. T. Compton
Psychiatry and Behavioral Sciences, Emory University, Atlanta, GA, USA

Understanding relatives' beliefs about the causes of schizophrenia is an important step toward clarifying the factors that influence help-seeking and attitudes about mental health services. This pilot study investigated etiological attributions of relatives of urban African American hospitalized patients with schizophrenia. Sixty-one relatives of 38 patients hospitalized in a psychiatric unit in a large, public-sector hospital completed a 30-item questionnaire on possible causes of schizophrenia. Among the patients, 52.5% were hospitalized for a first episode of psychosis. Item frequencies were examined and chi-square analyses were conducted to test differences between relatives of the two groups of patients. Mothers comprised 31.1% of the sample, and other participants included 2 fathers, 19 siblings, and 21 others (other relatives and friends). Of the 30 possible causes of schizophrenia, the five that were most commonly reported as "likely" or "very likely" were *disturbance of brain biochemistry* (67.2%), *hereditary factors* (54.1%), *infection in the brain* (47.5%), *drug/alcohol abuse* (45.9%), and *failure in life* (39.3%). Among these five causes, one significant difference was found between relatives of first-episode patients and relatives of chronic patients. Relatives of first-episode patients more commonly reported *failure in life* as a cause than did relatives of chronic patients (χ^2=7.03; df=1; p<.01). Interestingly, 28 participants (45.8%) reported one or more esoteric causes as "likely" or "very likely". These causes included *environmental pollution, lack of vitamins, possession by evil spirits, punishment from God, radiation, and unfavorable horoscope*. However, among these 28 participants, 23 also reported one or more biological causes as "likely" or "very likely". These findings indicate that relatives of patients with schizophrenia are more likely to endorse biological, personal, or societal factors as being likely causes of schizophrenia, but that many relatives also attribute schizophrenia to esoteric factors. This preliminary research provides important insights into the beliefs about the causes of schizophrenia among relatives of African American first-episode and chronic patients, and suggests a need for greater public awareness about schizophrenia. More research is needed on the associations between causal attributions and perceived stigma, help-seeking behavior, and attitudes about mental health services.

LIFE COURSES OF SCHIZOPHRENIA SPECTRUM DISORDERS OBSERVED FROM BIRTH

B. Fish,* S. L. Hans, J. Marcus, J. G. Auerbach
Psychiatry & Neurobehavioral Science, University of California @ Los Angeles, Los Angeles, CA, USA

We observed the courses of schizophrenia spectrum disorders (SZSD) from birth in 2 prospective studies of infants at risk for schizophrenia. The New York Infant Study (NYIS) used a putative index for defective neural integration in infants, termed "pandysmaturation" (1977). This required retarded cranial growth plus retarded and erratic gross motor development on a single exam. Twelve infants of hospitalized schizophrenic mothers and 12 infants in a community clinic were examined 10 times between birth and 2 years. The Jerusalem Infant Development Study (JIDS) examined 58 infants 5 times between birth and 1 year; 19 of schizophrenic parents, 20 of parents with other disorders and 19 of parents with no mental illness. In the NYIS psychiatric interviews and psychological testing were done at 10, 15 and 22 years, plus interviews at 27-35. In the JIDS a battery of cognitive and motor neurodevelopmental tests was given at 10 and 16-19 years, plus psychiatric interviews at 19. In the NYIS 6 infants had "pandysmaturation" at 2, 6 or 13 months. K.S. Kendler blindly diagnosed the 5 with "pandysmaturation" by 8 months as having lifetime SZSD. "Pandysmaturation" was related to later SZSD (X2 = 11.43; p < 0.0005) (2005). In the JIDS, 2 offspring of schizophrenics had probable "pandysmaturation" at 8 months, with retarded cranial and motor development; 4 had possible "pandysmaturation", with retarded motor development (cranial growth data were unavailable). At 10 years, in 15 JIDS offspring of schizophrenics, only cognitive dysfunction was related to "pandysmaturation". We therefore predicted that subjects with "pandysmaturation" who continued to have abnormal cognitive function would be the most likely to have SZSD as adults (1992). At 16-19 years, of the 5 JIDS subjects with "pandysmaturation" who had abnormal cognitive scores, 3 were blindly diagnosed as SZSD and one refused an interview. Of our combined total of 8 subjects with SZSD, 5 needed treatment by 10 years. Three were blindly diagnosed SZSD at 10 years; 4 additional were diagnosed in adolescence and the last at 24 years. One 10 year old with SZSD became psychotic at 15. Brain pathology points to abnormalities in pre- and early postnatal neurodevelopment in SZSD. "Pandysmaturation" appears to be a gross clinical reflection of such maldevelopment which can be measured

directly in pre-SZSD infants. Probable "pandysmaturation" could be calculated from archived infant data of population cohort studies.

CLINICAL OUTCOMES IN PUTATIVE SCHIZOTYPES: THE ROLE OF GENDER AND INDIVIDUAL DIFFERENCE VARIABLES

C. B. Forbes,* W. W. Leung, M. C. Mann, K. A. Adams, L. M. Collins, J. J. Blanchard
University of Maryland at College Park, College Park, MD, USA

Social anhedonia is considered a defining feature of schizophrenia, and has been shown to be a promising predictor that may help identify those at risk to develop schizophrenia or related disorders. Yet, these putative schizotypes exhibit heterogeneity in clinical outcomes ranging from normal functioning to the development of schizophrenia spectrum personality disorders. This variability may be accounted for by individual differences in personality traits other than anhedonia as well as family and other social supports. Further, these variables may be differentially related to clinical symptomatology on the basis of sex. The present study examined the hypothesis that within social anhedonics clinical severity in spectrum symptomatology is related to magical ideation, perceptual aberration, family environment and perceived social support. Further, these relations were examined separately for men and women. This study utilized a representative community sample selected from 2,226 18-year olds who completed a screening packet containing the Revised Social Anhedonia Scale (RSAS; Eckblad et al., 1982). Recruited individuals were identified by elevated scores on the RSAS (N =86) and matched with non-anhedonic controls (N=88). Participants also completed measures of magical ideation, perceptual aberration, family environment, and social support. Diagnostic interviews were conducted to obtain ratings of schizotypal, schizoid and paranoid personality disorders. Social anhedonics reported greater schizophrenia spectrum symptomatology and poorer functioning than controls (ps <.05). Main effects were obtained, and there were no sex by group interactions for any of these clinical variables. Correlational analyses by gender revealed differing patterns of relationships between family environment, traits and spectrum symptoms. Females' ratings of family expressiveness correlated significantly with schizotypal and schizoid symptoms (ps<.05), whereas all three family subscales were significantly related to paranoid symptoms for males (ps<.05). Perceptual aberration scores did not correlate significantly with spectrum symptoms for either sex. Magical ideation scores were significantly related to paranoid symptoms for males, but did not correlate with symptoms for females. Results will be discussed with regard to understanding the role of gender and individual differences in traits and social factors in determining clinical outcomes in putative schizotypes.

DEVELOPMENT OF NEW RATING SCALE FOR NEGATIVE SYMPTOMS

M. Goggin,* F. Tremeau, L. Citrome, D. Antonius, J. Volavka
Nathan Kline Institute, Orangeburg, NY, USA

Based on the identification of specific behavior related to negative symptoms (1), we aimed to develop a new rating scale for negative symptoms (the Motor-Affective-Social Scale, MASS) that will show good psychometric properties. During a 5 minute structured interview, hand coverbal gestures, spontaneous smiles, voluntary smiling, questions asked by the interviewer and counting speed were counted and rated with 27 inpatients with a SCID diagnosis of schizophrenia or schizoaffective disorder. Information on social behavior (hygiene, participation in groups, and verbal interaction) was obtained from nursing staff. Eight items were selected and were rated from 1 to 4. Inter-rater reliability was calculated between 4 raters with 12 patients for the MASS interview and with 24 patients for the social behavior. Intra-class correlation coefficients for each item were all above 0.90 (for single rater and for average of raters). Internal consistency (Cronbah alpha) reached 0.79 (raw) and 0.80 (standardized). Validity was first evaluated by correlation between MASS total score (range: 8-32, a higher score meaning less negative symptomatology) and clinical ratings. Correlation with the SANS (obtained during MASS interview) was -0.87, with the PANSS Negative Symptom Scale (obtained from a blinded rater) was -0.83. No significant correlation was found between MASS score and the PANSS Positive Symptom score, and with the MADRS score. Correlation with education level reached 0.43. Reliability overtime was above 0.80 for the MASS total score, the MASS interview score and the MASS social score. The MASS is based on the findings that negative symptoms can be grouped into two categories: expressive behavior during an interview and social behaviors. For the interview, specific behaviors are defined, and their occurrences are counted, which avoids subjective impressions and the influence of global impressions on item ratings. The MASS can be easily learned, is easily administered and is short (five minutes). Future research involves the use of the MASS with other patient populations (outpatients, patients with depression). Its sensitivity during clinical trials and the influence of gender (patient and interviewer's gender) should also be evaluated.
1- Tremeau F, Malaspina D, Duval F, Correa H, Hager-Budny M, Macher JP, Gorman J. Facial expressiveness in patients with schizophrenia as compared to depressed patients and nonpatients controls. *American Journal of Psychiatry*.

SENSITIVITY TO HEAT STIMULI IN SCHIZOPHRENIA

M. Goldman,* J. H. Meador-Woodruff, K. L. Casey, G. W. Dalack
Psychiatry, University of Michigan, Ann Arbor, MI, USA

Although insensitivity to heat and pain has been reported in individuals with schizophrenia for over 100 years, the prevalence and clinical significance of this phenomenon remain unknown. We hypothesize that altered sensitivity to painful stimuli in schizophrenia is under central nervous system control and may reflect abnormalities in central glutamatergic neurotransmission. As a first step in examining this hypothesis, we compared heat sensitivity in 17 individuals with schizophrenia and 20 medical controls using a rigorous quantitative sensory testing methodology. Medical chart reviews and face-to-face interviews were conducted to obtain information about demographics, medical history, and current symptoms. A precise computer-controlled device, TSA-II (Medoc U.S., Durham, NC), was used to generate and to record responses to highly repeatable thermal stimuli delivered via a thermode placed on the ventral surface of the forearm. Subjects responded to increasing standardized heat stimuli (32° to 50°C) by pressing a response button to indicate thresholds for warmth (WS, first sensation of warmth), heat-pain (HP, first sensation of pain) and heat-pain tolerance (HT, limit of tolerance for pain). In addition, visual analog scales (VAS) were used to record subject ratings of intensity and unpleasantness for 5 different temperatures. Results showed that WS thresholds were significantly higher in individuals with schizophrenia compared to con-

trols (mean (SD) in °C: 36.5 (3.6) vs 34.5 (0.8); p<.01). In contrast, HT thresholds were lower in those with schizophrenia (47.7 (2.2) vs 49.2 (1.0); p<.02). The two groups did not differ significantly on heat pain (HP) thresholds. VAS scores of heat/pain intensity and unpleasantness were higher for individuals with schizophrenia at all temperatures, but none of these differences attained statistical significance in post-hoc comparisons. The data also showed a positive correlation between WS thresholds and negative symptomatology (e.g., WS and BPRS negative symptom scores: r = .55, p<.03). These results suggest that real differences in warmth and pain sensation exist between schizophrenia subjects and controls, but that the relationship is complex. Further studies are warranted to examine whether the thermal paradigm can be used to identify a subset of patients with schizophrenia who might benefit from targeted pharmacologic interventions. Supported by a grant from Veterans Education and Research Association of Michigan.

PERSISTENT AUDITORY HALLUCINATIONS: A PHENOMENOLOGICAL APPROACH

J. Gonzalez,* E. J. Aguilar, C. Leal, V. Berenguer, J. Sanjuan
Psiquiatria, Hospital Clinico, Valencia, Valencia, Spain

There is still a significant proportion of psychotic patients who suffer from persistent auditory hallucinations in spite of the treatment. The objective of our study is to analyze those clinical dimensions that characterize persistent hallucinators in comparison with episodic ones. A total of 91 DSM-IV schizophrenic patients with auditory hallucinations were assessed through semi-structured interviews. The interviews included the PSYRATS scale for auditory hallucinations and the Krawiecka scale. They elicited descriptions about the persistence of auditory hallucinations, existence of pleasurable hallucinations and other types of hallucinations. Forty-five patients fulfilled criteria for reported persistent auditory hallucinations since they fulfilled the following criteria: (i) Voices talking about them, at least once a day over a period of no less than two years. (ii) At least three periods (of six months each) in the preceding 2 years of treatment, with conventional and atypical antipsychotics, at a dose equivalent to at least 1000mg chlorpromazine per day, without relief in hallucinations Persistent hallucinators showed greater scores in frequency and duration of hallucinations, Krawiecka total score and incoherence of speech. Moreover, pleasurable experiences were more frequent in this group of patients. A logistic regression analysis rendered a model with the following variables: duration of voices, degree of control and pleasurable hallucinations. Specific dimensions of auditory hallucinations can predict the possibility of treatment resistance. Falloon IR, Talbot RE. Persistent auditory hallucinations: coping mechanisms and implications for management. *Psychol. Med* 1981; 11: 329-339. Sanjuan J, Gonzalez JC, Aguilar EJ, Leal C, Van Os J: Pleasurable auditory hallucinations. *Acta Psychiat Scand* 2004, 110: 273-278.

COURSE OF ILLNESS IN SCHIZOPHRENIA: IS THERE A RELATIONSHIP WITH PREMORBID SOCIAL ADJUSTMENT?

J. M. Harkavy-Friedman,* D. Kimhy, R. R. Goetz, D. Malaspina
Psychiatry, Columbia University/New York State Psychiatric Institute, New York, NY, USA

In the 1960's, premorbid asociality was found to be related to poor prognossis in schizophrenia (Gittelman-Klein, 1969). Early attempts to assess the relationship between premorbid social adjustment and prognosis for course of illness in schizophrenia relied on clinical chart review and impressionistic ratings of course of illness. We have attempted to standardize the assessment of both premorbid adjustment and course of illness in order to carefully examine their relationship. We assessed premorbid social adjustment with the Premorbid Adjustment Scale (PAS; Cannon-Spoor et al.) and course of illness with the course of illness variable from the Diagnostic Interview for Genetic Studies (DIGS; item K102; Neurenberger et al., 1992) in 149 individuals with schizophrenia or schizoaffective disorder hospitalized on the Schizophrenia Research Unit of New York State Psychiatric Institute (NYSPI). Scores for the subscales of the PAS were compared for individuals with mild/moderate deterioration (n=72) and those with severe deterioration or low functioning stable individuals (n=77). Age, sex, SES, age of onset and duration of illness were included in analyses as potential covariates. The PANSS (Kay and Opler) was used to assess current clinical symptoms of schizophrenia. The validity of the course of illness variable was supported by our finding that those with a severe course of illness were currently more symptomatic than those with a mild/moderate course. Using regression techniques we found that social but not academic premorbid adjustment related to course of illness. This suggests that using total scores for the PAS may obscure group differences. Age, sex, SES, age of onset of illness and duration of illness were not significantly related to course. We did find that many who functioned well initially (i.e., during childhood) evidenced social impairment as early as middle school and continued to decline prior to illness onset. Early evidence of social decline can be measured prior to illness. Subtle decline, once identified, may warrant early intervention. It will be important develop and evaluate early intervention programs.

PATTERNS OF PRE-ONSET COURSE OF ADJUSTMENT AND SHORT-TERM SYMPTOMATIC OUTCOME IN ADOLESCENT ONSET FIRST-EPISODE PSYCHOSIS

M. R. Hollmann,* C. M. Klier, M. H. Friedrich, G. P. Amminger
Child and Adolescent Psychiatry, Medical University of Vienna, Vienna, Austria

PURPOSE: To identify patterns of premorbid functioning in first-episode psychosis in relation to short-term symptomatic outcome (eight weeks). METHOD: Retrospective case study of 93 consecutive patients experiencing a first episode of psychosis in adolescence (mean age 15.8; SD = 1.0 years). Premorbid functioning in childhood and early adolescence was assessed by the Cannon-Spoor et al. Premorbid Adjustment Scale (PAS). Criteria for clinical outcome were based on Pearlson et al. who defined three grades of treatment response (complete remission, partial remission and no response), according to the degree of positive symptoms. We subtyped premorbid functioning in a longitudinal manner using the median to split the sample into good and poor adjustment in both, childhood and early adolescence, to define four patterns of development from childhood to adolescence: stable good, increasing, decreasing, stable poor functioning. All individuals fulfilled criteria for DSM-III-R schizophrenia or schizoaffective disorder (Amminger et al., 1997). RESULTS: Stable good, increasing, decreasing, stable poor premorbid functioning was observed in 43.0%, 11.8%, 11.8%, and 33.3%, respectively. Proportions of complete remission of positive symptoms at 8-weeks follow-up were 67.5% in individuals with stable good, 72.7% in individuals with increasing, 36.4% individuals

with decreasing, and 9.7% in individuals with stable poor premorbid functioning. Developmental groups of premorbid functioning significantly differed in relation to symptomatic outcome (complete remission vs. partial or no remission) (Chi-square=27.54, df=3, p<0.0001). CONCLUSIONS: Longitudinal patterns of premorbid functioning are strongly associated with short-term treatment response in first-episode psychosis. Amminger GP, Resch F, Mutschlechner R, Friedrich MH, Ernst E. Premorbid adjustment and remission of positive symptoms in first-episode psychosis. Eur Child Adolesc Psychiatry, 6:212-8, 1997

INTERNALIZED STIGMA OF SCHIZOPHRENIA AND DEPRESSION

T. Hwang
Psychiatric Rehabilitation and Community Mental Health, Yongin Mental Hospital, Yongin City, Kyonggi Province, South Korea

Objective; Stigma is a social construction that defines people in terms of a distinguishing characteristics or mark and devalues them as a consequences. This study is to develop 29 item Korean version of ISMI (Internalized Stigma of Mental Illness) scale developed by Ritsher in the US and apply it people with schizophrenia and depressive disorders. Method; The ISMI (Internalized Stigma of Mental Illness) scale is to measure the subjective experience of stigma with subscales of Alienation, Stereotype Endorsement, Perceived Discrimination, Social Withdrawal and Stigma Resistance. The survey participants included 194 people with schizophrenia and 200 people with depressive disorders diagnosed by DSM-IV in the inpatients units, outpatients units, and community mental health center. Other measures were Korean version of CES-D (Center for Epidemiological Studies-Depression) scale and Rosenberg Self-esteem scale for the construct validity of the ISMI. Result; The Korean version ISMI had high internal consistency reliability coefficient (Alienation 0.88, Stereotype Endorsement 0.78, Discrimination Experience 0.89, social withdrawal 0.88, stigma resistance 0.74). ISMI was positively associated with CES-D depressive symptoms and was inversely associated with self-esteem. ISMI and depressive symptoms were significantly higher in schizophrenia group and self-esteem was slightly higher in schizophrenia group, but stigma resistance was significantly higher in depression group. No sexual differences are in ISMI subscales except higher stigma resistance in women. The inpatients perceived higher stigma compared with the outpatients in the community, but showed no differences in depressive mood and self-esteem, and stigma resistance was higher among the outpatients. Conclusion; Korean version of ISMI was a useful instrument for measuring internalized stigma of the mentally ill patients, who were suffering from it. Perceived stigma was higher in schizophrenia group than depression group and it was related with low self-esteem and depressive mood. Psychiatric interventions and psychosocial rehabilitation should lessen the stigma and help the patients to overcome the stigma for the recovery, which is the good indicator of the treatment outcome.

OUTCOME AND COGNITIVE IMPAIRMENT OF DSM-IV SCHIZOPHRENIA: A 5-YEAR FOLLOW-UP

H. Hwu,* T. Hwang, S. Liu, C. Liu, M. Hsieh
Psychiatry, National Taiwan University Hospital and College of Medicine, National Taiwan University, Taipei, Taiwan

For invesstigating the 5-year follow-up outcome and cognitive impairment of DSM-IV schizophrhenia (SCH). Consequtively admitted patietns of SCH were recruited after signedthe informed consent. A total of 225 cases were successfully recruited. The psychopathological assessments included DIGS, Syndrome Scale od PANSS, and Basic Clinical Data. The clinical outcome was evaluated annually, and the congitive functions of attention (measured by CPT), executiove function (evaluated by WCST), memory (by WMS-III), Visual-motor function (trail A and B) and general intellectial function (WAIS-R) were assessed in three successive years. The cases were divided into two gropus of first(GFA) and multiple (GMA) admission; and two group of early onet (below or equal to 25 years old: GEOS) and lated onset (over 25 years old: GLOS) for data analyses. Among 225 cases, 112 cases (50%) were male, 167 cases(74%) were single. Mean age of onset of initial nonspefcific symptoms was 21.6 y/o and of psychotic symptom was 23.0 y/o.The mean score of symptom dimensions of negative, deluson/hallucination, hostility, thought disorganization on admission were 19.7, 11.9, 17.5, 13.5, respectively; and were 15.7-16.5, 7.8-9.1, 9.8-11.3, and 7.2-8.7, respectively in the 5 year follow-up course. The global social function (4-28 score) in the 5-year follow-up course ranged from 12.2 to 15.9 annually. The global improbvement(1-4 score) ranged from 2.9 to 3.0 annually. The rate of being on job (any kind) decreased steadily from 40% to 16% in 5 year period. The rate of tardive dyskinesia increased steadily from 5 % to11% up to 5th year of follow-up. The cognitive funxctions of attention, executive function, memory, trail A and trail B and general intellectual functions impaired over 3 successive years of evaluations. Hoever, the year by year corelation was not significantly stable. The GFA and the GMA showed mainly no significant difference outcomes and cognitive function impairment. As compared with the GLOS, the GEOS did have worse outcome as shown in higheer score in delusion/hallucination ans hostility/excitement and in worse social function score and cognitive function variables. However, this difference in clinical outcome was found only in the early coursee of follwo-up. We concluded that DSM-IV SCH did have stable clinical outcome and cogntive function impairment. Early age onset was revealed to have clinical sifnificance.

LONGITUDINAL ASSESSMENT OF NEGATIVE SYMPTOMS IN SCHIZOPHRENIA: AN ANALYTICAL APPROACH TO ASSOCIATIONS WITH POSITIVE SYMPTOMS OVER TIME

M. E. Kelley,* G. L. Haas, D. P. van Kammen
Biostatistics, Emory University, Atlanta, GA, USA

Objective: Recent studies of the efficacy of antipsychotics, including serotonin-dopamine antagonists, now focus on the treatment of both negative as well as positive symptoms. However, the treatment of negative symptoms has been confounded by the distinction between those symptoms that are primary to the illness, and those that are secondary to psychosis. There have been many attempts to disentangle these separate targets of treatment, including clinical evaluation, statistical adjustment, and screened sample selection. Method: The current study employed the use of repeated measurements of negative symptoms in two separate research designs: the first weekly following drug withdrawal, in both patients who experienced a worsening of psychotic symptoms (n=44) and those who remained clinically stable (n=56), and the second in a group of first episode patients (n=62) initiated into treatment for the first time and followed for one year. The measures of interest included the affective flattening and diminished motivation factors of Kelley et al (1999), as well as specific items such as affective flatten-

ing, poverty of speech, avolition and anhedonia. Longitudinal mixed effects models were used for the subscale items, while repeated ordinal regression using GEE was used for the item-level analyses. Results: The first episode patients had a significant linear decrease in psychosis over time [$p < 0.0001$]. In both cohorts, the diminished motivation factor as well as the avolition item showed changes that paralleled the changes in psychotic symptoms evidenced by significant relapse*time effects [p=0.002, p=0.01, respectively] for the drug withdrawal cohort, and time effects [p< 0.0001, p=0.002, respectively] for the first episode cohort. In contrast the affective flattening factor, as well as the affective flattening and poverty of speech items, remained relatively stable over time [relapse*time effects: p=0.344, p=518, p=0.213, respectively, time effects: p=0.859, p=0.939, p=0.147, respectively]. Conclusions: These data indicate that under controlled conditions, certain negative symptoms may be used as indicators of primary negative symptoms, while others are clearly secondary, i.e., related to the path of psychotic relapse or remission. Studies supported by NIH grants R01MH44-841 (PI DvK), P50MH45156-14 (PI D.A. Lewis) and the Veterans Affairs Research Merit Review Board.

FACTOR STRUCTURE AND SEVERITY OF DELUSIONS IN INDIVIDUALS WITH SCHIZOPHRENIA DURING EARLY VS. LATER COURSE

D. Kimhy,* C. Corcoran, R. Goetz, D. Malsapina
Psychiatry, Columbia University, New York, NY, USA

Introduction: The stability of the factor structure of delusions and their severity among individuals with schizophrenia over the course of illness remains unclear. Method: We examined cross-sectionally the factor structure of delusions and severity of delusions in subjects with DSM-IV schizophrenia/schizoaffective disorder during Early (0-2 years following onset) vs. Later (3+ years following onset) periods using the Scale for Assessment of Positive Symptoms (SAPS). Results: The factor structure of delusions narrowed from four factors during the Early period to three factors during the Later one. A factor containing Schneiderian-type delusions remained relatively stable. Additionally, persecutory delusions changed their association over the course of illness. Severity of delusions among subjects assessed during antipsychotic-free status (Early: N = 21; Later: N = 73) was significantly higher among the Later group for delusions of being controlled $t(59.34) = 2.32$, $p = .02$, mind reading $t(71.87) = 3.26$, $p < .00$, thought broadcasting $t(83.83) = 4.86$, $p < .00$, thought withdrawal $t(54.83) = 2.55$, $p = .01$, reference $t(50.89) = 1.97$, $p = .05$, and grandiose delusions $t(77.85) = 3.19$, $p < .00$. The factor structure of delusions in each period was assessed using medicated subjects (Early: N = 38; Later: N = 247) due to low number of neuroleptic-free subjects. Discussion: The factor structure of delusions changed over the course of illness with a more narrow structure characteristic during the Later period. A factor consisting of Schneiderian-type delusions of being controlled, mind reading, thought broadcast, thought withdrawal, and thought insertion remained relatively stable, suggesting common underlying neurobiology of these delusions. The severity of all delusions increased over time with significant increases in Schneiderian-type delusions of being controlled, mind reading, thought broadcasting, thought withdrawal, as well as delusions of reference and grandiosity. Implications of the results for future research are discussed.

AN EXPERIENCE SAMPLING STUDY OF THE RELATIONSHIP OF SOCIAL ANHEDONIA WITH SOCIAL CONTACT, STRESS, AND EMOTION

T. R. Kwapil,* P. J. Silvia, I. Myin-Germeys, L. H. Brown, A. J. Anderson, S. A. Coates
Psychology, UNC-Greensboro, Greensboro, NC, USA

The present study employed the experience sampling method (ESM) to explore the relationship of daily life experiences with the schizotypic trait of social anhedonia. ESM is a daily structured diary technique in which participants are prompted at random times during the day to complete an assessment of their current experiences. The present study examined the relationship of social contact, affect, and stress across levels of social anhedonia in a sample of 56 college students using personal digital assistants. As hypothesized, elevated scores on the Revised Social Anhedonia Scale (Eckblad et al., 1982) were associated with increased social isolation, diminished social interest, and decreased positive affect from social contact. Multilevel hierarchical linear modeling revealed that social contact was associated with lower levels of stress and increased positive affect in nonanhedonic individuals, but with increased stress and reduced positive affect in highly anhedonic individuals. Social anhedonia was associated with diminished reactivity to stress in terms of positive affect, but not negative affect. ESM appears to be a promising method for examining the daily life experiences of schizotypic individuals.

PREVALENCE OF TOXOPLASMA INFECTION IN FIRST-EPISODE SCHIZOPHRENIA AND COMPARISON BETWEEN TOXOPLASMA-POSITIVE AND TOXOPLASMA-NEGATIVE SCHIZOPHRENIA

W. H. Ling
Psychiatry Department, Renmin Hospital of Wuhan University, Wuhan, Hubei Province, China

Several studies have shown that the level of antibodies to Toxoplasma gondii in first-episode schizophrenia is higher than in controls. It is hypothesized that this widespread and neurotropic intracellular protozoan may contribute to the development of schizophrenia. The aim of the present research is to study the differences in clinical features between Toxoplasma-negative, first-episode schizophrenia (FES) and Toxoplasma-positive FES. Antibodies to T.gondii in schizophrenic patients and their mothers were examined and compared. Six hundred patients with first-episode schizophrenia or schizophreniform disorder were studied. The controls included 200 healthy people and 200 inpatients with physical diseases in the same hospital. Blood samples were obtained from them and 252 mothers of the patients. The levels of IgG and IgM antibody to T.gondii were measured by ELISA. The clinical symptoms of the patients were assessed by use of Positive and Negative Symptoms Scale (PANSS). The rate of reactivity to antibodies to T. gondii, especially IgG class antibody, in the mothers of the first-episode schizophrenic patients was higher than that in the schizophrenic patients, and that in the schizophrenic patients was higher than in the controls. Compared to seronegative schizophrenia, the mothers of the seropositive schizophreniahad a higher rate of seropositivity to T. gondii (for IgG $P<0.01$; For IgM $P<0.05$). Also, the clinical symptoms of seropositive schizophrenia were statistically different from seronegative schizophrenia in some items of PANSS ($P<0.01$), that is, excitation (P4), hostility

(P7), mannerisms and posturing (G5), disturbance of volition (G13), poor impulse control (G14), anger (S1), difficulty in delaying gratification (S2), and suspiciousness (P6). In conclusion, the research further supports the hypotheses that Toxoplasma infection is an important candidate etiological factor of schizophrenia and that Toxoplasma-positive patients with functional psychosis have some special clinical features. Clinicians should be aware that a patient with major psychosis who has obvious excited, agitated, disorganized behavior may suffer from latent Toxplasma infection.

CLINICAL, FUNCTIONAL, NEUROPSYCHOLOGICAL AND BRAIN IMAGING CORRELATES OF NAILFOLD PLEXUS VISIBILITY IN SCHIZOPHRENIC PATIENTS AND FAMILY MEMBERS

J. Liska,* J. P. Vuchetich, D. P. Dionisio, J. J. Stanwyck, K. A. McGuire, S. R. Sponheim
University of Minnesota, Minneapolis, MN, USA

Nailfold Plexus Visibility (NPV) is a well-replicated marker for a subset of schizophrenic patients characterized by high levels of negative symptoms and a poor prognosis. As this trait appears heritable, high levels of NPV may also designate a genetic endophenotype for a clinical subtype of schizophrenia. We studied 24 individuals with schizophrenia and 28 of their relatives using a variety of clinical scales, measures of occupational & social functioning, and neuropsychological variables tapping frontal lobe function in order to further characterize this endophenotype. We assessed NPV with the Plexus Visibility Scale (PVS). In addition, we had Structural Magnetic Resonance and Diffusion Tensor Imaging data on a subset of these subjects. In keeping with the literature, we found an increased prevalence of high NPV in our schizophrenic patients relative to community norms, and found that high NPV patients had significantly more negative symptoms and poorer functioning in terms of social relations and ability to work. Levels of those negative symptoms consistent with a deficit syndrome discriminated High from Low NPV patients even better than more broadly defined negative symptom indices. High NPV patients tended to score more deviantly on the Wisconsin Card Sort Test (WCST) and the Controlled Oral Word Association Test (COWAT) than low NPV patients, as has been seen previously. Level of NPV was correlated with the pathological brain imaging findings of increased ventricle size and reduced fractional anisotropy of frontal lobe white matter tracts in the subset of patients with brain imaging data. In our sample these two indices of brain pathology were highly and significantly intercorrelated. As predicted, the prevalence of high NPV was much greater in first-degree relatives of schizophrenic patients with high NPV than in relatives of low NPV schizophrenic patients. These two relative groups did not differ on overall level of schizotypy symptoms as assessed by the Schizotypal Personality Questionnaire or on the "negative symptom schizotypy" Chapman scales: Social Anhedonia and Physical Anhedonia. However, relatives of low NPV patients scored significantly higher on Perceptual Aberration and Magical Ideation, the Chapman scales measuring "positive symptom schizotypy". Our results provide further evidence that schizophrenic patients with high NPV form a distinct clinical subgroup and that this trait may identify a genetic endophenotype.

EVIDENCE OF ABNORMAL INTERHEMISPHERIC INTERACTION IN SCHIZOPHRENIA

J. Lohr,* M. Caligiuri, J. Hellige, B. Cherry, L. Lulow, W. Kwok
Psychiatry, UCSD, La Jolla, CA, USA

Considerable evidence implicates interhemispheric problems in schizophrenia, including differences in corpus callosum shape and size, and lateralized functional difficulties. One relevant issue is how the brain controls information processing when both hemispheres have access to the information. An important concept is metacontrol, in which one hemisphere asserts control when both receive information. To study this, Hellige et al (1989) employed the consonant-vowel-consonant (CVC) task, in which three-letter nonsense syllables were presented in vertical alignment to each hemisphere separately and also together, with the finding that the right hemisphere (RH) processes letter by letter, whereas the LH processes the entire syllable more as a unit, phonetically. Surprisingly, bilateral presentation in healthy subjects showed a RH-like error response, not LH. This suggests that when CVC information is presented bilaterally, the LH switches into more of a RH type of processing. We reasoned that if schizophrenia is associated with reduced interaction between the hemispheres, then bilateral presentation would show an error pattern more LH-like. The primary measure was the % qualitative error score (% last letter errors - first errors divided by total errors), where a larger value suggests greater RH type of processing. Age, gender, and handedness comparable subjects with schizophrenia (n=28), bipolar disorder (n=51), and healthy controls (n=50) were studied. The results for the primary measure are shown in the Table below. We found a significant diagnosis x visual field effect (p=0.023). The Table shows that the error pattern for the control and bipolar subjects during bilateral CVC presentation reflected a RH error pattern. Schizophrenia subjects were unable to switch to a RH processing mode under conditions of bilateral stimulus presentation. Information processing deficits in schizophrenia may be associated with impairment in hemispheric control characterized by an inability to switch from a LH to a RH type of functioning as needed. If the normal response represents a metacontrol process, then this process may be abnormal in schizophrenia.

Mean (sd) Percent Error Scores for 3 Stimulus Presentation Modes for 3 Subject Groups

IS THERE A CONTINUITY BETWEEN PREMORBID ADJUSTMENT AND PERSONALITY IN PSYCHOTIC PATIENTS AND THEIR SELF-RATED SCHIZOTYPAL SYMPTOMS?

J. Lopez-Ilundain,* I. Mata, M. Beperet, F. Perez-Nievas
Fundacion Argibide, Pamplona, Navarra, Spain

Poor adjustment and abnormal personality during childhood and adolescence have been considered as risk factors or early manifestations of psychotic disorders. Poor premorbid adjustment has been related to numerous clinical variables in psychosis patients, including insid-

ious mode of onset, chronic course, and poor outcome. However, premorbid adjustment has been found to be better represented by two specific domains consisting in social and school adjustment, which might predict different clinical characteristics. Abnormal personality has been reported as being more frequent among psychotic patients than their siblings or healthy controls. Although the continuity between premorbid personality traits and symptom patterns in psychosis is still under debate, several studies have reported a higher degree of negative symptoms among patients with more premorbid schizoid or schizotypal traits. The aim of this study was to investigate the possible continuity between parent-rated premorbid adjustment and premorbid schizoid and schizotypal traits during childhood and adolescence, and self-rated schizotypal symptoms in a sample of psychosis patients. A sample of 90 psychotic patients completed the Schizotypal Personality Questionnaire (SPQ). Their parents were interviewed using an instrument to assess adjustment during childhood and adolescence (PSA), and schizoid and schizotypal personality traits during the same period (PSST). Correlation analyses were then calculated adjusting for the most relevant variables. The results of these analyses showed that, while poor premorbid social adjustment did not predict the degree and pattern of schizotypal symptoms, poor premorbid school adjustment predicted a higher degree of schizotypal, mainly disorganized, symptoms. Furthermore, a higher degree of premorbid schizoid and schizotypal traits predicted a higher score on the SPQ interpersonal factor. This study provides preliminary evidence of a continuity between poor premorbid school adjustment and disorganized schizotypal symptoms, and gives further evidence for the continuity between childhood and adolescence abnormal (schizoid and schizotypal) personality and negative (schizotypal) symptoms.

MALE GENDER AND POSITIVE FAMILY HISTORY REDUCE AGE OF ONSET IN SCHIZOPHRENIA AND THESE EFFECTS INTERACT: A META-ANALYSIS OF 46 STUDIES

J. H. MacCabe,* S. S. Eranti, P. K. Sham, B. S. Everitt, R. M. Murray

Psychological Medicine, Institute of Psychiatry, London, London, United Kingdom

Background: Previous studies have shown that male gender and positive family history tend to confer an earlier age at onset (AAO) in schizophrenia. Aims: We aimed to derive pooled estimates of the gender difference and family history difference in AAO and to examine whether these effects interact. Methods: A search of the Medline and Web of Science databases, from 1987-2001, was performed and the resulting papers were examined. Studies were only included if diagnoses used ICD-9, DSM-III-R or later versions. 46 studies reported separate AAO by gender and 13 reported gender-specific AAO for subjects with and without a family history of schizophrenia. A random-effects meta-analysis was performed to obtain pooled estimates of age differences by gender and family history. The method of Copras and Chi was used to assess publication bias. A meta- regression analysis examined the impact of heterogeneity between studies on gender difference (diagnostic system, inclusion of schizoaffective disorder, prospective, retrospective and first-onset study designs, and economic development (developing/developed country)). Results: There was no evidence of publication bias. A Q-test indicated a high degree of heterogeneity between studies. Differences in study design did not affect estimates of gender difference. Males became ill 2.5 years (95% CI 1.8-3.1) earlier than females. Subjects with a positive family history of schizophrenia had a significantly earlier age of onset, and the onset-advancing effect of family history was significantly greater in females (4.7 years, 3.0-6.4) than in males (1.5 years, 0.1-2.9). Conclusions: The analysis confirmed that males have an earlier onset than females. This effect seems independent of study design. The interaction between gender and genetic effects could be explained by a late-onset, non-genetic subtype of schizophrenia, which is more common in females.

VARIANTS OF SCHIZOPHRENIA: CARVING NATURE AT ITS JOINTS

D. Malaspina,* R. Goetz, J. Harkavy-Friedman, R. Wolitzky, C. Corcoran, H. Ahn

New York State Psychiatric Institute, Columbia University, New York, NY, USA

Schizophrenia is frequently studied and discussed as if it were a unitary condition, although it is actually a syndrome comprised of different variants, yet to be clearly demarcated. Recent epidemiology studies consistently show advancing paternal age as an independent risk factor for schizophrenia, explaining up to 25% of all cases. We characterized 265 schizophrenia patients as to demographics, symptoms, and cognition (WAIS-R, Wechsler Scales). Paternal age related schizophrenia (PARS) was defined as family history negative (sporadic) cases with paternal age >33 yrs. We used multivariate statistics to compare PARS to other schizophrenia cases and then we confirmed the characteristics of the PARS cases using K-means clustering techniques that included paternal age and family history as clustering variables to identify latent classes amongst the entire sample. PARS cases had superior WAIS-R IQ scores, greater medication free positive symptoms, and less deficit syndrome schizophrenia than familial cases. A group by sex interaction showed that PARS females were significantly more cognitively impaired than PARS males, with the converse being true in other cases. Independently, the K-means cluster analysis yielded 5 clusters and strengthened the evidence that PARS was a specific variant. There were 3 sporadic (S1, S2, S3) and 2 familial (F1, F2) clusters. S1 included 78% of the cases we defined as PARS, had the largest Verbal vs. Performance IQ difference (VIQ, PIQ: 94, 84.1), 13.8 yrs education, and onset at 20.4 (5.1) yrs. The other 2 sporadic and 2 familial subgroups showed distinct profiles with regard to IQ scores, education and age of onset. The five clusters showed differences in positive and negative symptoms and their responsiveness to antipsychotic medications. They also showed differed in attention, Wechsler memory scales, deficit syndrome, and in psychophysiological measures. These findings support the hypothesis that paternal age related schizophrenia (PARS) is a specific variant of schizophrenia and that segregating it from other forms of the disease can significantly reduce the remaining unexplained variance in the schizophrenia syndrome. These results may provide methods to distinguish disease variants in early illness for targeted treatment studies, to trace pathophysiological pathways to disease, and to clarify phenotypes for genetic studies.

THE IMPACT OF SMOKING HISTORY AND MOTIVATION TO CHANGE ON SMOKING CESSATION IN SCHIZOPHRENIA

M. C. Mann,* M. E. Bennett, E. Weiner, R. W. Buchanan, P. M. Ball

Psychology, University of Maryland, College Park, MD, USA

Research indicates that schizophrenia patients have higher rates of smoking than the general population and are less likely to receive

smoking cessation interventions. While schizophrenia patients may be less able to comply with traditional smoking cessation programs, research suggests that these patients will respond when psychoeducational smoking cessation programs are modified to meet their needs. Several studies have found support for the efficacy of bupropion SR for smoking cessation in nondepressed patients; however, there have been no such studies conducted in schizophrenia patients. In addition, research has not addressed the influence that motivation to quit and smoking history might have on changes in smoking following smoking cessation treatment. This poster will present data on current smoking behavior, smoking and quit histories, and motivation to quit among a group of schizophrenia patients who participated in a larger randomized trial of bupropion SR plus a psychoeducational intervention to treat smoking in schizophrenia. Data are taken from 22 patients who completed both baseline and post treatment follow-up assessments of nicotine dependence, smoking quantity and frequency, and motivation to change. Expired carbon monoxide levels were measured weekly during the treatment phase and monthly thereafter. We have three study aims. First, we will present detailed descriptive data on smoking in our sample of schizophrenia patients attending a smoking cessation program, including smoking severity, the number and nature of past quit attempts, and patients' understanding of the negative consequences of smoking. Second, we will describe motivation to quit smoking in our sample, including stages of change at baseline (as measured by the University of Rhode Island Change Assessment Scale, Smoking Version), temptation to smoke in different situations, and self-efficacy to cope with situations without smoking (Abstinence Self-Efficacy Scale). Third, we will examine changes in motivation to quit from baseline to post treatment, and how motivation to quit is related to smoking cessation, as measured by self reports of smoking and expired CO. Implications for the development of smoking cessation programs for individuals with schizophrenia will be included.

TWELVE-MONTH PROSPECTIVE FOLLOW-UP OF PATIENTS WITH SCHIZOPHRENIA-SPECTRUM DISORDERS AND SUBSTANCE ABUSE: CHANGES IN PSYCHIATRIC SYMPTOMS AND SUBSTANCE USE

H. C. Margolese,* J. C. Negrete, R. Tempier, K. Gill
Department of Psychiatry, McGill University, Montreal, QC, Canada

Co-occurring substance use disorders are common among patients with schizophrenia and related psychoses (1). While dual diagnoses (DD) patients are often more difficult to manage, surprisingly little literature explores what happens to psychiatric symptoms over longer treatment durations. This prospective 12-month study evaluated changes in psychiatric symptoms and substance use to ascertain if substance use disorders lead to greater psychiatric instability. 147 outpatients with severe and persistent mental illness were followed prospectively. Psychiatric symptoms were assessed at baseline and 12-month follow-up using the Positive and Negative Symptom Scale (PANSS) and Hamilton Depression Rating Scale (HAM-D); subjective psychological distress was measured with the Brief Symptom Inventory (BSI); quality of life by the Satisfaction with Life Domains Scale (SDLS). The Addiction Severity Index (ASI) was used to determine drug and alcohol use at baseline and follow-up. 74 patients were diagnosed as DD (50 lifetime, 24 current), 73 as single diagnosis (SD) (without substance use disorder) Among DD patients the most common primary substances of abuse were alcohol (35.6%) and cannabis (35.1%). Severity of substance use measured by ASI composite scores did not differ significantly between baseline and 12-months. DD subjects had higher baseline PANSS positive scores but experienced a greater reduction compared to SD patients, so that at 12 months all groups had similar positive symptom expression. All groups had some reduction in their BSI subjective level of distress (measured by Global Severity Index (GSI)), but scores remained most elevated for current DD subjects. Furthermore, while all had some reduction in Positive Symptom Total (PST) scores, DD-current group remained the most symptomatic, followed by DD-lifetime group [$F(2,142)=10.30$ $p<0.001$] DD patients with schizophrenia and related psychoses treated for their psychiatric illness demonstrated a reduction in psychosis despite continued use of substances. 1. Margolese HC, Malchy L, Negrete JC, Tempier R, Gill K: Drug and alcohol use among patients with schizophrenia and related psychoses: Levels and consequences. *Schizophr Res* 2004, 67:157-166.

THE DEVELOPMENT OF QUALITY OF LIFE IN FIRST EPISODE PSYCHOSIS

I. Melle,* S. Friis, U. Haahr, J. O. Johannessen, T. K. Larsen, S. Opjordsmoen, B. R. Rund, P. Vaglum, T. McGlashan
Institute of Psychiatry, University of Oslo, Oslo, Norway

Quality of life (QoL) is increasingly recognized as a valid part of outcome assessments in schizophrenia. QoL measures should include both assessments of the patient's actual situation (objective QoL) and patient's satisfaction (subjective QoL). Most studies have focused on chronic patient samples where objective QoL have been poor, and have regularly found a discrepancy between objective and subjective measures attributed to lack of insight. The generalizability of these findings is not known. Few studies have focused on first episode patients and follow-up studies of such samples are rare. The present study includes a representative sample of 282 patients with first-episode psychosis. QoL was measured by Lehman's Quality of Life Interview. At one-year follow-up 214 patients completed the interview. There were no significant differences between patients attending or not attending follow-up. There was a significant improvement in satisfaction with life in general, daily activities, family, living situation and personal safety, in number of daily activities and frequency of family contact, and significant correlations between subjective and objective measures from the same domain. Further assessments of the relationship between QoL measures, pre-treatment characteristics and clinical symptoms will be presented at the conference.

SUBTLE FLUCTUATIONS IN PSYCHOTIC PHENOMENA AS FUNCTIONAL STATES OF ABNORMAL DOPAMINE REACTIVITY IN INDIVIDUALS AT RISK

I. Myin-Germeys,* M. Marcelis, L. Krabbendam, P. Delespaul, J. van Os
Psychiatry and Neuropsychology, Maastricht University, Maastricht, Limburg, Netherlands

Subjects at increased risk for psychosis experience continuous variation in the intensity of subtle psychotic experiences in response to minor stressors, a phenomenon described as behavioral sensitization to daily stress. It was investigated whether this type of behavioral

sensitization in individuals at risk for psychosis is the exophenotypic expression of an underlying endophenotype characterized by dopamine (DA) sensitization. In order to study the possible association between behavioral sensitization and DA sensitization, antipsychotic-naive subjects at risk of measurable expression of psychotic experiences are required. Non-medicated first-degree relatives of psychotic patients are such a group as they, on average, display higher levels of psychotic experiences, including subtle psychosis-like, or schizotypal, experiences. Non-medicated first-degree relatives (n=47) and control subjects (n=49) were studied with the Experience Sampling Method (ESM is a structured diary technique assessing current context and psychopathology in daily life) to assess psychotic experiences in response to daily life stress. A metabolic perturbation paradigm (administration of 2-deoxy-D-glucose inducing a mild state of glucoprivation) causing plasma elevation of homovanillic acid (HVA) was used as a proxy of DA sensitization. Multilevel regression analyses revealed that the interaction between HVA-reactivity and daily stress in their effect on psychotic experiences differed according to underlying vulnerability. Stratified analyses separate for each group demonstrated no significant interaction effect between HVA-reactivity and stress in their effect on ESM psychotic experiences in controls ($B = -0.03$ ($SE = 0.06$), $p = 0.63$), while in the relatives a large and significant interaction effect was found indicating that in this group the degree of underlying HVA-reactivity modified ESM psychotic experiences in response to daily life stress ($B = 0.12$ ($SE = 0.06$), $p < 0.04$). The results suggest that psychotic experiences in response to minor stresses in the flow of daily life may be functional states of an underlying abnormal DA reactivity in subjects with a higher than average risk to develop psychosis. The results, therefore, add credence to the suggestion that abnormal DA reactivity may be part of the substrate that increases risk for psychotic symptoms in individuals at risk.

INPATIENT ASSAULTS: PSYCHOPATHOLOGY, PSYCHOPATHY, AND IMPULSIVITY

K. A. Nolan,* C. B. Shope, P. Czobor, J. Volavka
Nathan Kline Institute, Orangeburg, NY, USA

Aggressive behavior among psychiatric inpatients disrupts the therapeutic environment, complicates discharge planning and community re-entry. Advances in the treatment and prevention of aggression depend upon improved understanding of the causes of such behavior. We previously developed a semi-structured interview to elicit patients′reasons for assaulting others and to determine the extent to which psychosis, disordered impulse control and psychopathy contribute to inpatient assaults. Data obtained in 55 assailant interviews were analyzed and have been published[1]. Factor analysis revealed two psychopathology factors, one related to positive psychotic symptoms and the other to psychotic confusion and disorganization, as well as a third factor that appeared to differentiate impulsivity versus psychopathy. We have since collected data for 57 additional assaults. Analysis of the second, independent set of assailant interviews revealed a similar, three-factor structure with good factor matching. Factor analysis of the combined data from both sets of interviews is shown in the table. Three factors account for 58.25% of the total variance in the combined set. The interview items related to psychotic symptoms have high loadings on the first factor, which accounts for nearly 26% of the total variance. Partial denial and amnesia have high loadings on the second, psychotic confusion/disorganization factor. The third factor is bipolar, contrasting planning (psychopathy) with remorse and provocation (impulsivity). These data suggest that although effective treatment of psychosis may be an important strategy for reducing inpatient assaults, additional positive effects may be derived from therapies focused on anger management, impulse control, and improving interpersonal skills. [1]Nolan, KA et al. 2003. Characteristics of assaultive behavior in psychiatric inpatients. *Psychiatric Services*.54,1012-1016.

Factor analysis of assailant interviews (n=112)

SELF-IDENTITY CHANGE IN CHRONIC SCHIZOPHRENIA

P. Olgiati,* G. Guaiana
Villa Cristina Hospital, Turin, Italy

Self-identity delusion (SID) is the morbid conviction of being another person, generally more famous, wealthier or endowed with more powers. This phenomenon, which can be observed in a few psychotic patients, is still poorly understood from the standpoint of prognostic implications. This is a preliminary report on four schizophrenic patients with SID (3 women and 1 men) who were compared with twenty non-SID schizophrenics matched by gender and age, randomly selected from a pool of one hundred consecutively admitted inpatients . Standardized instruments (PANSS, CGI, GAF) were used to assess symptom profile, illness severity and clinical response. Due to the small number of cases statistical analysis was performed with nonparametric tests. SID was found to be associated with more disorganization, greater severity, greater functional impairment and poorer response to treatment. The study emphasizes the strength of self-identity delusion and its negative consequences for the prognosis of schizophrenia. Such findings are consistent with an extensive disruption in self-identity which would lead to a compensatory grandiose identity.

PATHOGENESIS OF SCHIZOPRENIA: A PSYCHOPATHOLOGICAL PERSPECTIVE

D. G. Owens,* P. Miller, S. M. Lawrie, E. C. Johnstone
Psychiatry, University of Edinburgh, Edinburgh, United Kingdom

Despite interest in early treatment of schizophrenia, premorbid and prodromal symptomatology remains poorly delineated. This study aims to compare pre-illness symptomatology in subjects of the Edinburgh High Risk Study (EHRS) at high familial risk of schizophrenia who progress to illness with that of similar high risk subjects who remain well and normal controls. Scales of severity of groups of symptoms were derived from the Present State Examination (Wing et al. 1974), using data from 250 individuals suffering a first schizophrenic illness (Johnstone et al. 1986). Scores on these scales were compared for the first and last PSEs in all subjects of the EHRS. At entry, when still well, high

risk individuals who subsequently became ill (mean time to diagnosis 928 ± s.e. 138 days) scored significantly higher on 'situational anxiety', 'nervous tension', 'depression', 'changed perception' and 'hallucinations' than those remaining well and normal controls, who did not differ. With illness onset, affective symptomatology scores remained high but were essentially stable. It is concluded that in individuals predisposed to develop schizophrenia for familial genetic reasons, affective and perceptual disorders are prominent before the behavioural or subjective change that usually characterises the shift to schizophrenic prodrome or active illness. References: Wing, J. K., Cooper, J. E. & Sartorius, N. (1974) *The Description and Classification of Psychiatric Symptoms. An Instruction Manual for the PSE and Catego Systems*. Cambridge: Cambridge University Press. Johnstone, E. C., Crow, T. J., Johnson, A. L., et al (1986) The Northwick Park Study of first episodes of schizophrenia. I. Presentation of the illness and problems relating to admission. *British Journal of Psychiatry*, 148, 115-120.

ONE YEAR SOCIAL AND CLINICAL OUTCOME IN FIRST EPISODE OF PSYCHOSIS: INFLUENCE OF DUP AND PAS

J. M. Pelayo-Teran,* R. Perez-Iglesias, M. L. Ramirez-Bonilla, I. Martinez-Gonzalez, O. Martinez, G. Pardo, C. Gonzalez-Blanch, J. L. Vazquez-Barquero, B. Crespo-Facorro
Department of Psychiatry, University Hospital Marques de Valdecilla (HUMV), Santander, Cantabria, Spain

The main purpose of the study was to investigate the relationship between the Duration of Untreated Psychosis (DUP) and psychopathological and social measures of medium term outcome in patients with a First Episode of non-affective psychosis and describe any association with other predictor factor as the premorbid function. 100 patients (68 M, 32 F) with non-affective psychosis were included. Inclusion criteria were DSM IV diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or non specified psychotic disorder. Exclusion criteria: neuroleptic treatment superior to 12 weeks, diagnosis of substance abuse, mental retardation or organic brain disease. Psychopathological outcome measures included BPRS, SANS and SAPS and Social outcome was measured with the Disability Assessment Schedule (DAS), recorded at baseline and after 1 year of treatment. Premorbid function was evaluated with the Cannon-Spoor's Premorbid Adjustment Scale (PAS). DUP was defined as follows: interval (months) between the onset of marked delusions, hallucinations or formal thought disorder and the implementation of the first antipsychotic treatment. Correlational analysis (Spearman's rank-order) was used to detect associations between DUP, PAS and outcome measures. Mean DUP was 13,13 m (SD: 30,24). DUP showed a weak association with the initial Negative dimension (SANS), but was no associated with any other initial, final (or the difference initial-1 year) measure of clinical or social outcome. DUP also showed a weak association with total PAS score (r=0,247) and late adolescent PAS score (r=0,299). Total PAS and late adolescent PAS score showed association with DAS, BPRS, SAPS and Psychotic dimension (SAPS) at 1 year. Early adolescent PAS score showed these same associations and also correlated with Negative dimension. Our results show that DUP is not directly associated with the medium term outcome of psychosis, although it is related with a well known prognostic factor as it is premorbid adjustment. Research grant: Instituto Salud Carlos III FIS- exp.: PI 020499.

CAN THE PRESENCE OF PSYCHOTIC SYMPTOMS BE EVALUATED BY A SELF-REPORT SCHIZOTYPY QUESTIONNAIRE IN PSYCHOTIC PATIENTS?

F. Perez-Nievas,* I. Mata, M. Beperet, J. M. Lopez-Ilundain, A. Albeniz
Fundacion Argibide, Pamplona, Spain

Several studies have reported that poor insight in psychotic patients is correlated with higher negative, disorganized, and delusional symptoms. Some studies have explored the capacity of psychotic patients to self-report their symptoms by comparing self-assessment and objective measures, finding that self-administered responses for positive symptoms may be more valid than those for negative symptoms, and that persecutory delusions and some negative symptoms may be the symptoms with a lower reliability. The aim of this study was to examine if the degree and pattern of self-rated schizotypal symptoms was correlated with an "objective" measure of lifetime and current psychotic symptoms in a sample of patients with functional psychoses. A sample of 105 psychotic patients was asked to complete the Schizotypal Personality Questionnaire (SPQ). Their lifetime and current symptomatology was assessed by means of the OPCRIT checklist and the PANSS scale. Correlation coefficients between the SPQ total and factor scores, and the factor analysis-derived OPCRIT dimension and PANSS subscale scores were calculated, adjusting for the effect of age and sex. We found that scores on two ("first-rank delusions" and "auditory hallucinations") of the three OPCRIT positive dimensions were significantly correlated with the SPQ total score and the SPQ cognitive-perceptual and disorganized factor scores. Scores on the OPCRIT "paranoid", disorganized", and "negative" dimensions were not correlated with any SPQ score. Finally, the OPCRIT "depressive" dimension was positively correlated, and the "manic" dimension negatively correlated, with the SPQ total score and all the three SPQ factor scores. Results of the present study would suggest that psychotic patients' self-report of schizotypal positive symptoms might be a somehow reliable measure of the presence of first-rank delusions and hallucinations but not paranoid symptoms, while patients' self-report of schizotypal negative and disorganized symptoms might not reflect the presence of these type of symptoms. Furthermore, psychotic patients with more depressive symptoms but not those with more manic symptoms, might show and be aware of the presence of schizotypal symptoms. Probably, lack of insight of negative, disorganized, and manic symptoms account for these results.

OLFACTORY IDENTIFICATION FUNCTION IN INDIVIDUALS AT-RISK FOR PSYCHOSIS

D. O. Perkins,* H. Gu, K. Graham, M. Siegel, J. Lieberman
Psychiatry, University of North Carolina, Chapel Hill, NC, USA

Introduction: Individuals with schizophrenia have impairments in odor detection threshold, identification, and memory. The timing of

emergence and course of olfactory deficits is not well understood. Olfactory identification deficits are present in never medicated patients at first treatment contact and the severity of these deficits does not change over 6 month follow-up. In chronic patients the severity of olfactory deficits significantly correlates with duration of illness and with severity of negative but not positive symptoms. A recent study found that individuals At-Risk for psychosis performed similar to healthy subjects on a test of olfactory identification. Those At-Risk subjects who subsequently developed psychosis performed comparably to those who did not develop psychosis and to healthy subjects. However those individuals who developed schizophrenia scored marginally significantly worse than healthy and other At-Risk subjects. Methods: The University of Pennsylvania Smell Identification Test (UPSIT, range 0-40, a score <35 suggests microsmia) was administered to 28 subjects at-risk for psychosis by meeting Criteria of Prodromal States (COPS) and to 21 healthy subjects at baseline and every 6 months for up to two year follow-up. Results: At baseline the mean UPSIT score was similar for healthy and At-Risk subjects [36.0 (2.2) and 34.8 (5.3) respectively, p=0.32]. Follow-up data was available for 23 At-Risk subjects (5 subjects received antipsychotics as part of a separate clinical trial or at the discretion of the treating clinician and so were excluded from follow-up analyses). Olfactory identification ability was similar for At-Risk subjects who did (n=8) and did not (n=15) develop a psychotic disorder [35.9 (1.9) and 35.3 (3.2) respectively, p=0.63]. Similarly there was no difference in olfactory identification ability in individuals who developed schizophrenia (n=5) [35.4 (2.1)] and other subgroups. A similar proportion of healthy and prodromal subjects scored in the microsmic range (19% and 29%, respectively); microsmia was not more prevalent in individuals who developed or who did not develop a psychotic disorder or schizophrenia. Conclusion: Individuals At-Risk for psychosis do not have significant deficits in olfactory identification. Olfactory deficits may emerge at a stage later than the prodrome.

WHERE DO WE STAND IN THE SCHIZOPHRENIA SPECTRUM AND THE SEARCH FOR BIOLOGICAL MARKERS?

S. Phansalkar,* A. S. Kablinger
Psychiatry, LSUHSC, Shreveport, LA, USA

The purpose of this presentation is to visually present the various biological markers that have been studied in the schizophrenia spectrum populations and assess the areas still in need of evaluation. Multiple risk factors have been identified that increase the chance that a person may develop schizophrenia. Such factors include heredity, maternal infection during the second trimester, perinatal complications and/or hypoxia, cognitive impairment in specific arenas, social isolation, and early chronic cannabis use to name a few. Biological markers, on the other hand, are objective, measurable phenomena that may identify subjects at increased risk for disease development. Biological markers under current investigation include eye tracking dysfunction, prepulse inhibition (PPI) abnormalities, neuroimaging findings, and plasma homovanillic acid (HVA) levels. Risk factors are often identified retrospectively while markers can be assessed in a prospective format. Methods include a summary of the existing literature on biological marker research. PPI, neuroimaging and cognition have been extensively studied in schizophrenics, first-degree relatives, and subjects with schizotypy. Other markers have not been investigated over the spectrum. Combining information learned from both risk factors and biological markers in patients with schizophrenia and those at increased risk of the disease can aid in identifying those most vulnerable to the development of schizophrenia. This can lead to early intervention and, perhaps, delay or ameliorate symptoms of schizophrenia. Integrating the existing literature allows researchers to plan and explore future domains.

DERMATOGLYPHIC INDICES OF DYSMORPHOGENESIS PREDICT NEUROLOGICAL SOFT SIGNS IN SCHIZOPHRENIA AND BIPOLAR DISORDER BUT WITH OPPOSITE GENDER SPECIFICITIES

J. Quinn,* A. Corvin, P. Scully, A. Kinsella, J. Owens, J. Waddington
Department of Psychiatry, Naas General Hospital, Kildare, Ireland

Though Dermatoglyphic abnormalities have been widely studied as indices of dysmorphogenesis in schizophrenia (SZ), their relationship to neurological soft signs (NSS) as an index of neuronal dysfunction in adulthood has yet to be compared systematically across psychotic illness. We have previously identified and assessed the cognition and psychopathology of an epidemiologically complete population of 214 cases of such psychoses [109 SZ, 32 schizoaffective (SA), 73 bipolar (BP)] within a rural Irish catchment area, population 29,542. Among this cohort, it was possible to follow up 115 cases [60 SZ, 18 SA, 37 BP]. NSS were assessed as total score on the Neurological Evaluation Scale [NESt]; dermatoglyphic abnormalities were assessed in terms of total a-b-ridge count [TABRC] using the inkless method. Correlation analyses indicated that in SZ, lower TABRC was associated with higher NESt in female [r= -0.55, P<0.005] but not in male [r= -0.07, NS] patients. Conversely in BP, lower TABRC was associated with higher NESt in male [r= -0.57, P<0.07] but not in female [r= -0.25, NS] patients. The number of SA patients was too small for independent analysis. Linear regression indicated that higher NESt was predicted by increasing age [P<0.001] and independently by a TABRC x diagnosis [SZ vs BP] x gender interaction [P<0.001]. In SZ, lower TABRC predicted higher NESt in females but not in males; in BP, lower TABRC predicted higher NESt in males, but not in females. It appears that extent of abnormality in TABRC is predictive of increasing NESt in both SZ and BP, indicating a relationship between extent of dysmorphogenesis and increasing neurological dysfunction in adulthood. However, the double-dissociation in terms of the gender specificities of these relationships suggests (1) that the dysmorphogenic process is related intimately to aspects of sexual dimorphism and (2) that the relationship between dysmorphogenesis and sexual dimorphism differs between these diagnoses. These studies were supported by the Stanley Medical Research Unit.

CHILDHOOD TRAUMA AND THE FIRST EPISODE PSYCHOSIS

N. Rahaman,* T. Craig
Health Services Research Dept., Institute of Psychiatry, London, United Kingdom

The stress-vulnerability hypothesis of the aetiology of schizophrenia is now well established. This supposes an interaction between a (biological) vulnerability to the disorder and an environmental trigger such as a stressful life event. Traumatic experiences that result in many serious mental health problems are often those which are prolonged and repeated, sometimes extending over years of a person's

life. Links with childhood trauma have been reported for many disorders including schizophrenia. We hypothesised that: 1. Childhood trauma will be more commonly reported by patients with a first episode of psychosis. 2. The number and intensity of positive psychotic symptoms will be greater among patients with a history of childhood trauma. 3. Patients reporting childhood trauma will have poorer engagement. METHOD: A cross-sectional case-control study design was used to compare 50 patients with a first episode of psychosis and 50 of age, ethnicity and sex matched healthy controls. After screening for schizophrenia spectrum disorder, the measures at baseline were SCAN, miniCECA and s-LEDS. The patient sample was followed up with measures of recovery, relapse and engagement with the clinical service over the subsequent year. PRELIMINARY RESULTS: There is a 51% incidence of severe childhood trauma in the patient sample group. The control sample is not yet fully collected, but previous studies would indicate a significantly lower expected rate in the general population. Further analysis is underway. CONCLUSIONS: As has been observed for depression, childhood trauma might increase the occurrence of stressful events in adulthood that in turn precipitate onset in people with a vulnerability. Childhood trauma might influence the content of psychotic symptoms.

MENTAL ILLNESS AND MENOPAUSE: SUBJECTIVE EXPERIENCE AMONG WOMEN WITH BIPOLAR DISORDER, SCHIZOPHRENIA, AND MAJOR DEPRESSION

M. Sajatovic,* S. Hatters Friedman, I. Schuermeyer, M. McDougall, R. Safavi, R. V. Ignacio, F. C. Blow
Psychiatry, Case Western Reserve University, Cleveland, OH, USA

Menopause is a significant event in the life of every woman. Women with serious mental illness (SMI), such as depression, bipolar disorder and schizophrenia experience menopause, as do their peers without mental illness, however the effects of menopause on underlying SMI have not been well studied. It is possible that lack of knowledge regarding menopause and possible fear concerning its physical and psychological effects may influence the menopause experience for those with mental illness. To examine expectations and concerns regarding menopause from a patient centered viewpoint among women with SMI, a prospective assessment of individual perception of effects of menopause on women with schizophrenia/ schizoaffective disorder (N=30), women with bipolar disorder (N=25), and women with major depression (N=36) was conducted. The three groups were compared regarding knowledge on menopause, expectations of effect of menopause on illness outcome, and menopause-related quality of life. All women in this study had deficits in fund of knowledge regarding menopause. Slightly more than half of the total sample (53.8%) agreed that they felt more stressed due to menopause or approaching menopause, and 51.6% felt that menopause has had a negative effect on their emotional state. Perceptions of menopause effect on emotional states between women with schizophrenia, bipolar disorder and depression were fairly similar. The top five symptoms experienced by women with serious mental illness were all problems related to psychological issues: feeling depressed (88%, N=80), feeling anxious (88%, N=80), feeling tired or worn out (87%, N=79), feeling a lack of energy (86%, N=78) and experiencing poor memory (84%, N=76). Longitudinal and larger-scale studies evaluating the effects of menopause on serious mental illness are needed to clarify how menopause affects symptom presentation and outcomes.

SELF-EXPERIENCED COGNITIVE DISTURBANCES PREDICT FIRST-EPISODE PSYCHOSIS

F. Schultze-Lutter,* S. Ruhrmann, A. Wieneke, H. Picker, J. Klosterkoetter
FETZ, Psychiatry, University of Cologne, Cologne, Germany

In research on early detection and intervention, the widely applied 'ultra-high risk' (UHR;1) criteria of the prodrome of first-episode psychosis aim at the description of an imminent risk of psychosis. A complementary approach to an earlier detection is using basic symptoms (BS; 2,3). To improve identification of at-risk subjects by BS, the Schizophrenia Prediction Instrument, Adult version (SPI-A), was empirically developed comprising of 6 subscales and a 7-points severity scale was introduced with frequency of occurrence as the guiding criterion. It was evaluated for its predictive value in the present study. Method: The sample consisted of 146 subjects in a potentially prodromal state. In line with CER- results, a prodrome was defined by any 1 of the ten predictive BS. A transition to first-episode psychosis was defined in line with (1) by the PANSS. The SPI-A, Structured Interview for Prodromal Syndromes (SIPS; 4) and PANSS were applied; baseline subscale totals were compared between transited and not-transited subjects. Results: 43 (29.3%) potentially prodromal subjects transited to frank psychosis within on average 11.1 months (SD=8.3). Subjects who developed psychosis had significantly higher baseline scores in the SPI-A dimensions 'Cognitive disturbances', Disturbances in experiencing self and surrounding' and 'Affective-dynamic disturbances' and the SIPS scales 'Positive symptoms', 'Negative symptoms' and 'Disorganized symptoms'. This was most pronounced for 'Cognitive Disturbances'. Conclusion: The assessment of subjective disturbances might further enhance the current UHR approach to early detection of psychosis. References (1) Phillips LJ, et al: Identification of young people at risk of psychosis: validation of Personal Assessment and Crisis Evaluation Clinic intake criteria. *Aust NZ J Psychiatry* 2000; 34(Suppl.):S164-S169 (2) Ruhrmann S, et al: Early detection and intervention in the initial prodromal phase of schizophrenia. *Pharmacopsychiatry* 2003; 36(Suppl.3):162-167 (3) Klosterkoetter J, et al: Diagnosing schizophrenia in the initial prodromal phase. *Arch Gen Psychiatry* 2001; 58:158-164 (4) Miller TJ, et al: Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of Interrater reliability and predictive validity. *Am J Psychiatry* 2002; 159:863-865

EXPLORING THE CLINICAL HETEROGENEITY OF SCHIZOPHRENIA EARLY IN THE COURSE OF ILLNESS

A. E. Silverman,* A. Rogers, M. Jessani, M. Breecher, R. Josiassen
Arthur P. Noyes Research Foundation, Norristown, PA, USA

OBJECTIVE: Patients with schizophrenia present different combinations of symptoms with varying degrees of severity. The symptoms range across cognitive, emotional, and behavioral domains and influence psychosocial performance and potential for social integration. It is well known that etiological and treatment studies are confounded by the degree of clinical heterogeneity, and underscores the need to define more homogeneous subgroups of schizophrenic patients. Numerous studies have addressed the clinical heterogeneity in schizophrenia using factor analytic techniques, with converg-

ing results suggesting the existence of at least three distinct dimensions (Liddle, 1987; Andreasen et al., 1995) and perhaps five distinct dimensions (Toomey et al., 1997). Our objective was to explore further the potential dimensions of schizophrenia in a sample of patients early in the course of illness using the Positive and Negative Symptom Scale (PANSS) that captured the heterogeneity of symptoms. METHODS: Screening PANSS ratings (N = 398 subjects, 288 males, 110 females) from an ongoing first-episode psychosis project and from two registration trials. The group mean age was 22.32 years (SD = 2.1), and duration of illness was 2.9 years (SD = 2.7). The PANSS scores were then factor analyzed (eigenvalues >1, quartermax rotation). RESULTS: The factor analysis of PANSS scores showed, similar to results from previous studies, that a five-factor solution which accounted for 57.0% of the total variance. The five factors represented the commonly observed domains: (1) negative symptoms (26.9% of variance), cognitive impairment (12.7%), hostiliy/ aggression (7.6%), positive symptoms (5.0%), and mood disorder (4.7). Individual factor scores for these five factors were then generated for each individual subject. Next, the factor scores were explored using an hierarchical cluster analysis. Results from the cluster analyisis showed that after 5 clusters, the rate of change of the sum of squared differences became small and flattened out. CONCLUSION: Factor analysis of PANSS scores from a large sample showed that even early in the course of schizophrenic illness, symptoms captured by the PANSS are optimally described by five unique factors. An hierarchical cluster analysis suggested that a number larger than five clusters yielded modest additional gains in description.

SEX DIFFERENCES IN AGE AT ONSET OF SCHIZOPHRENIA IN INDIA: A SECOND LOOK

S. Sira Mahalingappa
Psychiatry, National Institute of Mental Health and Neuro Sciences, Bangalore, Karnataka, India

Females have been known to have higher age at onset (AAO) of schizophrenia. There have been discrepant findings regarding gender differences in AAO from India. AAO is also affected by birth order. This study was undertaken to examine the gender difference and influence of birth order on AAO of schizophrenia. 75 drug naive subjects in the age group of 18 to 45 years with DSM IV diagnosis of schizophrenia were included in the study. AAO was determined using Interview for Retrospective Assessment of Onset of Schizophrenia. Information of patients birth order and diagnostic information about the members for the family was recorded using The Family Interview for Genetic Studies. Psychopathology of the patients was assessed using PANSS. We found that, in the present study the males (n=42) had significantly earlier AAO (26.6years SD=7.3) than females (n=33) (30.6years SD=8.9) (p=0.037). Earlier birth order (1&2) was significantly associated with earlier AAO in males (mean age= 24.9years, SD=4.54 years) than the late born (3 & more) (mean age=28.18years SD=9.6 t=2.72, p=0.01). Such an association was not found in females (mean age in earlier born = 30.68 years SD=8.31, mean age in late born = 30.52 years SD=9.65, t=0.70 p=0.49) There was no significant correlation between AAO and severity of illness in either of the sexes. Earlier studies from India have reported an earlier AAO in females (Murthy et al 1998, Gangadhar et al 2002). Attrition of birth trauma due to high infant mortality rate was implicated for this. In the present study males had a significantly earlier AAO than females. We suggest that better obstetric facilities over the past decade are reflected in the changing trend of the sex differences in the AAO of schizophrenia. Males are associated with greater risk of subtle brain damage during labor and this risk is higher for earlier birth order. This may explain the association of earlier birth order and early AAO only among males. Social factors like the early born males having to shoulder more responsibility in Indian society may also contribute to this association. It would be interesting to replicate these findings and explore further, the possible causes of earlier birth order in males with schizophrenia in a community sample.

THE CANNABIS EXPERIENCES QUESTIONNAIRE: ITS DEVELOPMENT AND CORRELATES

J. D. Stirling,* E. Barkus, S. Lewis, R. Hopkins
Psychology and Speech Pathology, Manchester Metropolitan University, Manchester, United Kingdom

The Cannabis Experiences Questionnaire (CEQ) is a recently developed measure intended to record the wide range of phenomenological experiences associated with the drug's use. In addition to recording information about frequency of use plus anecdotal qualitative experiences related to cannabis (optional section), the questionnaire comprises a 56 item checklist of experiences to which individuals respond using a five-point Likert scale. The CEQ has now been piloted on three separate cohorts of non-clinical respondents. Previously, we (Barkus et al; 2003) reported provisional findings that amongst cannabis users, high schizotypy is associated with more psychotic-like and unpleasant effects during intoxication. We now confirm these findings with a larger sample. Factor analysis with pooled data from over 300 respondents indicates that items on our checklist aggregate into three domains; pleasurable/euphoric experiences, psychoto-mimetic experiences and after-effects. We also report the results of an item analysis illustrating the varied effects of cannabis on psychological functioning. Finally, we report preliminary results about the CEQ's test-retest reliability and construct validity.

EXPRESSED EMOTION AND ELECTRODERMAL ACTIVITY IN RECENT-ONSET SCHIZOPHRENIA

M. Tchillingarian,* K. L. Subotnik, A. M. Schell, M. E. Dawson, J. Ventura, K. A. Kelly, J. Mintz, K. H. Nuechterlein
Department of Psychiatry, UCLA, Los Angeles, CA, USA

High expressed emotion (EE) in the family environment has been shown to be associated with increased likelihood of relapse in schizophrenia, but the mechanism underlying this well-replicated correlation is not understood. It has been hypothesized that this predictive relationship might occur through the influence of EE on the patient's autonomic activation. Previous research has shown that a patient's electrodermal activity (EDA) is high while in the presence of a family member who has high EE (Hi-EE) as compared to family members with low EE attitudes. However, it is unclear if the increased EDA continues when the family member is not present. Only continued effects on EDA would be expected to have enough impact to alter relapse risk. EE was assessed for the immediate family members of 104 recent-onset schizophrenia patients at study entry. EDA was assessed at the patient's index hospitalization and again approximately three months later while receiving outpatient treatment. EDA was measured without presence of family members. At the three-month outpatient point, high EE in the family environment was found to be significantly associated with a higher total number of skin conductance orienting responses (SCORs) elicited by non-task-relevant

tones in the laboratory. Path analyses were used to examine possible ways in which both psychobiological vulnerability factors in the patient and family environmental stressors jointly influence the course of psychotic symptom presentation. These analyses support the view that the impact of EE on psychotic symptom presentation is partially mediated by the patient's electrodermal activity.

EMOTION AND SCHIZOPHRENIA: A REVIEW OF CLINICAL STUDIES

F. Tremeau
Nathan Kline Institute, Orangeburg, NY, USA

Emotion research in schizophrenia has focused on three types of impairments: deficits in the non-verbal expression of emotions (encoding deficits), deficits in the experience of emotions, and deficits in the recognition of emotions (decoding deficits). We reviewed all the clinical studies published in English, that used diagnostic criteria and that involved facial or acoustic expressions of emotions. Studies on encoding deficits (30 studies) showed that, when compared to nonpatient controls, patients with schizophrenia are impaired in the voluntary and spontaneous expressions of emotions, for all emotions and independently of medication regimen. Most studies could not find any differences between schizophrenia and depression. These types of deficits appear to be part of a more general deficit in expressiveness. Studies in the experience of emotions report that patients with schizophrenia rate higher on anhedonia scales (25 studies) than nonpatient controls, they report a lower degree of positive affect and a higher degree of negative affect in everyday life (7 studies) and, in laboratory conditions (25 studies) they report the same degree of positive affect and a higher degree of negative affect. Very few studies have used medication-free subjects. Studies on facial affect recognition (108 studies) and acoustic emotional recognition (20 studies) consistently report impairment in schizophrenia. Some studies report emotion-specific impairments for schizophrenia, however methodological flaws prevent firm conclusions. Studies that controlled for task difficulty concluded that these recognition deficits are part of a general deficit. Correlations with some neurological deficits and some social deficits have been reported, but these results have been inconsistent. Overall these three types of deficits are independent, and consequently blunted affect cannot be simply explained by a reduced emotional life. Similarities in emotion deficits between schizophrenia and depression need further understanding, and consequently schizophrenia cannot be simply considered as a "non-affective disorder". The relationship between these three types of deficits and clinical symptoms, neurological deficits and social functioning should be further clarified. Future research should look at other aspects of emotion research that have been rarely studied in schizophrenia, and more findings and concepts from basic emotion research should be integrated into schizophrenia research.

ASSESSMENT OF CEREBELLAR FUNCTIONS IN SCHIZOPHRENIA: A CLINICAL STUDY

S. Varambally,* T. Jagadisha, N. Janakiramaiah, B. N. Gangadhar
Psychiatry, NIMHANS, Bangalore, Karnataka, India

Aim: To study the cerebellar function in a group of patients with neuroleptic naive schizophrenia using clinical tests and compare with healthy controls. Methods: 32 treatment naive patients with schizophrenia (DSM IV) and 32 healthy controls were recruited after matching for age, sex, handedness, and education. Written informed consent was taken from all subjects and assessments were done before starting treatment in the patients. Instruments used included The International Cooperative Ataxia Rating Scale (ICARS) for cerebellar function, The Positive and Negative Syndrome scale of Schizophrenia (PANSS), The Scale for Assessment of Negative Symptoms (SANS), the Neurological Evaluation Scale (NES), and the Simpson Angus Extrapyramidal Side Effects Scale (SAS). Results: Patients with schizophrenia had more cerebellar dysfunction (mean ICARS scores) and Neurological Soft Signs (mean NSS scores) than healthy controls (see Table). They also had higher extrapyramidal scale scores than healthy controls. Patients who had more cerebellar dysfunction and Neurological Soft signs had higher negative symptom scores than the rest of the patients. There were no other significant differences between these two groups. Conclusions: This study provides comprehensive clinical evidence of cerebellar dysfunction in schizophrenia, lending support to the concept of cognitive dysmetria in schizophrenia. It also corroborates earlier studies that have reported an excess of neurological soft signs and extrapyramidal symptoms in patients with schizophrenia, and underlines the importance of a comprehensive neurological examination in patients with schizophrenia. Source of Support: Dissertation grant from NIMHANS.

Mean ± SD Cerebellar Dysfunction (ICARS) Scores and Neurological Soft Signs (NSS) in Patients Vs Controls

#Independent samples t test;
***Equal variances not assumed**

RELATIONSHIP BETWEEN ONSET OF PSYCHOSIS, COGNITIVE DECLINE, AND SOCIAL WITHDRAWAL IN CHILDREN AND ADOLESCENTS WITH SCHIZOPHRENIA SPECTRUM DISORDERS

T. White,* A. Guimaraes, J. Wozniak, M. Kendi, S. C. Schulz
Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA

Introduction: Children and adolescents who develop schizophrenia tend to have greater impairments than those who develop the illness in adulthood. Reports have shown greater rates of cognitive deficits in those who have an earlier onset of the illness. Some youth have both social and cognitive deficits from very early in development, whereas others show a more marked decline following a fairly typical early development. The purpose of this study is to determine the trajectory of cognitive decline and social withdrawal in relation to the onset of psychosis in children and adolescents with schizophrenia spectrum disorders. Methods: 18 children and adolescents between

the ages of 8 and 19, mean age 15.4 years (S.D. 2.75) with a history of a schizophrenia spectrum disorder underwent a semi-structured diagnostic interview using the Kiddie-SADS. In addition, a timeline was constructed covering the development of psychotic symptoms, social withdrawal and cognitive decline. This information was obtained separately from both the parent and the child and, when possible, was confirmed by school records or other collateral sources. Results: The mean age for the presentation of moderate to severe psychotic symptoms was 13.3 years (S.D. 3.3), whereas the mean age for moderate to severe cognitive decline and social withdrawal was 11.9 years (S.D. 3.2) and 10.5 (5.0), respectively. Cognitive decline followed a similar trajectory as the onset of psychosis, but worsening significantly approximately two years prior to the onset of psychosis. The trajectory of social withdrawal, however, tended to be present years before the onset and follow a separate trajectory. Discussion: On average, children and adolescent with schizophrenia begin to show moderate to severe cognitive deficits two years prior to the onset of psychosis. Social withdrawal is seen earlier and on average gradually worsens up to the onset of psychosis. Recruitment is ongoing to parse out the considerable heterogeneity in the sample.

OBSESSIVE-COMPULSIVE SYMPTOMS (OCS) IN SCHIZOPHRENIA: ASSOCIATIONS WITH PERSONALITY AND COPING STYLE

K. A. Whitney,* L. W. Davis, P. H. Lysaker
Roudebush VA Hospital, Indianapolis, IN, USA

While recent studies suggest that OCS in some individuals with schizophrenia are associated with worse psychosocial and neuropsychological functioning, the purpose of the present investigation was to examine whether or not OCS in schizophrenia might also be linked with certain psychological attributes, such as coping style and personality. We hypothesized that OCS might, by their very nature, be associated with a decrease in the use of effective problem-solving strategies and personality traits that are characterized by the experience of subjective distress and focus on inner experiences. Participants in the study included 46 individuals with schizophrenia and 21 individuals with schizoaffective disorder, all of whom were in a stable or post acute phase of their disorder. As part of a larger study, all participants were administered the Yale-Brown Obsessive-Compulsive Scale, the Ways of Coping Questionnaire, and the NEO Five Factor Personality Inventory. Study participants were divided into two groups, those with and those without a significant level of OCS. MANOVA analysis revealed an overall significant between group difference for scores on measures of coping style and personality (Hotelling's Trace = 316.34 $p < .05$). Independent sample t-tests indicated that, when compared to individuals with schizophrenia without OCS, the scores of individuals with schizophrenia and OCS suggested higher levels of neuroticism, and lower levels of extraversion and conscientiousness ($p < .05$). In addition, when compared to study participants with schizophrenia without OCS, the group of participants with schizophrenia and OCS were more apt to describe their coping style as being typified by ignoring and being resigned in the face of recent stressors, rather positively approaching and reappraising them ($p < .05$). The results of the study, taken together with results of previous studies which suggest greater functional impairment in individuals with comorbid schizophrenia and OCS, emphasize the importance of assessing OCS in this patient population. Future studies may address the efficacy of various treatment strategies for individuals with these comorbid processes.

PHENCYCLIDINE EFFECTS IN HUMANS—PSYCHOSIS OR DELIRIUM?

M. Willeit,* S. Kapur
Schizophrenia PET Research Program, Centre of Addiction and Mental Health, Toronto, ON, Canada

Effects of phencyclidine (PCP) intake have frequently been compared to primary schizophrenic symptoms and interpreted as a drug model for schizophrenia. In contrast to amphetamines, PCP is said to elicit symptoms closely resembling the negative and cognitive dimensions of the illness, and to cause long-lasting exacerbations of primary schizophrenic symptoms in patients with schizophrenia (1). We reviewed the literature and so far identified reports on controlled administration of PCP to a total of 1360 adult human subjects. These subjects include 1021 surgical and obstetric patients to whom PCP was administered as an anesthetic, 23 patients with neurological conditions, 135 healthy control subjects, and 181 patients with psychiatric disorders, 88 of whom with a diagnosis of schizophrenia. There were no reports of prolonged psychoses among patients anesthesized with PCP or healthy volunteers receiving a single subanesthetic dose of PCP. Symptom duration in almost all cases closely matched systemic PCP elimination time. Of 55 psychiatric and neurological patients receiving PCP over weeks, one 64 year old patient with preexisting ischemic brain damage developed a lasting paranoid psychosis. Within patients with schizophrenia, there were four described cases of symptom deterioration lasting for weeks after a single dose of PCP. The remainder of the patients showed short-lasting symptom deterioration or improvement. Fluctuation of consciousness, disturbances in orientation, body image and equilibrium, nystagmus, dysarthria, and amnesia for the time of intoxication are among the most frequently reported symptoms after acute PCP administration in psychiatric patients and healthy subjects. According to the reviewed literature, PCP causes a global disturbance of orientation, memory, perception, and basal executive functions - and they occur in the context of the disturbances noted above. Considering the time course, the variety of neurological symptoms, and disturbances in consciousness and orientation, it seems (at least if one uses the DSM-IV (2) diagnosis scheme) that the cases of controlled PCP administration to humans produce a state closer to substance-induce delirium rather than substance-induced psychosis. (1) Javitt and Zukin. Recent advances in the PCP model of schizophrenia. *Am J Psychiatr*y 1991, 148:1301-1308 (2) *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington D.C.: American Psychiatric Association, 1994.

MALADAPTIVE PSYCHOTIC-LIKE EXPERIENCES IN A NON-PSYCHOTIC POPULATION OF YOUNG PEOPLE I: BASELINE FINDINGS

A. Yung,* J. A. Buckby, S. M. Cotton, C. A. Stanford, K. A. Godfrey, E. M. Cosgrave, E. J. Killackey, P. D. McGorry
ORYGEN Research Centre, Parkville, VIC, Australia

Background: Psychotic-like experiences (PLEs) have been found to be a risk factor for development of full blown psychotic disorder. However, they are also common in the general population. Thus central issues are whether potentially malignant PLEs can be distinguished from more benign forms and whether any correlates of PLEs which make transition to psychotic disorder or poor functional outcome more likely can be identified. Method: Young people aged 15-24 presenting to a mental health service with non-psychotic complaints were assessed at baseline for presence of PLEs, level of

depression and functioning. Results: Factor analysis of PLEs revealed 3 distinct types: bizarre experiences, persecutory ideation and magical thinking. Bizarre experiences and persecutory ideation were associated with depression and poor functioning but magical ideation was not, unless associated with distress. However, the association between PLEs and functioning was no longer significant after adjusting for depression. This was not surprising in our cohort, which had high levels of depression. In fact, depression level accounted for nearly 20% of the variance in functioning in the sample. Conclusion: Bizarre experiences and persecutory ideation are possibly maladaptive. However magical ideation may be a more normal phenomenon in adolescents and young adults.

SYMPTOM DIMENSIONS OR DIAGNOSTIC CATEGORIES? AN ANALYSIS OF THE AESOP FIRST ONSET PSYCHOSIS SAMPLE

A. Demjaha,* K. Morgan, P. Dazzan, N. Kennedy, K. Dean, H. Wickham, B. Chapple, P. Fearon, R. Mallett, J. Leff, R. Murray
Institute of Psychiatry, London, United Kingdom

The aim of this study was to explore underlying psychopathological dimensions in patients with first onset psychosis and to examine the extent to which symptom dimension ratings correspond to a more traditional diagnostic classification. The sample comprised of 335 patients (57% female; mean age 30.12 ± 9.9; 49% DSM IV schizophrenia/schizophreniform disorder, and 51% other psychotic disorder). We analysed a wide range of symptoms and signs with ratings obtained from the SCAN (WHO). A principal component factor analysis was performed on symptom scores, using Varimax rotation. An eigenvalue greater than one was set as the criterion for the retention of factors. The symptom dimension scores were then compared across diagnostic categories. The factor analysis revealed six factors accounting for 51% of the variance, giving rise to the following dimensions: Factor 1 Manic (14% variance) Factor 2 Negative (9% variance) Factor 3 Depressive (9% variance) Factor 4 Reality distortion (7% variance) Factor 5 Disorganisation (5% variance) Factor 6 Non specific psychotic (5% variance) Reality distortion was the highest dimensional rating for: 60% of the patients with schizophrenia; 45% of those with schizoaffective disorder and 37% of patients with brief and other psychosis. 60% of the patients with bipolar (manic) disorder rated highest on the manic dimension. Depresssive was the highest dimensional rating for 40% of patients with depressive psychosis. The pattern of item segregation shows that dimensional structure previously reported in patients with chronic psychosis emerges even in first onset psychosis. Furthermore, these dimensions show high correspondence with diagnostic categories, suggesting that the dimensional approach may play an important role in re-classification of psychotic disorders with ultimate use in clinical practice.

3. Epidemiology

STIGMATIZATION OF SCHIZOPHRENIA AMONG PSYCHIATRISTS

B. B. Akdede,* A. Mantar, D. Ozbay, K. Alptekin
Psychiatry, Medical School of Dokuz Eylul University, Izmir, Turkey

Introduction: Stigmatization of schizophrenia is common not only in the society but also among psychiatrists. In a recent study, it was reported that total of 42.7% of 60 psychiatrists never informed patients of the diagnosis of schizophrenia and 40.7% informed on a case-by-case basis. The aim of the present study was to investigate stigmatization and attitudes towards patients with schizophrenia among psychiatrists in Turkey. Method: A questionnaire was distributed to psychiatrists to investigate their attitudes toward patients with schizophrenia. Ninety psychiatrists (42 women and 48 men) from four different regions of Turkey completed the questionnaire. The mean age of the psychiatrists was 6.29 years. On the second step the questionnaire was given to the physicians working at different departments (other than psychiatry) of Dokuz Eylul University. Seventy three physicians completed the questionnaire. The mean age of the physicians was 33.04. The comparisons of categorical variables between two groups were conducted by chi-square test while continuous variables were compared by t-test. Results: Total of 97.3 % of the physicians and 75.3 % of the psychiatrists stated that the patients should be informed of schizophrenia diagnosis. The comparison of two groups were significant (df: 4, p: 0.02). The psychiatrists (20.4%) and the physicians (24.0) stated similar rates for violence in schizophrenia (p>0.05). The psychiatrists (35.2%) and physicians (33.2 %) stated similar recovery rates for schizophrenia (p>0.05). Conclusion: The present study revealed evidence for stigmatization of schizophrenia among psychiatrists. The stigmatization among psychiatrists might lead to stigmatization and discrimination of patients with schizophrenia in the society, as well. References: 1. Schulze B, Angermeyer MC. Subjective experiencess of stigma. A focus group study of schizophrenic patients, their relatives and mental health professionals. *Soc Sci Med* 2003; 56: 299-312. 2. Ucok A, Polat A, Sartorius N, Erkoc S, Atakli C. Attidudes of psychiatrists toward patients with Schizophrenia. *Psychiatry and Clin Neuroscie* 2004; 58: 89-91.

RISK FACTORS AND PREVALANCE OF PSYCHOTIC SYMPTOMS IN THE GENERAL POPULATION IN IZMIR-TURKEY

K. Alptekin,* S. Semin, B. B. Akdede, G. Ergor, Y. Akvardar, Y. Demiral, M. Tumuklu, H. Ulas, A. Kitis, B. Unal
Department of Psychiatry, Dokuz Eylul University, School of Medicine, Izmir, Turkey

Many individuals may have susceptibility candidate genes which do not let to develop schizophrenia, but show threshold psychotic symptoms, not interfering with daily life functions. Hence it is of importance to assess the frequency of these symptoms and related risk factors in the population. The existence of psychotic symptoms may take part in a continuum of experiences of psychotic symptoms on one edge, and schizophrenia on the other edge (1, 2). The aim of this study was to find risk factors and identify prevalance of psychotic symptoms in the general population in Izmir-Turkey. The sample was selected with the systematic sampling method from the residents, above 18 years of age, of the 3 districts in the urban area of Izmir-Turkey with the population of 80721. The sample size was calculated as 1500 for the prevalance of 1 % with a 95 % CI. Composite International Diagnostic Interview (CIDI) was administered by lay interviewers to all the participants, a total of 1280 individuals. Final response rate for all the sample size was 84.5 %. CIDI psychotic symptoms were found in 3.6 % of the study group. Most frequent symptoms were thought broadcast (1.4%), delusions of persecution (1%) and catatonia (1%). CIDI (+) group had significantly less social and financial support, more alcohol use and heavy early morning cigarette smoking compared to CIDI (-) group. Only 3 individuals had substance abuse (cannabis) and none of these were CIDI (+). Logistic regression analysis showed that being a female (OR=2.4 95 % CI = 1.2-5.1), having a first degree family history of any mental disorders (OR=13.9 95 % CI = 5.7-34.3), lack of social support (OR=4.5 95 % CI= 2.3-8.6) and alcohol use (OR= 4.9 95 % CI = 2.3-10.6) were all related to psychotic symptoms. Having more risk in females in contrast to the Western populations may be due to the severe social pressure on the female gender in Turkey (1, 2). We also note that alcohol might be considered as a risk factor for developing psychotic symptoms in the Turkish cultural setting, such as cannabis abuse in the other cultures. References: 1. Os, J. Van, Hanssen, M., Bijl, R.B., et al., 2000. Strauss (1969) revisited: a psychosis continuum in the general population. *Schizophr. Res*. 40, 11-20. 2. Os, J. Van, Hanssen, M., Bijl, R.B., et al., 2001. Prevalance of psychotic disorder and community level of psyhotic symptoms: an urban-rural comparison. *Arch. Gen. Psychiatry* 58, 663-668.

THE NORTHERN IRELAND FIRST-EPISODE PSYCHOSIS STUDY: EPIDEMIOLOGY OF FIRST-EPISODE PSYCHOSIS IN NORTHERN IRELAND

R. Anderson,* C. C. Mulholland, T. M. Rushe, R. McCaul, S. Barrett, A. McKinney, R. Barr, M. Finnerty, S. J. Cooper
Division of Psychiatry and Neuroscience, Queens University, Belfast, Northern Ireland, United Kingdom

The aim of this study is to examine the epidemiology of first-presentation psychosis, and of schizophrenia in particular, in a large urban and rural Northern Irish population (study population 770,884). Prospective ascertainment of cases of psychosis presenting for the first time to adult psychiatric services within a 2 year period (Jan.2003–Dec.2004). Leakage study of hospital discharge records to maximize case-finding. Subjects aged 18-64 with no obvious organic cause for psychotic symptoms. Clinical, diagnostic, neuropsychological and social assessment of subjects carried out at enrolment with 1 and 3 year follow-up examinations. Diagnosis at enrolment based on ICD-10 criteria using the Schedule for Clinical Assessment in Neuropsychiatry (SCAN). Confirmation of diagnosis at 1 year follow-up using OPCRIT. In the first 18 months 250 suitable cases were identified, of whom 194 agreed to participate. The incidence of psychosis in the study area was 3.40/10,000 popln at risk/year. The modal diagnosis was schizophrenia (40%; incidence 1.35/10,000 popln at risk/year). Males had 1.8 times increased incidence of all psychosis relative to females (2.15 vs 1.21/10,000/year) and 2.6 times increased incidence of schizophrenia (0.92 vs 0.35/10,000/year). The age at presentation of patients with schizophrenia was similar for males and females (29.4 vs 29.3 years respectively). There was no evidence of an increased rate of psychosis or

schizophrenia in urban relative to rural areas. There was a significant rate of co-morbid substance misuse (40%) with the most common substances being alcohol and cannabis. The incidence of psychosis and schizophrenia in the study area is slightly higher than previous findings in Ireland and Nottingham. However, in contrast to most previous published work there is evidence of a higher incidence rate in males compared to females. Again, in contrast to previous studies, we have not found an increased rate of psychosis in urban areas. This finding is likely to reflect particular socio-economic factors prevalent in Northern Ireland. 1. Scully, P. et al *British Journal of Psychiatry* (2002), 181, s3-s9.First-episode schizophrenia, bipolar disorder and other psychoses in a rural Irish catchment area: incidence and gender in the Cavan-Monaghan study at 5 years. 2. Brewin, J. et al *British Journal of Psychiatry* (1997), 171, 140-44.Incidence of schizophrenia in Nottingham: a comparison of two cohorts, 1978-80 and 1992-1994.

TWIN PAIRS DISCORDANT FOR SCHIZOPHRENIA: PSYCHOPATHOLOGY IN THE NON-SCHIZOPHRENIC CO-TWINS

S. Argyropoulos,* M. Picchioni, S. Kalidindi, D. Castle, R. Murray
Institute of Pscyhiatry, London, United Kingdom

Background: Schizophrenic patients are more likely to suffer from mood and anxiety disorders compared with the general population, even after the impact of psychotic symptoms have been accounted for (Tibbo et al 2003). The vulnerability of their non-psychotic relatives is more controversial, but studies have failed to show an increased prevalence of depression or anxiety (Lyons et al 2000). Methods: We studied thirty-three non schizophrenic co-twins from twin pairs discordant for schizophrenia (19 M / 14 F, 20 MZ / 13DZ, mean age: 35.9). They were paired for age, sex and zygosity with fifty-four control subjects (mean age: 36.7) (both members of the control pair were used, if available). Non-psychotic Axis I psychopathology of the participants was assessed using the Schedule for Affective Disorders and Schizophrenia-Lifetime version (SADS-L) (Endicott and Spitzer 1978). Binary logistic regression was employed in the analysis (STATA). Four predictive factors were entered: class (co-twin or control), age, sex, and zygosity. Results: When compared with control twins, non schizophrenic co-twins had significantly increased rates of depression ($p<0.01$, OR=5.5, 95%CI: 1.6-18.8), overall anxiety disorders ($p=0.01$, OR=4.3, 95% CI: 1.4-13.5), and GAD ($p= 0.03$, OR=4.6, 95% CI: 1.2-18.2). A trend was also observed in panic disorder ($p=0.07$) and phobias ($p=0.06$). Gender had a significant effect on depression and panic disorder, and age had a significant effect on panic disorder alone. Discussion: Our results in contrast with a previous report (Lyons et al 2000), suggest that non- schizophrenic co-twins had significantly higher prevalence of depression and anxiety disorders compared with control twins. We conclude that schizophrenia may share risk factors with other psychiatric disorders. Future studies should attempt to investigate whether the high prevalence reported here could be an indication of shared genetic vulnerability or environmental effect. References Endicott J, Spitzer RL (1978): A diagnostic interview: the schedule for affective disorders and schizophrenia. *Arch Gen Psychiatry* 35: 837-844. Lyons MJ, Huppert J, Toomey R, Harley R, Goldberg J, Eisen S et al (2000): Lifetime prevalence of mood and anxiety disorders in twin pairs discordant for schizophrenia. *Twin Res* 3: 28-32. Tibbo P, Swainson J, Chue P, LeMelledo JM (2003): Prevalence and relationship to delusions and hallucinations of anxiety disorders in schizophrenia. *Depress Anxiety* 17: 65-72.

SEX DIFFERENCES AND REPRODUCTIVE PATTERNS IN FAMILIES AFFECTED WITH SCHIZOPHRENIA AND OTHER FUNCTIONAL PSYCHOSES

N. J. Bass,* J. Bourke, M. Anandamurugan
Psychiatry, Royal London Hospital, St. Clement, London, United Kingdom

A retrospective case-note study in an East London (inner city) catchment area is ongoing which aims to document family structures in families multiply affected with psychoses and to compare them with families containing only singly affected cases.This aims to help determine whether a genetic aetiology may plausibly account for both familial and sporadic cases and to determine whether reproductive patterns e.g. sex ratios of offspring and siblings and also fertility may also be a function of a putative genetic risk factor. East London has the most ethnically diverse population in the UK and possibly in Europe and recent census data (2001) now emerging show that although the population of the UK is largely static or even falling in places Tower Hamlets (one of the three east London boroughs) has the fastest growing population in the country. This is a relatively young population with a high percentage under 16 years of age and one third of the borough is of Bangladeshi origin. Birth rates in this community are perhaps the highest in the UK and local data as yet unpublished suggests the rates of schizophrenia and affective psychoses are higher than expected compared to the general population. Data on psychiatric diagnoses (ICD-10) routinely recorded in case notes is being systematically gathered and routinely acquired casenote data on family histories has been analysed. Size and structure of families for both sporadic and familial cases has been compared. Differences in the rates of illness for men and women are found as reported commonly in many studies but we have also looked at sex ratios and fertility rates in the siblings and offspring of family members even when unaffected by psychosis which seem to confirm patterns previously described in a more preliminary report and non-epidemiological family data for linkage studies.

THE HIDDEN MORBIDITY OF FIRST PSYCHOSIS AMONG REFERRALS TO DUTCH MENTAL HEALTH CARE: A LEAKAGE STUDY OF UNDETECTED INCIDENT CASES AND THEIR TREATMENT

N. Boonstra,* A. Wunderink, P. De Wit, E. Noorthoorn, D. Wiersma
GGZ Friesland, Leeuwarden, Netherlands

The Mesifos-RCT designed to compare two treatment strategies for first episode psychotic patients (see abstract Wunderink et al.) has been used for the calculation of 2002 incidence rates in various catchment areas in the North, East and Southwest of the Netherlands. Incidence differed between areas from 1.0 to 2.2 per 10.000 population at risk (overall rate 1,6) and between sexes (M:F ratios) from 1.1 to 3.7; overall, males outnumbered females by three times. The variation in rates and gender distribution between areas requires an explanation. Are women less liable to develop psychosis? Do psychotic women hide in other diagnoses? Or do psychotic symptoms affect women in a less disturbing way? We conducted a leakage study in two catchment areas of mental health services (with 1 million inhabitants) which participated in the Mesifos-study to find out why less women with psychotic symp-

toms were referred to the Mesifos trial, and whether they had been classified among other diagnoses. Method was first a screening of the medical files of all new referrals (n=8000) to the mental health services in 2002 on conceivable psychotic symptoms at first contact, irrespective of the assigned clinical diagnosis. Next, clinicians of patients mediated between patients and researchers to complete a clinical interview (short SCAN) and a self-report questionnaire (CAPE-42 for detection of psychotic symptoms). Data will be reported on the detection rate, the real(corrected) incidence rate and gender differences. The discussion will focus on the degree to which psychotic symptoms are recognised and treated accordingly.

SEROLOGIC EVIDENCE OF PRENATAL EXPOSURE TO TOXOPLASMOSIS IN THE ETIOLOGY OF SCHIZOPHRENIA

A. S. Brown,* C. A. Schaefer, C. P. Quesenberry, L. Liu, V. Babulas, E. S. Susser
Psychiatry, Columbia University, New York State Psychiatric Institute, New York, NY, USA

Purpose: We conducted serologic analyses to examine the relationship between maternal antibody to toxoplasmosis and risk of schizophrenia and other schizophrenia spectrum disorders in the offspring. Toxoplasmosis is a known cause of both subtle and severe congenital CNS anomalies. Method: In the Prenatal Determinants of Schizophrenia Study, a nested case-control design of a large cohort, born from 1959-1967, we conducted assays for toxoplasma antibody on archived maternal serum specimens from pregnancies giving rise to cases of schizophrenia and other schizophrenia spectrum disorders (N= 63) and controls (N=123) matched on length of membership in the cohort, date of birth, gender, and availability of maternal sera. Toxoplasma IgG antibody was quantified using the Sabin-Feldman dye test, the reference standard for the serologic detection of toxoplasma antibody. The IgG titers were classified into three groups: negative (<1:16) (reference), moderate (1:16-1:64), and high (>1:128). Results. The prevalence of high toxoplasma IgG antibody titers was 20.6% in pregnancies giving rise to schizophrenia/schizophrenia spectrum disorder cases and 10.6% in pregnancies giving rise to controls. The odds ratio (95% CI) of schizophrenia/schizophrenia spectrum disorders for subjects with high prenatal toxoplasma IgG antibody titers was 2.61 (1.00, 6.82), p=.051. There was no association between moderate IgG antibody titers and risk of schizophrenia/spectrum disorders (OR=1.11, 95% CI=0.30-4.05, p=0.88). Adjustment for maternal education, maternal ethnicity, and gestational age of the serum specimens had no appreciable effect on the results. Conclusions. These findings provide the first serologic evidence that prenatal exposure to toxoplasmosis may be a risk factor for schizophrenia. Strengths of the study include prospectively collected, archived maternal serum specimens and a well-characterized, representative birth cohort. The results may be accounted for by teratogenic effects of re-activated toxoplasma infection and elevated toxoplasma antibody. Given that toxoplasmosis is a preventable infection, the findings, if replicated, may have implications for reducing the incidence of schizophrenia. Reference: Brown AS, Schaefer CA, Quesenberry CP, Liu L, Babulas V, Susser ES: Maternal exposure to toxoplasmosis and risk of schizophrenia in adult offspring. *Am J Psychiatry* (in press)

COMPARATIVE INCIDENCE AND CHARACTERISTICS OF PSYCHOSIS IN MAJOR DEPRESSIVE DISORDER AMONG AN EPIDEMIOLOGICALLY COMPLETE POPULATION: THE CAVAN-MONAGHAN FIRST EPISODE STUDY AT 9 YEARS

D. J. Browne,* P. J. Scully, J. F. Quinn, M. M. Morgan, P. A. Baldwin, A. Kinsella, J. M. Owens, E. O'Callaghan, J. L. Waddington
Stanley Medical Research Unit, St. Davnets Hospital, Monaghan, Ireland

While first episode studies generally focus on non-affective psychoses, psychosis in major depressive disorder has received little systematic attention. Though potentially informative, greater understanding is predicated on systematic, comparative data in epidemiologically complete, homogeneous populations. Since 1995 we have incepted into this study "all" first episode presentations of non-affective and affective psychosis and of bipolar disorder in Cavan-Monaghan, a population of 103,054, to public or private psychiatric services. Over 9 years there were 223 cases of any first episode psychosis at 6-month follow-up [32.3/100,000 (95% CI 28.2-36.9)]; risk was greater in males [38.2 (95% CI 32.0-45.2)] than in females [26.2 (95% CI 21.0-32.2); relative risk 1.46 (95% CI 1.12-1.91), P<0.01]. Schizophrenia spectrum psychoses [10.1 (95% CI 7.9-12.8)] were more common in males [13.9 (95% CI 10.3-18.3)] than in females [6.4 (95% CI 3.9-9.5); relative risk 2.21 (95% CI 1.33-3.70), P<0.01]; schizophrenia [6.5 (95% CI 4.8-8.7)] was particularly more common in males [9.9 (95% CI 6.9-13.8)] than in females [3.0 (95% CI 1.4-5.5); relative risk 3.32 (95% CI 1.65-6.72), P<0.001]. Affective psychoses [12.3 (95% CI 9.8-15.2)] did not differ between the genders; neither bipolar disorder [5.9 (95% CI 4.3-8.1)] nor psychosis in major depressive disorder [6.4 (95% CI 4.8-8.6] differed between the genders. Other psychoses [9.9 (95% CI 7.7-12.5)] were more common in males [12.4 (95% CI 9.0-16.7)] than in females [7.1 (95% CI 4.6-10.6); relative risk 1.74 (95% CI 1.06-2.87), P<0.05]. Each category was diagnostically stable over 6-month follow-up and had its own epidemiological characteristics. Schizophrenia: decreased risk in females; older age at inception in females. Bipolar disorder: similar overall incidence and age at inception; no gender differences. Psychosis in major depressive disorder: similar overall incidence but older age at inception; no gender differences. Psychosis in major depressive disorder is a neglected entity whose omission may give an incomplete perspective on early psychotic illness.These studies were supported by the Stanley Medical Research Institute.

INTERNATIONAL SCHIZOPHRENIA RESEARCH AND THE CONCEPT OF PATIENT-CENTEREDNESS—AN ANALYSIS OVER TWO DECADES

T. Calton,* A. Cheetham, K. D'Silva, C. Glazebrook
Division of Psychiatry, University of Nottingham, Nottingham, United Kingdom

Background: Since the late 1980s a dialectic has existed in psychiatry between the 'medical model', which espouses a fact-laden and objective view of mental disorders as diseases, and the 'patient-centered ethos', which emphasizes the value-laden and subjective experience of illness. We sought to determine the extent to which the

'patient-centered ethos' (as evidenced by 'subjective experience' research) penetrated the international schizophrenia research effort between 1988 and 2004. *Method*: We developed a definition of 'subjective experience research' that incorporated the patients' individual feelings as 'lived emotional experiences', their ideas and expectations about their illness and their ownership of the research process. Using this definition, all non-duplicated research abstracts (n=9284) presented at the Biennial Winter Workshop on Schizophrenia and the International Congress on Schizophrenia Research between 1988 and 2004 were categorized into 'subjective experience' or 'non-subjective experience' research. Data were also collected on independently assigned category of study and country of origin. *Results*: Abstracts from 50 countries were presented, with America (42%) and the UK (20%) dominating. Europe and North America together accounted for 92% of all abstracts presented. Biologically orientated research was the main theme of 75% of the abstracts, with psychosocial research constituting less than 5% of the total. Only 183 (2%) abstracts met our criteria for 'subjective experience' research ($p<0.0001$). Variables associated with 'subjective experience' research included Psychosocial research (OR=14.63, 95%CI:10.68-20.04), and six countries: The Netherlands (OR=5.16, 95%CI:3.44-7.75), Belgium (OR=6.69, 95%CI:3.40-13.14), Canada (OR=1.76, 95%CI:1.05-2.97), Austria (OR=3.25, 95%CI:1.36-7.27), Norway (OR=5.78, 95%CI:2.27-14.76) and Israel (OR=3.48, 95%CI:1.25-9.7). Biological research (OR=0.13, 95%CI 0.10-0.19), America (OR=0.49, 95%CI:0.35-0.68) and the UK (OR=0.65 95%CI:0.43-0.99) were inversely associated with the production of 'subjective experience' research. Psychosocial research was the best predictor of 'subjective experience' research (adjusted OR=4.52 95%CI:2.89-7.08) *Conclusion*: *Over the last two decades the international schizophrenia research effort has not been patient-centered*. If both facts and values, the subjective and objective, are necessary to understand mental ill-health, *is it any wonder that schizophrenia remains an enigma?*

WHAT EXPLAINS THE INCREASED RISK OF SCHIZOPHRENIA FOUND IN SECOND-GENERATION IMMIGRANTS IN DENMARK?

E. Cantor-Graae,* C. B. Pedersen
Community Medicine, Lund University, Malmo, Sweden

Background: An increased risk of schizophrenia has been found in 2nd-generation immigrants in Denmark, the UK, and The Netherlands. Such risk may partly be due to parental characteristics (mental illness, increased age at child's birth, geographical region of birth) and/or to urbanicity of the child's birthplace. Many 2nd-generation immigrants are born in urban areas. Urbanicity is also strongly implicated as a risk factor for schizophrenia. Objective: To determine whether the increased risk of schizophrenia in 2nd-generation immigrants is related to parental characteristics (age, geographical region, mental illness) and/or to urbanicity of the child's birthplace. Design: Cohort study of incidence of schizophrenia. 11684 persons developed schizophrenia during 36 million person-years of follow-up (1970-2001). Setting: Danish population-based register study. Participants: Using data from the Danish Civil Registration System, we established a population-based cohort of 2.22 million people born in Denmark including information on parental country of birth. Schizophrenia in cohort members and mental illness in a parent or sibling were identified by linkage with the Danish Psychiatric Central Register. Main outcome measure: Incidence of schizophrenia in relation to parental geographic region of birth. Results: Persons with one or more foreign-born parents (i.e. 2nd-generation immigrants) had a 1.92 (1.78-2.06) increased risk of schizophrenia compared to persons of Danish parentage. This effect was independent of which parent was foreign-born (mother vs. father) and their age at child's birth. After adjustment for mental illness in a parent or sibling and urbanicity at birth, the overall risk was reduced to 1.59 (1.48-1.71), albeit with significant geographic regional variation (range 1.22-2.84). Interestingly, the effect of urbanicity at birth was significantly lower among 2nd-generation immigrants than among Danes. Conclusions: Some of the increased risk found in 2nd-generation immigrants was explained by urbanicity at birth and mental illness in a parent or sibling. However, after adjustment for both these factors, the increased risk of schizophrenia in 2nd-generation immigrants still remained significant. This study has been supported by the Stanley Medical Research Institute.

IN UTERO EXPOSURE TO THE UNDERLYING IMMUNOLOGIC MECHANISMS INVOLVED IN THE ETIOLOGY OF PREECLAMPSIA AND SUBSEQUENT DEVELOPMENT OF SCHIZOPHRENIA AND OTHER PSYCHOSES OF ADULTHOOD: A POPULATION-BASED, PROSPECTIVE STUDY USING PROPENSITY SCORE METHODS

S. Cherkerzian,* G. Fitzmaurice, J. M. Goldstein, B. L. Harlow, L. J. Seidman, M. T. Tsuang, S. L. Buka
Department of Society, Human Development and Health, Harvard School of Public Health, Boston, MA, USA

Researchers have identified preeclampsia as a replicated risk factor for schizophrenia. The underlying immunologic mechanisms involved in the pathogenesis of preeclampsia may be critical to understanding this association. Data from the National Collaborative Perinatal Project were used to test the hypothesis that immunologic mechanisms involved in the etiology of preeclampsia are associated with the subsequent development of schizophrenia and other psychoses of adulthood. The study sample included 15,581 men and women born to a community sample of women between 1959 and 1966. Subjects with DSM-IV schizophrenia and other major psychoses were identified based on best-estimate consensus diagnoses using interview data collected using the Structured Clinical Interview for DSM-IV (SCID) and medical record review (n = 106). A predictive model, or propensity score, for preeclampsia based on immunologic variables was used to calculate the probability of preeclampsia for each cohort member. Subjects with and without psychosis were compared with respect to these probabilities. The specificity of this association was determined by comparing the association between psychosis and a predictive model for gestational hypertension. Subjects at elevated risk for preeclampsia (those whose propensity scores exceeded the 75th percentile of the control sample) had an adjusted odds ratio of 1.8 (95% C1: 1.2 - 2.8) for major psychosis. Among psychosis subtypes, risk for preeclampsia was specific to schizophrenic psychoses ($OR_{Adjusted}$ = 2.7, 95% CI: 1.4 - 5.2). In contrast, elevated risk for gestational hypertension (propensity score > 75th percentile) did not predict psychosis ($OR_{Adjusted}$ = 0.8, 95% CI: 0.4 - 1.3). In conclusion, the results of this investigation suggest that immunologic factors involved in the pathogenesis of preeclampsia are associated with the subsequent development of psychosis, and particularly of schizophrenic psychoses. This study was supported by the Stanley Medical Research Institute and the National Institute of Mental Health.

RELAPSE PREDICTORS IN FIRST-EPISODE SCHIZOPHRENIA—A 3-YEAR LONGITUDINAL STUDY

C. P. Chiu,* E. Y. Chen, C. W. Law, C. L. Hui, R. C. Chan, E. L. Dunn, M. Y. Miao, W. S. Yeung, C. K. Wong, W. F. Chan, W. N. Tang
Psychiatry, Queen Mary Hospital, Hong Kong, China

The relapsing nature of schizophrenia poses great challenge in terms of treatment and recovery. Identification of relapse predictors would be of utmost importance and relevance in the management of schizophrenia. In this naturalistic study, potential relapse predictors in terms of demographics, clinical symptomatology and cognition were investigated. 153 consecutive patients with first-episode psychosis were recruited, of which 138 fulfilled DSM-IV criteria for schizophrenia, schizophreniform disorder or schizoaffective disorder upon review at 3 years. Of the 138 eligible subjects, 93 completed the study at 3 years. They were 42 men and 51 women with a mean age of 31.2 (S.D.= 9.6), mean duration of untreated psychosis of 474 days (S.D.= 768), and mean educational attainment of 10.54 years (S.D.=2.9). 55 patients (605) experienced no relapse at 3 years, 25 (27%) had one relapse and 12 (13%) had 2 or more relapses. Those who relapsed have significantly poorer medication adherence (year 1: t=-3.4, p=0.002; year 2: t=-3.6, p=0.001; year 3: t=-3.4, p=0.002) and lower age at presentation (t=3.27, p=0.002). They also tended to have more life events prior to onset (t=-1.687, p=0.097) and more years of education (t=-1.99, p=0.049). No significant effect was found with regard to pre-morbid personality and gender. Our findings suggest that medication adherence and younger age at presentation are significant predictors of the number of relapses in first-episode schizophrenia patients in the first three years. Efforts should target at enhancing medication adherence and engagement of patients, especially those of younger age.

SOCIAL ISOLATION: A CRITICAL INTERVENTION TARGET IN PRODROMAL RESEARCH

B. A. Cornblatt,* T. Lencz, C. Smith, C. Correll, A. Auther, E. Nakayama
Psychiatry Research, The Zucker Hillside Hospital, Glen Oaks, NY, USA

The intervention strategy of the Recognition and Prevention (RAP) program, derived from its neurodevelopmental model, is based on the notion that there are two independent pathways leading to schizophrenia, one involving non-specific, negative deficits, making up the biological core, and the other, gradually emerging positive symptoms. Impaired social skills and school failure are considered two important components of the negative symptom core, since both are considered likely to reflect underlying brain abnormalities and both are the building blocks for independent adult functioning. Among prodromal RAP patients, social difficulties and poor school performance are the most frequently reported symptoms at baseline, with 94% of the RAP sample reporting one or both. To date, over 150 adolescents have completed comprehensive in-person clinical and neurocognitive assessments at baseline. Follow-up information is collected every three months by telephone or clinical interviews. The current sample consists of 54 adolescents with both attenuated positive and negative symptoms at baseline and a minimum of two years of follow-up. Of these subjects, 24% have developed a psychotic disorder over the follow-up period. A high level of social dysfunction was displayed by the remaining subjects who did not convert to psychosis. Converging preliminary data support our model by indicating: 1) social isolation was quite stable over the follow-up period (ICC=.73, p<.001); 2) while some improvement was observed with treatment, 60% of subjects remained socially isolated at moderate to above levels, and about a third were considered severely isolated; and 3) a significant relationship was found between baseline cognitive deficits and subsequent social skills (wald=3.95; p<.05). By contrast, school performance, which was not related to social skills at either baseline or follow-up, was far more variable. School performance at baseline was not significantly related to school performance at follow-up. With treatment, functioning at school underwent substantial improvement, and only 37% of subjects continuing to display poor school performance. These findings suggest that school difficulties may be amenable to early treatment. By contrast, increasing social isolation may be a more difficult, but essential, target of early intervention. The possibility that treatment of early cognitive deficits may impact later emerging social difficulties will be discussed.

HOW DO GENERAL PRACTITIONERS MANAGE SUBJECTS WITH EARLY SCHIZOPHRENIA? THE CRUCIAL ROLE OF GPS NETWORKS WITH MENTAL HEALTH SERVICES

A. Cougnard,* S. Grolleau, R. Besson, F. Delcroix, H. Verdoux
EA 3676, Bordeaux Cedex, France

Objective: General practitioners (GPs) play a key role in the pathways care of subjects with early psychosis. The aim of the study was to explore how GPs manage patients with early schizophrenia in clinical practice. Method: Survey questionnaires exploring clinical practice in patients with early psychosis and relationships with mental health professionals were mailed to all GPs of the Aquitaine region in South-Western France (n= 3829). Results: The response rate to the survey was 23%. More than half GPs (57%) diagnosed at least one possible case of early schizophrenia, and more than one out of three (34%) hospitalized at least one patient with early schizophrenia over the last year. When early schizophrenia was suspected, and in cases without prominent emergency, most (96%) often/very often referred the patient to a psychiatrist, a majority (59%) of GPs did not or rarely initiate psychotropic drug treatment, although half (52%) subsquently prescribe the antipsychotic treament when the diagnosis was confirmed. Convincing the patient to consult a psychiatrist frequently (40%) took more than one month, and a rapid (< two weeks) consultation with a public psychiatrist could be obtained in less than half patients (40%). GPs with regular contacts with a public psychiatric team (30%) were more likely to refer the patient to public psychiatrists (OR=3.3, 95%CI 2-5.6), to obtain a rapid consultation (OR= 1.7, 95%CI 1.2-2.6), to hospitalize the patient (OR=1.6, 95%CI 1.1-2.5), and to subsequently prescribe the antipsychotic treatment (OR=1.5, 95%CI 1-2.2). Conclusion: Having regular contacts with a public psychiatric team had a major impact on GPs practice in subjects with early psychosis. These findings highlight that promotion of networking between GPs and mental health services is required to reduce delayed access to care in subjects with early schizophrenia.

PHYSICAL RESTRAINTS FOR AGITATED PATIENTS IN PSYCHIATRIC EMERGENCY HOSPITALS IN RIO DE JANEIRO, BRAZIL: A PREDICTIVE MODEL

E. S. Coutinho,* G. Huf, M. H. Allen, C. E. Adams
Epidemiology, Fundacao Oswaldo Cruz, Rio de Janeiro, Rio de Janeiro, Brazil

Background: Aggressive or agitated mentally disturbed people who are dangerous to themselves or others are commonly restrained. This study investigates factors that appear to be predictive of being physically restrained in the psychiatric emergency rooms of Rio de Janeiro. Methods: We extracted variables potentially predictive of the use of physical restraints from the near complete dataset of a large pragmatic randomised trial and constructed a predictive model using only variables clearly preceding the restraints. Variables with p-values greater than 0.10 were excluded and fit of model evaluated. We calculated the percentage of people correctly classified, the area under the ROC curve, and drew diagnostic plots to identify outliers. Results: Of the 301 agitated, aggressive people, in the trial 73 (24.5%) were restrained at some time during the first two hours of admission. Physical restraints were more likely to be used for younger people, those attending for the first time, with more severe aggression and when their aggression was attributed to substance abuse. Hospital, sex and trial medication were not associated with the risk of being restrained. The final model showed a good fit (chi-squared=7.86; p=0.45) and correctly predicts use of restraints for 80% of patients attending psychiatric emergency rooms in Rio de Janeiro. Discussion: Practice of restraining agitated/aggressive patients in Rio seem to be consistent and based on swift clinical assessment. Local predictive factors for physical restraint may vary and it would seem reasonable that use of physical restraints, or restraining techniques, is monitored and causes and consequences researched.

EARLY INSIGHT PREDICTS DEPRESSION AND SUICIDALITY AFTER FOUR YEARS IN FIRST EPISODE SCHIZOPHRENIA AND SCHIZOPHRENIFORM DISORDER

N. Crumlish,* P. Whitty, M. Kamali, M. Clarke, O. McTigue, A. Lane, A. Kinsella, C. Larkin, E. O'Callaghan
Stanley Research Unit, Cluain Mhuire Service, Dublin, Ireland

Objective: To map the development of insight in the four years after presentation with first-episode schizophrenia and schizophreniform disorder, and to determine the effects of evolving insight on depression and suicidality. Method: We used the Positive and Negative Syndrome Scale (PANSS) to measure depression and insight in 101 individuals at the time of first presentation, six months after presentation and four years after presentation. We also used the Birchwood self-report insight scale, allowing separate evaluation of three dimensions of insight: recognition of mental illness, recognition of need for treatment and ability to relabel psychotic symptoms. We identified suicide attempts using the Structured Clinical Interview for DSM-III-R (SCID). We performed repeated measures analysis of variance to measure the change in insight over time and used stepwise regression modelling to identify cross-sectional and longitudinal relationships between insight, depression and suicidality. Results: Seventy of 101 participants completed a PANSS at presentation, six months and four years. Thirty-eight of the participants completed a Birchwood scale at each assessment. Insight improved with time and the improvement in Birchwood insight was mostly accounted for by improved recognition of mental illness rather than improved recognition of need for treatment or improved ability to relabel psychotic symptoms. Recognition of mental illness at six months predicted depression at four years, and was the only variable that predicted whether or not participants would attempt suicide before four-year follow-up.

ENDOGENOUS AND EXOGENOUS CANNABINOIDS IN THE DEVELOPMENT AND COURSE OF SCHIZOPHRENIA: WHAT IS THE EVIDENCE?

D. D'Souza,* R. Murray, M. Weiser, A. Green, M. Leweke
Psychiatry, Yale University School of Medicine, West Haven, CT, USA

Recent advances in the understanding of brain cannabinoid receptor function have renewed interest in the association between cannabis and psychosis/schizophrenia. The goal of this workshop is evaluate the evidence of this association. Several epidemiological studies from New Zealand, the Netherlands and Sweden suggest that cannabis use was associated with a higher risk of psychosis even after attempting to account for the possibility that those individuals were destined to develop schizophrenia. Further, cannabis use also alters the course of early psychosis and established schizophrenia. However, data from a recent study of Israeli conscripts questions the role of cannabis in the development of schizophrenia. In addition to epidemiological data, controlled laboratory studies demonstrate that delta-9-THC induces transient schizophrenia-like behavioral and cognitive symptoms in healthy controls carefully screened for any risk of psychosis, and exacerbates symptoms in schizophrenia patients. Finally, recent neurochemical data suggest alterations in the brain endogenous cannabinoid system in schizophrenia. Levels of CSF anandamide, the endogenous cannabinoid, are significantly elevated in acute, antipsychotic-naive, first-episode schizophrenic patients when compared to controls. This effect is reversed by exposure to D2 antagonists but not D2-5HT2 antagonists. Furthermore, in antipsychotic-naive, acute schizophrenia subjects, CSF anandamide was negatively correlated with psychotic symptoms.

PRENATAL LOSS OF FATHER AND SUBSEQUENT PSYCHOSIS—A NATIONAL COHORT STUDY

C. Dalman,* S. Wicks, P. Allebeck
Public Health Sciences, Karolinska Institutet, Stockholm, Sweden

Death of partners and children during pregnancy constitutes a severe maternal stress and has been demonstrated to increase the risk of psychiatric disorders as well as cranial-neural-crest malformations in the child. Animal studies have shown that stress may have long-lasting effects on the development of the brain, e.g. alterations of the hippocampus and the symmetry between brain halves. Maternal stress during pregnancy has been investigated as a risk factor for subsequent psychosis in a number of studies. Results are conflicting, presumably due to methodological issues (individual vs. common stress, timing of the exposure, ecological design, small numbers). In the present study the risk associated with prenatal loss of fathers, due to accidents and natural deaths, was investigated in a Swedish national cohort consisting of all persons born 1961-1985. We followed up 2.6 million children, 827 exposed to paternal death, with regard to a diagnosis of non-affective or affective psychosis (19,571 unexposed

and 15 exposed cases) in the National Inpatient Register. Possible confounders (SES, paternal age, parental psychiatric illness and drug abuse) were taken into account. The information was available through a linkage of four national registers. Paternal death during foetal life was associated with an increased risk of developing psychosis later in life (HR 2.4, 95% CI 1.4-4.0). In a model adjusting for possible confounders the estimate decreased somewhat but was still elevated (HR 2.2, 95% CI 1.3-3.7). In conclusion, although the numbers are small, prenatal loss of fathers is associated with an increased risk of subsequent psychosis. Our future analyses will include a larger number of exposed persons. To what extent the association is due to foetal and/or childhood stress and/or inherited personality traits, e.g. associated with proneness for accidents, has to be further clarified.

NEUROLOGICAL SOFT SIGNS IN FIRST EPISODE PSYCHOSES: THEIR PREVALENCE AND PREDICTIVE POWER

P. Dazzan,* T. Lloyd, J. Zanelli, K. D. Morgan, K. Orr, C. Morgan, G. Hutchinson, P. Fearon, J. Holloway, R. Mallett, J. Leff, G. Harrison, P. B. Jones, R. M. Murray
Division of Psychological Medicine, Institute of Psychiatry, London, United Kingdom

Neurological soft signs (NSS) are minor neurological abnormalities in sensory and motor performance, indicating non-specific cerebral dysfunction. Their presence has been extensively documented in schizophrenia but the same can not be said for the first psychotic episode. We examined the rates and predictive power of NSS in a large epidemiological sample of first episode psychosis patients. We investigated 313 first episode psychosis patients (53% females; mean age 31 years; 47% schizophrenia, 18% mania, 18% depression, 17% other psychosis), and 141 healthy controls (48% females; mean age 33 years). We used an expanded version of the Neurological Evaluation Scale, which is composed by four subscales: Primary, Sensory Integration, Motor coordination, Motor sequencing. We then investigated to what extent each NSS subscales was predictive of diagnostic group membership. Patients had significantly higher rates of NSS for Primary signs, Motor Coordination and Motor sequencing ($p < 0.001$). There was no difference between patients and controls in Sensory Integration signs. Motor Coordination signs were a good predictor of diagnostic group, with 85% of controls and 60% of subjects with schizophrenia correctly identified. Although NSS rates are generally higher in subjects with psychosis, motor coordination disturbances may be the best predictor of psychosis status.

AGGRESSIVE BEHAVIOUR ASSOCIATED WITH FIRST PRESENTATION PSYCHOSIS IN THE AESOP STUDY

K. Dean,* C. Morgan, G. Hutchinson, P. Fearon, K. Morgan, P. Dazzan, R. Mallet, T. Craig, G. Harrison, P. Jones, J. Leff, R. Murray
Division of Psychological Medicine, Institute of Psychiatry, London, United Kingdom

Development of a psychotic illness is known to increase risk of aggression. We sought to investigate the associations between specific symptoms and aggressive behaviour in a cohort presenting to services for the first time with psychosis. The sample comprised 299 patients with first presentation psychosis identified as subjects in the AESOP (Aetiology and Ethnicity of Schizophrenia and other Psychoses) study. The main reasons for presentation were assessed using the Psychiatric and Personal History Schedule. Those identified as having committed assault or other violent act in the context of first presentation were compared with those who were not so identified. Other clinical and demographic information was also available. Analysis was performed using logistic regression to produce odds ratios adjusted for gender, age and ethnicity. Fifty nine (19.7%) patients were found to have committed an act of aggression at the time of presentation to services. Another 65 (21.8%) were perceived as presenting a serious risk of harm to others. With regard to symptomatology, those who were violent were more likely to have the behavioural and psychotic features associated with a diagnosis of mania such as: heightened subjective functioning (OR 2.53 CI 1.04-6.20), rapid subjective tempo (OR 2.84 CI 1.24-6.48), expansive delusions or hallucinations (OR 3.16 CI 1.54-6.50) and overactivity (OR 2.62 CI 1.25-5.50). No associations were found with ICD-10 diagnosis, expansive mood, delusions of control or persecutory delusions. Almost one-fifth of our first-episode sample were violent at first presentation to services. The behavioural and psychotic symptoms commonly associated with a diagnosis of mania were associated with such violence.

FAMILY HISTORY AND SEVERITY OF ILLNESS IN FIRST EPISODE PSYCHOSIS

M. M. Di Forti,* S. Tosato, A. Miorelli, J. Boydell, C. Morgan, P. Dazzan, P. Fearon, G. Hutchinson, R. Mallett, J. Leff, P. Jones, R. M. Murray
Psychological Medicine, Institute of Psychiatry, London, United Kingdom

The lifetime risk of developing schizophrenia in the general population is 1%. This risk increases up to 9% when a sibling is also affected, and up to 46% when both parents are affected. We investigated whether a positive family history of mental illness influences the severity of illness in a first episode psychosis sample. We interviewed a first degree relative for 58 first episode psychosis subjects to obtain information on family history using the FIGS (Family Interview for Genetics Studies). We defined family history as positive when DSMIV criteria for a diagnosis of mental illness had been fulfilled. We examined the association between family history and socio-demographic variables (age of onset, gender, marital status, employment), severity of symptoms (IGC score, self harm, harm to others, mode of contact with services), and duration of untreated psychosis. Family history was not significantly associated with demographic characteristics, severity of illness, or duration of untreated psychosis. However, there was a trend for a significant association between positive family history and: living alone ($p=0.06$) and self harming behaviour ($p=0.09$). Our preliminary results suggest that family history is not associated with demographic characteristics and severity of illness. However, a larger sample might be able to further clarify its role.

MINOR PHYSICAL ABNORMALITIES AND SOFT SIGNS RELATES TO CLINICAL AND COGNITIVE VARIOABLES OF SCHIZOPHRENIA

M. Dolz,* S. Ochoa, V. Villalta, M. Vilaplana, J. Usall, J. Haro
Research Unit, Sant Boi, Barcelona, Spain

Objective: To relate developmental markers with clinical and neuropsychological variables in outpatients with schizophrenia.

Method: A random sample of 96 outpatients with schizophrenia (DSM IV criteria) were interviewed on a battery of neurodevelopemental markers: neurological soft-signs (NES), obstetric complications (Lewis-Murray) and minor physical abnormalities (Waldrop). They also were administered a neuropsychological battery that includes Stroop test, Trail Making Test A-B, WAIS sub-scales, WCST and the CPT; a psychopathology scale (PANSS), and a extrapiramidal evaluation scale (SIMPSON). We also gathered information on socio-demographic data and evolution of the illness. Results: NES scale correlates with SIMPSON ($p < 0.001$), Waldrop total score ($p<0.001$), PANSS general subscale ($p<0.01$), PANSS positive subscale ($p<.0.05$), Stroop ($p<0.05$) and WCST ($p<0.001$). Waldrop scale correlates with SIMPSON ($p < 0.001$), NES scale ($p<0.001$), Stroop ($p<0.05$) and WCST ($p<0.001$) Different linear regressions models were set between the Waldrop scale and PANSS sub-scales, SIMPSON, age of onset and cognitive variables. Using the stepwise method, the SIMPSON total score and age of onset explained the 34 % of the variability of the Waldrop scale. Conclusions: Minor physical abnormalities are more present in patients with more extrapramidal symptoms, cognitive impairment and soft signs. Neurological soft-signs correlate with positve and general psychopathology, expiramidal symptoms, worse cognitive functioning and more physical abnormalities. References: Murray RM, Lewis SW. Is Schizophrenia Neurodevelopmental disorder? *BMJ* 1987; 295, 681-682 McGrath J, Ossama El-Saadi. Minor Physical Anomalies and Quantitative Measures of the Head and Face in Patients with Psychosis. *Arch Gen Psychiatry* 2992;59, 458-464.

THE EFFECTS OF MATERNAL SMOKING DURING PREGNANCY AND GENETIC VULNERABILITY FOR SCHIZOPHRENIA ON BIRTH OUTCOMES

L. M. Ellman,* M. Huttunen, J. Lönnqvist, T. D. Cannon
Psychology, University of California-Los Angeles, Los Angeles, CA, USA

The purpose of this study was to explore whether an increased incidence of obstetric complications (OCs) was associated with a family history of schizophrenia (gene-environment co-variation model) and/or health-risk behaviors among schizophrenic pregnant women. A high-risk birth cohort was formed by searching the Finnish Perinatal Register for all babies born between 1991 and 2000 with arterial cord pH values below 7.20 (n=38,420), an indication of fetal asphyxia. The perinatal database was merged with psychiatric databases to determine psychiatric morbidity of the mothers and the mothers' first-degree relatives. Mothers were divided into 3 groups: women diagnosed with schizophrenia/schizoaffective disorder (Sz, n=60), mothers with a first-degree relative with schizophrenia/schizoaffective disorder (Fhx, n=611) and healthy controls (without a family history of psychosis, n=37,741). Results indicated that there was a significant difference between the 3 groups with respect to maternal age and smoking during pregnancy. Specifically, Sz and Fhx women were significantly older than controls, but there were no significant differences in age between Sz and Fhx women. In addition, Sz women smoked significantly more during pregnancy than both Fhx and controls, whereas there were no significant differences in smoking during pregnancy between Fhx and controls. Findings also suggested that psychotic status during pregnancy compared with control status was associated with a significant 0.55 decrease in 1-minute APGAR scores, a 31.3 times increase in eclampsia, a 2.1 times increase in neonatal hospitalization, and a 3.3 times increase in maternal treatment due to imminent premature delivery. No significant associations emerged between psychotic status during pregnancy and birth weight, vaginal bleeding, and maternal high blood pressure. Most strikingly, having a first-degree relative with psychosis and control status had no significant effects on any of the obstetric variables. The findings from this study weaken the gene-environment co-variation model, which predicts increases in OCs among mothers with a psychotic first-degree relative. Collectively, these data suggest that psychotic status during pregnancy may be an additive risk factor that could portend increased risk of OCs, possibly due to health-risk behaviors during pregnancy. This study was limited by the fact that only hypoxic births were included and only one health-risk behavior was examined.

PATTERNS OF PSYCHOSIS IN BLACK AND WHITE MINORITY GROUPS IN URBAN UK: THE AESOP STUDY

P. Fearon,* J. Kirkbride, C. Morgan, T. Lloyd, K. Morgan, P. Dazzan, G. Hutchinson, J. Holloway, J. Tarrant, R. Mallett, G. Harrison, J. Leff, P. B. Jones, R. M. Murray
Section of General Psychiatry, Institute of Psychiatry, London, United Kingdom

Numerous studies report raised rates of schizophrenia in the African Caribbean population in the UK. There is also evidence that they are more likely to develop affective symptoms than their White British counterparts. It is less clear whether other minority groups in the UK are at increased risk, whether such risk extends to non-British White people in the UK and whether this risk is specific to schizophrenia or extends to other psychotic disorders. The AESOP study identified all first presentation psychotic cases in 3 well-defined geographical areas: South East London and Nottingham over a 2 year period, and Bristol over 9 months. Sociodemographic information, including ethnic group classification (according to the UK 2001 census), was obtained and ICD-10 diagnoses were obtained blind to ethnic group status. Incidence rates were calculated and standardised to the population of England and Wales. Rate ratios were calculated using Poisson regression and adjusted for age and sex. 568 cases were identified during the incidence phase of the study. Rates and rate ratios were markedly elevated in both African Caribbeans and Black Africans, in both sexes, for all diagnoses. Non-British Whites had a twofold increased risk of schizophrenia, while the Asian and Mixed groups had a 2-4 times increased risk of affective psychosis. These findings suggest that raised rates of psychosis are not specific to any minority group. However, the pattern and extent of this increased risk varies between groups. These findings suggest that complex aetiological pathways are involved in the ultimate expression of psychotic illness in different minority groups, and add weight to the concept that both migrant status and ethnicity are important in understanding this increased risk of psychosis.

Rate Ratios

BIRTH ORDER AND SEVERITY OF ILLNESS IN SCHIZOPHRENIA

F. P. Gaughran,* R. Blizard, R. Mohan, S. Zammit, M. Owen
Psychological Medicine, Institute of Psychiatry, London, United Kingdom

A proposed risk factor for schizophrenia is materno-foetal incompatibility. We tested the hypothesis that, in multiply affected families, later born children would exhibit a more severe form of schizophrenia than their older siblings. Methods: The effect of birth order on 1) severity of the worst ever episode of illness; 2) deterioration from premorbid level of functioning; 3) age of onset; 4) response to medication; and 5) illness course, was assessed in 150 sibling pairs with schizophrenia and schizoaffective disorder. Results: Later birth order reduced the likelihood of regaining the premorbid level of functioning after an acute episode (McNemar p = 0.029), and was associated with earlier age of presentation (t= 2.091, p = 0.038) Conclusions: This study lends some support to the hypothesis that later birth order results in a more severe form of the disorder. Further work is needed to explore the possibility of maternal-fetal genotype incompatibility as a risk factor for schizophrenia

DURATION OF UNTREATED PSYCHOSIS IN FIRST EPISODE AFFECTIVE AND NON-AFFECTIVE PSYCHOSIS

H. Gijsman,* C. Morgan, P. Fearon, J. Lappin, R. Abdul-Al, K. Morgan, P. Dazzan, R. Mallet, J. Leff, P. Jones, R. Murray
Psychological Medicine, Institute of Psychiatry, London, United Kingdom

It is unclear whether the duration of untreated psychosis (DUP) differs between affective and non-affective psychosis and what factors may influence any differences found. This knowledge may be relevant in unravelling the etiology of these disorders as well as in designing early intervention services. We set out to test the hypothesis that DUP is longer for patients with non-affective psychoses (schizophrenia and related disorders) compared to those diagnosed with affective psychoses (manic psychosis and depressive psychosis), and that the latter group is more likely to have suffered from a higher rate of depression or anxiety prior to the onset of psychosis. We used information from 512 patients with a first episode of psychotic illness who were included in the AESOP study. These patients were ascertained over a period of two years from defined population bases in South London and Nottingham. Onset of psychotic symptoms and previous contact with mental health services for non-psychotic illness were obtained from interviews and/or case-notes. Onset of psychosis was defined as the first presence of one symptom of schizophrenia or of two definite changes of personality and behaviour. Diagnostic categories were compared with rank sum test, Chi-square test, survival analysis with logrank test and Cox regression analysis. DUP was available for 489 patients (350 schizophrenia, 70 mania and 69 depression) and ranged from 1 day to 30 years. It had a strongly asymmetrical frequency distribution with 25%, 50%, and 75% of patients with a DUP shorter than respectively 2 weeks, 2 months and 1 year. Median DUP was statistically significantly longer for schizophrenia (90 days) compared to depressive (49 days) and manic (30 days) psychoses. In multivariate analysis, DUP in non-affective psychoses compared to both affective psychoses together was 2.01 (95% CI 1.5 — 2.7) times as long in men and 1.4 (0.99 — 1.9) times as long in women. There was no difference in the rate of anxiety or depression prior to presentation between the three diagnoses. This study confirms that DUP is longer in patients with schizophrenia compared to those with affective psychoses. This effect may be stronger for men than for women. This analysis does not confirm our hypothesis that patients with affective psychosis have had more non-psychotic illness.

WHAT DO GENERAL PRACTITIONERS KNOW ABOUT SCHIZOPHRENIA?

S. Grolleau,* A. Cougnard, R. Besson, F. Delcroix, H. Verdoux
EA 3676, Bordeaux 2 University, Bordeaux, France

Objective: To explore knowledge of general practitioners (GPs) on basic epidemiological data regarding schizophrenia. Method: Survey questionnaires exploring practice in patients with early psychosis were mailed to all GPs of South-Western France (n= 3829). As part of this questionnaire, GPs were asked to anonymously fill out questions on basic epidemiological data concerning schizophrenia. Results: The response rate to the survey was 23.4%. Most GPs underestimated (57%) or did not know (30%) the prevalence of schizophrenia (only 10% correct answers), the frequency of suicide (do not know: 42%; underestimation: 30%; correct answers: 30%) and of unemployment (do not know: 34%; underestimation: 36%; correct answers: 29%). Regarding risk factors, only a minority of GPs (9%) totally dismissed the role of genetic factors. Most GPs (89%) considered disturbance of mother-baby interactions as a possible risk factor, and 40% considering that it is often/very often implicated in the aetiology of schizophrenia. A large majority considered that exposure to substances (91%) or stress (81%) could be risk factors for schizophrenia. No association was found between the answers to these questions and psychiatric hospital experience during medical training (39% of GPs). GPs who attended continuing medical education (CME) on schizophrenia over the last year (15%) were more likely to give a correct answer regarding the prevalence of schizophrenia (OR=2, 95%CI 1.1-3.3), and to consider that genetic (OR=2.5, 95%CI 1.1-6), toxic (OR= 2.7, 95%CI 1.2-6.4) or stress (OR=2.4; 95%CI 1.1-5.6) factors were very often implicated in the aetiology of schizophrenia. Conclusion: GPs have little awareness of the public health importance of schizophrenia, and they dramatically underestimate the frequency and the psychosocial consequences of this disorder. Regarding aetiological models, most GPs considered that schizophrenia is a multifactorial disease with both genetic and environmental risk factors. The highly prevalent conviction that mother-baby interactions play a key role in the aetiology of schizophrenia may be specific to French GPs, due to the still marked influence of the psychoanalytic model in France. As attending CME had an impact on knowledge on schizophrenia, these findings highlight the necessity to develop CME programs targeting GPs.

PATIENT COMPLIANCE IN SCHIZOPHRENIA: SUBJECTIVE SIDE EFFECTS HAVE GREATER IMPACT THAN SEVERITY OF ILLNESS

K. Hansen,* P. Bebbington
Health Economics and Epidemiology, H. Lundbeck A/S, Paris, France

Schizophrenia is a severe mental disorder often complicated by patient non-compliance with treatment recommendations. It remains

unclear why patients do not adhere to treatment regimens. Few studies have been conducted concerning this subject, most with contradictory results. The objective of the present study was to study associations between patient attitudes towards antipsychotic medication and varying factors such as sociodemographics, clinical data, quality of life, side effects and types of medication prescribed (typical vs. atypical antipsychotics). Data came from the European Schizophrenia Cohort (EuroSC) of 1,208 patients from Great Britain, France and Germany. Patient follow-up was every 6 months for 2 years. Several scales were administered at each visit including the Rating Of Medication Influences (ROMI) and the Subjective Side Effect rating Scale (SSES) questionnaires. Compliance was assessed by the a new criterion from the ROMI scale. Data were analysed using Chi-2 tests, logistic regressions and generalized estimating equations methods. Patient attitudes towards antipsychotics were more affected by adverse side effects than clinician observations might tend to indicate. Although psychiatrists and patients alike noted that atypical antipsychotics were effective in reducing many adverse effects, notably akathisia, tremor and rigidity, they also stopped treatment because of sexual dysfunction and weight gain which are more frequently associated with atypical treatments. We found that high compliance was more directly related to good physical health, individual independence in activities of daily living and financial status. Furthermore, non-compliant patients rarely consulted their doctors and, after 18 months, had significantly increased relapse rates as well as problems with the criminal justice system. Our findings suggest that patient perception of side effects is the major predictor of non-compliance. Progress has been made in diminishing extrapyramidal symptoms but other side effects appear and/or persist. There remains an unmet need for medications that will contribute to eliminating the reasons patients voluntarily cease treatment.

CANNABIS USE, PSYCHOSIS LIABILITY, AND PSYCHOTIC SYMPTOMS IN YOUNG PEOPLE

C. Henquet,* L. Krabbendam, J. Spauwen, C. Kaplan, R. Lieb, U. Wittchen, J. van Os
Dept. of Psychiatry and Neuropsychology, Maastricht University, Maastricht, Netherlands

Evidence is accumulating that cannabis is a risk factor for psychotic symptoms, especially after first exposure during adolescence. The possible causal nature of the association between cannabis and psychosis however, is still a matter of debate, the main discussion revolving around the role of pre-existing liability to psychosis and adjustment for confounders. The aim of the current study was therefore to investigate the relationship between cannabis use and psychotic symptoms in individuals with i) above average liability to psychosis and ii) use of cannabis during adolescence. Prospective data from a population-based sample (the EDSP study) were studied in 2437 young people (aged 14 to 24) with and without liability to psychosis. Assessment of substance use, psychosis liability and psychotic symptoms was based on standardized personal interviews at baseline and at follow-up, 4 years later. Similar analyses were conducted in the Dutch general population (the NEMESIS study; n=4845) to investigate cannabis as a shared risk factor for psychosis and mania. Cannabis use at baseline increased the cumulative incidence of psychotic symptoms at follow-up adjusted for age, sex, socio-economic status, urbanicity, childhood trauma, baseline psychosis liability and use of other drugs, tobacco and alcohol (adjusted OR=1.67, 95% CI: 1.13-2.46). The effect of cannabis was much stronger in those with expression of liability to psychosis at baseline (risk difference 18.6%; ?2 =5.56, df=1, P= 0.018) than in those without (risk difference 5.7%; ?2= 4.66, df=1, P= 0.031; additive interaction ?2 =4.59, df=1, P=0.032). Cannabis use increased the development of manic symptoms as well, independently of the emergence of psychotic symptoms (adjusted OR=2.87, 95% CI: 1.24, 6.64). Neither expression of psychosis liability nor manic symptoms at baseline predicted cannabis use at follow-up. In conclusion, cannabis use increases the risk of psychotic symptoms in young people, but has a much stronger effect in those with prior evidence of psychosis diathesis. In addition, cannabis is a risk factor for development of manic symptoms. Self-medication can explain only a limited part of the association between cannabis use and the emergence of psychosis and mania, since symptoms at baseline did not predict use of cannabis at follow-up.

THE 8 YEAR FUNCTIONAL AND SYMPTOMATIC OUTCOME OF FIRST EPISODE PSYCHOSIS (FEP)

L. P. Henry,* M. G. Harris, O. S. Schwartz, S. Farrelly, A. L. Prosser, H. P. Yuen, H. Herrman, P. D. McGorry
Psychiatry, ORYGEN Research Centre, University of Melbourne, Melbourne, VIC, Australia

The study purpose is to examine the 8-year functional and symptomatic outcome of a FEP cohort of 800 patients in addition to the course patterns of psychosis over time. The design is a naturalistic, prospective, longitudinal, 8-year follow-up study with multiple follow-up time points, on a representative multidiagnostic cohort of 800 patients with FEP from the Early Psychosis Prevention and Intervention Centre, which is a frontline public mental health service and its precursor service in Melbourne, Australia. Recruitment is ongoing. The preliminary results which follow concern the 470 subjects who have been interviewed to date. At 8-year outcome, analyses indicate that 74% remain unmarried, 54% are either working, studying or are homemakers. Mean scores on quality of life and social functioning measures indicate functioning in the good range. 75% are currently receiving psychiatric treatment, however 45% of these were being treated in the private health sector suggesting less severe illness and better functioning. Those taking an antipsychotic were on a CPZ equivalent mean low dose of 303mg. In terms of psychiatric hospital admission, 60% have not been admitted in the most recent two years and the mean number of admissions over the 8-year period was two. 47% have not been psychotic in the most recent 2 years and one quarter never had another psychotic episode after recovering from their first episode. Mean scores on psychopathology measures indicate minimal to low levels of current psychopathology. Comparison of these findings with the existing outcome literature of similar follow-up duration should be made with caution as the majority are of first episode schizophrenia. However our data concerning course type over the most recent two years is consistent with the findings of Mason et al. (1995) and Robinson et al. (2004). However our findings concerning the never psychotic course type over the entire follow-up period differs to that found by Thara et al. (1994). Our study reported a higher percentage (24%) than Thara et al. (1994) (17%) who had not been psychotic during the intervening years and over half of this group had completely remitted. Over half of our cohort was fully occupationally engaged compared with 19% reported by the Scottish Schizophrenia Research Group (1992). The findings from this study suggest patients with psychotic disorders can achieve symptomatic remission and good social and occupational functioning 8-years post FEP.

GUESS WHO IS COMING TO THE COURT CLINIC: AN EXAMINATION OF DEFENDANTS REFERRED FOR EVALUATION

D. Hrouda,* P. Resnick, P. Buckley
Department of Psychiatry, Case Western Reserve University, Brecksville, OH, USA

The criminalization of the mentally ill is a topic that is of enduring and increasing concern in the mental health and criminal justice fields. In addition to the stigma and personal costs to the mentally ill patient, the legal and mental health systems also suffer and incur costs in an effort to evaluate and plan for services in line with the crimes and sanctions levied against these patients. This study examined the presentation and clinical characteristics of defendants in the court system who were referred to a court psychiatric clinic for evaluation of either competency, sanity, or both. Data were collected for all consecutive, non-repeated defendants (n=114) over a nine-month period. Data were collected from review of the clinic record and all collateral information contained therein. Just over one third of the sample had a diagnosis of schizophrenia and more than half of these were dually diagnosed. The majority of patients were not in active treatment and only 9% reported being fully compliant with their medications. 61.9% were being evaluated in connection with a violent offense. Despite the high levels of disorder, only 5% were assessed as not sane at the time of the offense. Additional findings, including a comparison of the pattern of violent and nonviolent presentations in patients with schizophrenia versus other diagnostic groups will be presented at this meeting. The findings from this examination highlight the need to further examine the mental health and substance use factors that may contribute to involvement in the criminal justice system. Further research is needed to identify ways to better engage and retain patients with severe mental illnesses (especially in combination with substance misuse) in treatment. This project was funded by the Theodore and Vada Stanley Foundation.

OUTCOME AND ITS PREDICTORS IN SCHIZOPHRENIA BY THE AGE 35 WITHIN THE NORTHERN FINLAND 1966 BIRTH COHORT

M. Isohanni,* J. Veijola, J. Miettunen, P. Jones, W. Fenton, J. Koskinen, G. Murray, A. Alaraisanen, M. Karhu, I. Isohanni, E. Lauronen
Department of Psychiatry, University of Oulu, Oulu, Finland

The outcome in schizophrenia is heterogeneous, with the likelihood of full recovery remaining a particular controversy. Certain predictors of the course of illness have been identified, but their prognostic significance is often minor. Our aim was to examine recovery and related outcomes of schizophrenia before age 35 years in a longitudinal, population based birth cohort, and to test the prognostic significance of selected historical, developmental and illness-related variables. In the Northern Finland 1966 Birth Cohort all 146 living cases having known psychotic disorder were invited to the field study in 1999-2001. Among participating subjects there were 59 diagnosed as having DSM-III-R schizophrenia. Interviews and case registers were used to rate measures of outcome including clinical global impression, social and occupational functioning, positive and negative symptoms, occupational status, psychiatric hospitalizations and antipsychotic medication. Outcome was categorized as good/moderate or poor, and complete recovery was studied. In addition, by studying all schizophrenia cases in this Birth Cohort, we explored the associations between early development and later course of illness. As a result, approximately half of the schizophrenia cases had poor outcome, but only one was considered as fully recovered. When compared with good outcome cases, cases having poor outcome had earlier age of illness onset and poorer achievement at school. Few subjects had a favourable outcome of schizophrenia in this relatively early onset group. Only some variables were able to predict the course of illness in schizophrenia. Epidemiological, population-based cohort studies can bring novel, reliable information concerning the prognosis in schizophrenia. References Harrison G, Hopper K, Craig T et al. Recovery from psychotic illness: a 15- and 25-year international follow-up study. *Br J Psychiatry* 2001;178:506-517. Lauronen E, Koskinen J, Veijola J, Miettunen J, Jones PB, Fenton WS, Isohanni M. Recovery from schizophrenic psychoses within the Northern Finland 1966 Birth Cohort. *The Journal of Clinical Psychiatry*, In Press, 2004. Ram R, Bromet EJ, Eaton WW et al. The natural course of schizophrenia: A review of first-admission studies. *Schizophr Bull* 1992;18:185-207.

AUDITORY VOCAL HALLUCINATIONS IN PRIMARY SCHOOL CHILDREN: PREVALENCE, BURDEN, AND RELATION WITH BEHAVIOR PROBLEMS

J. A. Jenner,* G. van de Willige
Psychiatrie, Academisch Ziekenhuis, Groningen, Groningen, Netherlands

Intro:Population based studies of voicehearing in primary school children are few. Literature is equivocal on prevalence rate and relationship of voicehearing and psychiatric disorder in adulthood. Aim: To assess prevalence and subjective burden of voicehearing in primary school attenders & relations between voicehearing and psychoipathology. Longitudinal cohort study as to prediction of psychiatric disorder in adulthood. Instruments:Auditory Hallucination Rating Scale (adjusted for age); Children Behavior Check List. Design:All children 7 & 8 years of age attending primary school in a Dutch province (N=4886)were requested.No parental informed consent: 351; 28 not tested; 902 due to school refused participation. Results: Included: N=3605 children. One-year prevalence=8.7% independent of gender, 25% only with hypnagogic & hypnopompic voices. Severe burden in terms of frquence (>once a day), degree of loudness, negative content and interference with thinking occurred in about one-third.Intensity of suffering and anxiety were significantly greater in girls.

CRANIOFACIAL DYSMORPHOLOGY IN SCHIZOPHRENIA: A BLINDED STUDY FROM SWEDEN

B. D. Kelly,* A. Lane, I. Agartz, K. Henriksson, T. F. McNeil
Cluain Mhuire Centre, Stanley Research Unit, Co Dublin, Dublin, Ireland

Background: Compared to controls, individuals with schizophrenia have increased rates of a range of neurodevelopmental anomalies, including atypical dermatoglyphic patterns and subtle anomalies of craniofacial shape. The literature on craniofacial shape in schizophrenia, however, is limited by a lack of blinding in existing studies, the use of poorly-validated, subjective scales that assess a limited range of anomalies, and the absence of anthropometrically-based data from many countries. Objective: We aimed to perform detailed

assessments of craniofacial dysmorphology in individuals with schizophrenia and controls in Sweden. Method: Using the Lane Scale, we performed detailed, anthropometric assessments of craniofacial dysmorphology in males with schizophrenia (n=24), healthy controls (n=16), healthy siblings (n=2) and siblings with schizophrenia (n=2) in Sweden. Craniofacial assessments were performed by a single assessor who had never met any of the participants, was unaware of their diagnoses, did not speak Swedish, and had no previous contact with the Karolinska Institute and Hospital. Results: Individuals with schizophrenia evidenced significantly more craniofacial dysmorphology than controls, especially in the ears and mouth. At a group level, there was a dose-response type relationship between total dysmorphology score and patient/control status. Conclusion: The consistency of results across multiple studies supports the hypothesis that individuals with schizophrenia have increased rates of prenatal developmental disturbances compared to controls. The presence of a dose-response type relationship between total dysmorphology score and patient/control status supports the importance of neurodevelopmental disturbance as a contributory cause of schizophrenia. These results highlight the need for further research to identify the specific disturbances that increase risk of schizophrenia, and the need to devise a methodology to investigate the possibility of dose-response type relationships at the individual level, possibly relating the severity of developmental disturbance to the severity of schizophrenia or age at onset.

EXPOSURE TO PRENATAL MATERNAL STRESS FROM A NATURAL DISASTER EXPLAINS VARIANCE IN CHILDREN'S COGNITIVE, BEHAVIORAL AND DERMATOGLYPHIC CHARACTERISTICS

S. King,* D. P. Laplante, A. Brunet, M. Morin, K. Lane, A. Ciampi
Douglas Hospital Research Centre, Psychiatry, McGill University, Verdun, QC, Canada

Because retrospective studies suggest that stress to the pregnant mother increases risk for schizophrenia, our goal was to determine whether prenatal maternal stress can be shown to explain variance in childhood characteristics seen in pre-schizophrenic and high risk populations using a prospective approach. We have followed more than 150 children whose mothers were pregnant during the January 1998 Quebec ice storm crisis, contacting families up to 7 times since shortly after the disaster to determine if effects could be seen on the children's cognitive or behavioral development and on dermatoglyphic asymmetry. Ice storm stress was separated into objective aspects of exposure (e.g., days without power, financial loss) and subjective reaction (PTSD-like symptoms rated from the Impact of Event Scale - Revised). Results indicate significant effects of the severity of the objective exposure to the stressor on cognitive and language development at age 2 years: for children exposed during second trimester, Bayley MDI scores were significantly lower for the high stress group ($M = 95.1$) than for the low stress group ($M = 111.8$; $p < .001$); and children from the high stress group had an expressive vocabulary of 20 fewer words than for the low stress group ($p < .01$). Controlling for maternal anxiety, objective stress explained an additional 34% of variance in children's internalizing behaviors at age 3.5 ($p < .01$). At 5 years, there was a significant effect of the timing of the ice storm on Kiddie Continuous Performance Test scores suggesting that stress exposure *later* in pregnancy is associated with poorer sustained attention. Effects of exposure are also seen on physical markers: children whose mothers were without electricity at any point during weeks 14-22 of pregnancy, when fingerprints form, had significantly greater total finger ridge count asymmetry ($M = 18.3$) than other children ($M = 12.6$; $p < .01$) as is seen in schizophrenia. In conclusion, we are demonstrating in an on-going prospective study that prenatal maternal stress, especially during second trimester, is associated with a number of characteristics associated with risk for schizophrenia. This study has been supported by grants from the Stairs Memorial Fund (McGill University), Canadian Psychiatric Research Foundation, FRSQ Mental Health Research Network, & Canadian Institutes of Health.

SCHIZOPHRENIA RISK AND PRENATAL DISASTER EXPOSURE: A REPLICATION

D. K. Kinney
Genetics Laboratory, McLean Hospital, Belmont, MA, USA

This study investigated whether it was possible to confirm previous research finding that prenatal exposure to a natural disaster (a severe tornado) was associated with increased risk of schizophrenia. This new study used other disasters (unusually severe hurricanes) and deidentified data on the birth dates of all persons in the Massachusetts mental health system who were born 1950-1956 and received a diagnosis of schizophrenia. These data, together with census data on Massachusetts general population births during corresponding time periods, were used to calculate schizophrenia prevalence rates for birth cohorts that either a) were not in utero at the time of the hurricanes or b) would have been in different periods of gestation during the storms. As hypothesized based on the results of previous research, schizophrenia prevalence was significantly higher for the cohort that would have been in vulnerable weeks of gestation at the time of the storms. The results complement research finding that prenatal exposure to other, more common, types of stressful events is also associated with increased risk of schizophrenia. The results also support the hypothesis that prenatal exposure to environmental teratogens is especially likely to increase risk for schizophrenia if it occurs during certain periods of gestation.

INCIDENCE OF SCHIZOPHRENIA AND OTHER PSYCHOTIC SYNDROMES IN THREE UK CITIES: FINDINGS FROM THE AESOP STUDY

J. Kirkbride,* P. Fearon, C. Morgan, P. Dazzan, K. Morgan, J. Tarrant, T. Lloyd, J. Holloway, G. Hutchinson, J. Leff, R. Mallett, G. L. Harrison, R. M. Murray, P. B. Jones
Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom

It is uncertain whether the incidence of psychotic syndromes is uniform or shows variability, particularly in terms of place and ethnicity; these factors have not been considered together in detail in a single study. Demonstration of variation in incidence may have major implications for research strategies investigating etiology and for health service developments. A prospective, population-based survey of all people aged 16-64 presenting to secondary services with any psychotic symptom, in three well-defined geographical areas; Southeast London and Nottingham over a 2 year period, and Bristol over 9 months. Cases were ascertained using a broad screening procedure, and a leakage study identified missed cases. Consensus diagnosis was ascertained blind to ethnicity. Denominators were estimated using the UK 2001 census. Incidence rates were directly

standardised for age & sex to the population of England & Wales. Inter-centre comparisons were made using Poisson regression to obtain Incidence rate ratios (IRR) adjusted for age, sex and ethnicity. A total of 567 cases were identified. The standardised rate (per 100000 person-years) for all psychosis was significantly higher in London (95% CI.: 49.2; 43.4, 55.0) than Nottingham (23.9; 20.6, 27.2) or Bristol (20.4; 15.1, 25.8). Similar patterns were observed for schizophrenia, non-affective, and affective disorders. Centre differences disappeared for affective disorders after including ethnicity in the model, but rates remained lower in Nottingham (IRR: 0.5; 0.4, 0.7) or Bristol (IRR: 0.6; 0.5, 0.9) than London for schizophrenia, and all other outcomes. Schizophrenia was more common in men over the age range studied (IRR 1.8; 1.4, 2.3), but there was no evidence of this effect for affective disorders (IRR 1.0; 0.8, 1.4). All psychoses were more common in the Black & Minority Ethnic group (crude IRR: 4.0; 3.4, 4.7), with age, sex and centre differences accounting for ~25% of this effect (adj. IRR 3.2; 2.7, 3.8), with similar effects across diagnoses. The results display significant and independent variation of incidence of schizophrenia and other psychoses in terms of gender and age, and also notably for ethnicity and study centre after adjustment for confounders. This suggests environmental effects at the individual and, perhaps, neighbourhood level interact with each other, and with genetic factors in the aetiology of psychosis. Supported by MRC & Stanley Medical Research Institute.

MORPHOLOGICAL FEATURES IN XHOSA SCHIZOPHRENICS: A SIB PAIR STUDY

L. Koen,* D. Niehaus, G. De Jongh, J. Muller, E. Jordaan, C. Seller, C. Laurent, J. De Leuze, J. Mallet, R. Emsley
Ngaphakathi Workgroup, Department of Psychiatry, University of Stellenbosch, Tygerberg, South Africa

Schizophrenia seems to be a heterogeneous illness resulting from a complex interplay between genetic and environmental risk factors. Despite the apparent genetic contribution, the specific mechanism has yet to be found. In the search for the susceptibility genes several approaches have been advocated for the subtyping of schizophrenia and these include clinical symptoms, physical characteristics and early versus late developmental insult. Early developmental insults are of particular interest in terms of the neurodevelopmental model of schizophrenia since anthropometric studies have documented multiple anomalies of the craniofacial region in schizophrenic patients. An animal model of non-human primates showed that irradiation during thalamogenesis led to craniofacial abnormalities similar to those reported in schizophrenic subjects. This study therefore aimed to establish whether morphological differences, as measured by the Modified Waldrop Scale, exist between a group of Xhosa schizophrenics with and without an affected sibling. Methods: Xhosa sibpairs and singletons with Schizophrenia (DSM-IV) were recruited and assessed with the diagnostic interview for genetic studies and the Modified Waldrop scale. Results: 100 Xhosa subjects (81 males) were recruited. The group was stratified into a sibpair group (22 sibpairs and 1 sibship of four), a non-sibpair group (n=37) and a group of probands with an affected non-participating sib (n=17). Asymmetrical ears were significantly more common in the non-sibpair group (p=0.0031; 12/25 vs 5/36), while a gap between the 1st and 2nd toe was significantly more common in the sibpair group (p=0.015; 10/28 vs 2/34). Low set ears, adherent ear lobes, abnormalities of the palate, curved 5th finger, syndactalia and gap between 1st and 2nd toe had a higher than expected concordance for the presence of a morphological anomaly. Conclusion: Given the increased morbid risk for a sib of a schizophrenic this finding may suggest that the gap between the 1st and 2nd toe represents a developmental period of specific importance in familial cases of schizophrenia. The development of the toes takes place in the same time frame as the development of the thalamus. The thalamus serves as a relay station and thus could be involved in the pathophysiology of schizophrenia.

PSYCHIATRIC ADMISSION AMONG FIRST DEGREE RELATIVES AS A RISK FACTOR FOR INCREASED MORTALITY

T. M. Laursen,* P. B. Mortensen
NCRR, Aarhus University, Aarhus, Denmark

It has been shown that people with Schizophrenia, Schizoaffective, Unipolar or Bipolar Disorder suffer from an increased mortality rate from all causes of death. Our aim was to estimate and compare the mortality for people suffering from these psychiatric illnesses using Danish registers and to investigate whether psychiatric illness among first degree relatives was associated with an increased mortality. All persons alive or born in Denmark after January 1, 1973 who had not been admitted to a psychiatric hospital from 1969-1972 were studied for death from all causes from 1973 to 2001. Estimates of relative risks (mortality rate ratios) were calculated using Poisson regression. During 100 million person years 1.5 million people died. Overall 105,969 persons who had been admitted died. Among these 30,144 persons was admitted with a Unipolar Disorder, 3,954 with Schizophrenia, 1,263 with Schizoaffective Disorder and 3,672 with Bipolar Disorder. We found a mortality rate ratio of 2.32 (95 % CI: 2.30, 2.34) for women and 3.04 (3.02, 3.07) for men after first psychiatric diagnosis (adjusted for age and calendar period) compared to persons not admitted. However, there was a strong effect-modification by age; for younger persons, the mortality rate ratio after psychiatric admission (comparing with persons not admitted) was larger than in older people. After admission with Schizophrenia the mortality rate ratio (men and women combined) was 3.22 (3.12, 3.32), after Unipolar Disorder 1.93 (1.90, 1.95), after Bipolar Disorder 2.11 (2.04, 2.18) and after Schizoaffective Disorder 2.34 (2.22, 2.48) compared to persons not admitted. Psychiatric admission among 1st degree relatives was associated with an increased mortality rate ratio of 1.10 (1.04, 1.16) if the person had been admitted and an increase of 1.39 (1.34, 1.44) if the person had never been admitted. We conclude that there was an increased mortality in persons after any psychiatric admission, especially a diagnosis with Schizophrenia was associated with a high mortality; this mortality was significantly higher than after Bipolar, Unipolar and Schizoaffective Disorder admission. Admission of 1st degree relatives to persons never admitted lead to an increased mortality rate.

SCHIZOPHRENIA IN PRIMARY CARE SETTINGS

W. B. Lawson,* R. E. Graves, T. Alim
Psychiatry, Howard University, Washington, DC, USA

Recent evidence indicate that primary care providers often treat schizophrenic (SCZ) or schizoaffective patients (SA). We will report clinical characteristics of those seen in a primary care area. Diagnoses were determined with the Structured Clinical Interview for DSM IV (SCID) as part of a larger study exploring traumatic stress exposure and psychopathology in three primary care clinics.. Participation refusal rate overall was less then 50%. 17(12SCZ/5SA) of 244 total patients with SCIDs (7%) met criteria vs. 51% meeting criteria for any mental disorder. Most were from day treatment programs which managed their psychotropics. 60% were substance

abusers, 50% had other comorbid mental disorders, mostly PTSD. Additional research of this complicated population in an under studied area is warranted. Recent evidence indicate that primary care providers often treat schizophrenic (SCZ) or schizoaffective patients (SA). We will report clinical characteristics of those seen in a primary care area. Diagnoses were determined with the Structured Clinical Interview for DSM IV (SCID) as part of a larger study exploring traumatic stress exposure and psychopathology in three primary care clinics.. Participation refusal rate overall was less then 50%. 17(12SCZ/5SA) of 244 total patients with SCIDs (7%) met criteria vs. 51% meeting criteria for any mental disorder. Most were from day treatment programs which managed their psychotropics. 60% were substance abusers, 50% had other comorbid mental disorders, mostly PTSD. Additional research of this complicated population in an under studied area is warranted. Recent evidence indicate that primary care providers often treat schizophrenic (SCZ) or schizoaffective patients (SA). We will report clinical characteristics of those seen in a primary care area. Diagnoses were determined with the Structured Clinical Interview for DSM IV (SCID) as part of a larger study exploring traumatic stress exposure and psychopathology in three primary care clinics.. Participation refusal rate overall was less then 50%. 17(12SCZ/5SA) of 244 total patients with SCIDs (7%) met criteria vs. 51% meeting criteria for any mental disorder. Most were from day treatment programs which managed their psychotropics. 60% were substance abusers, 50% had other comorbid mental disorders, mostly PTSD. Additional research of this complicated population in an under studied area is warranted. supported by NIMH 01-D1-0017.

DEPRESSIVE SYMPTOMS AND SCHIZOPHRENIA: THE EUROPEAN STUDY COHORT PERSPECTIVE

A. Le Lay,* C. Lancon, C. Durlach-Misteli
Health Economics and Epidemiology, H. Lundbeck A/S, Paris, France

Depressive symptoms in patients with schizophrenia have been associated with increased mortality, morbidity and risk of suicide. Understanding the factors that influence the development of such symptoms is of primary concern. The aim of our study was to identify the clinical features of patients with schizophrenia who have depressive symptoms. The study population consisted of 590 patients with schizophrenia aged 18 to 64 years. Those that scored > 5 on the Calgary Depression Scale for Schizophrenia (CDSS) were defined as having significant depressive symptoms. Clinical severity of illness was assessed using the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression of Severity scale (CGI-S). Extra-Pyramidal Symptoms (EPS) and side effects were measured using the Simpson Angus Scale (SAS) and the Subjective Side Effects Scale (SSES). Fisher exact tests, t-tests and multivariate logistic regressions were performed. According to the PANSS total and CGI-S scores, patients with significant depressive symptoms were rated as more severely impaired than those without depressive symptoms ($p<0.001$). Multivariate analysis showed that when patients PANSS total and CGI-S scores increased by one unit, the risk of developing depressive symptoms increased 2.4% and 40.6%, respectively. Results also demonstrated that patients with depressive symptoms were more likely to develop EPS (SAS scores: 0.45 plus or minus 0.46 vs. 0.23 plus or minus 0.37, $p<0.001$). Results showed that patients with depressive symptoms suffered more often from subjective sexual dysfunctions as well as from anticholinergic effects ($p=0.02$ and $p<0.001$, respectively). Logistic regressions showed that length of patients current psychotic episode significantly affected their probability of developing depressive symptoms ($p=0.01$). Patients experiencing a psychotic episode of 1 year or more had twice as much chance of developing depressive symptoms than those experiencing a psychotic episode of less than 6 months (OR=2.08, 95% CI: 1.25-3.46).

SUBSTANCE USE PATTERNS IN FIRST EPISODE PSYCHOSIS

K. LeDrew,* T. Hearn, K. Hogan, G. Walsh
Psychiatry, Memorial University, St. John, NF, Canada

Objective: To determine prevalence of substance abuse in First Episode Psychosis in Newfoundland, Canada and compare with previously published results. To review substance use patterns after one year in a program without formalized treatment for substance abuse. Method: 92 patients involved in the program between 2001 and 2003 were examined. The Case Manager Rating Scale for Substance Use Disorders was used and abuse rates were compared to similar studies. 50 patients had one year follow-up. Results: Rates were significantly elevated compared to the general population as well as other published FEP samples. 89% reported at least some substance use in the year prior to symptom onset; 78% used alcohol and 68.5% used cannabis. 66% were classified as substance abusers at initial presentation. A clinically and statistically significant decrease in alcohol, cannabis and hallucinogen use was observed after one year with no significant increases in the use of any drug. Conclusion: Drug abuse in these FEP clients was higher than reported in the general population and other FEP studies. A significant decrease in abuse after one year was found despite no formalized substance abuse intervention.

LEVELS OF DISTRESS IN SAMPLES AT RISK OF PSYCHOSIS

S. Lewis,* A. Morrison, E. Barkus, R. Bentall, J. Stirling, R. Hopkins, P. French
University of Manchester, Manchester, United Kingdom

Severity of affective symptoms which accompany at risk psychotic states may (i) dictate the decision to seek help and (ii) predict increased risk of future transition to psychosis. We aimed to compare levels of depression and anxiety as measured by the GHQ-28 between four non-clinical groups ranked a priori on the basis of their probable psychosis proneness. Three of these subsamples were derived from an internet-ascertained sample of 1206 persons who completed a schizotypy questionnaire (the O-LIFE) on-line, divided in terms of being greater than 1 SD deviation above or below the group mean for schizotypy score (Barkus et al, 2004). The fourth group was a sample of 58 subjects of similar age seeking help for at risk mental states which met Yung and McGorry criteria (Morrison et al, 2004). Mean (SD) scores of anxiety and depression as measured on the GHQ-28 (0,0,1,1 scoring) was low schiztypy 4.3 (4.6, n=32); medium 6.4 (6.7, n=30); high 7.3 (6.7, n=34), with the at risk mental state subjects 14.1 (8.0, n=58). This significant gradation in affective symptoms ($p=0.01$) is likely to relate to degree of psychosis-proneness and may be a target for future intervention. Other determinants will be discussed.

TAXOMETRIC ANALYSES OF MULTIPLE SCHIZOTYPY INDICATORS SUGGEST TWO INDEPENDENT (POSITIVE AND NEGATIVE) LATENT CLASSES

R. J. Linscott
Department of Psychology, University of Otago, Dunedin, New Zealand

Most taxometric studies of schizotypy focus on the latent structure of single negative or positive indicators, such as anhedonia or perceptual aberration, analysed in isolation. Thus, although this literature has yielded consistent support for the view that schizotypy is a discrete latent class comprising about 10% of the population, it is possible that distinct indicators are not identifying a unitary latent taxon. The aim of this study was to determine whether the latent taxa identified with maximum covariance (MAXCOV) analyses of positive and negative measures of schizotypy are redundant or independent. Undergraduates (n = 1462) completed a self-report measure of social and physical anhedonia, disorganized thinking, fearful suspicion, hallucinatory tendency, magical and self-reference ideation, and perceptual aberration, called the Thinking and Perceptual Style Questionnaire. Two sets of empirical subscales were identified by independent factor analyses (principal components, varimax extraction) of item responses: 6 negative subscales and 8 positive subscales. MAXCOV analyses were performed separately on each set (all possible triads, slab width = 0.25 *SD*). Classification of participants to taxa was based on the resulting posterior probabilities (threshold $p = 0.5$). The positive and negative sets of subscales each yielded covariance plots with right-end peaks, non-uniform membership probability distributions, homogeneous base-rate estimates (with $M \pm SD$ of 8.6% ± 5.4% and 13.9% ± 5.8%, respectively), and reasonable validities ($M = 1.20$ and $M = 1.31$, respectively). The mean base-rate for the negative subscales was greater than 10% ($p < 0.01$) whereas the mean base-rate for the positive subscales was not significantly different to 10% ($p > 0.05$). Posterior probabilities placed 194 people in the positive taxon and 157 in the negative taxon. Only 24 were in both taxa. The overlap of group membership was not greater than chance ($\chi^2 = 0.62$, $p = 0.43$). Thus, two latent classes were identified. Data from the positive subscales replicates extant evidence on the latent structure and prevalence of schizotypy. In contrast, the negative subscales tapped a taxon with a base-rate greater than 10%. The degree of overlap in membership of these taxa was no greater than chance suggesting the taxa are independent. The results do not resolve the question of which taxon, if either at all, represents a latent predisposition for schizophrenia.

MORTALITY IN SCHIZOPHRENIA OVER THE LAST 70 YEARS IN THE TOWNSHIP OF MALMO

B. Logdberg,* L. Nilsson
Psychiatry, Lund University, Malmo, Sweden

Introduction: The organization of psychiatric care for the seriously ill has changed dramatically in Sweden and other countries in Western Europe and North America over the last few decades, with the processes of deinstitutionalisation and sectorization. The objective of the present study was to analyse consequences of this change on the standardized mortaly ratio (SMR) for patients with schizophrenia in the township of Malmo, in Sweden, over the last 70 years. Materials and methods: The standardized mortality ratio (SMR) for patients with the diagnosis of schizophrenia or dementia praecox (between 25-64 years of age) in the township of Malmo (population about 250,000) in Southern Sweden was studied from about 1935 until 2005, by analyses of patients records. The number of beds available to patients with schizophrenia was analysed over the same time period. Results and Discussion: From about 1935-1960 most of the patients diagnosed with schizophrenia/dementia praecox were living at the mental hospital, and the mortality was similar to the age-matched general population, i e the standardized mortality ratio was about 1. Over the ensuing decades, the standardized mortality ratio increased from about 1 to 2 between 1960-1980, remained unchanged around 2 between 1980-1990, but then increased again from about 3 to more than 5 between 1990-2005 concommittant with the full sectorization of psychiatry and the final closure of the mental hospital. The results furthermore showed that over the last 65 years there appears to have been a striking inverse relationship between the number of beds and the standardized mortality ratio for patients with schizophrenia in the township of Malmo. One mechanism for the increased SMR is likely to be the changed and often adverse social environment of the patients following the reduction of available beds, which, particularly in view of the impaired social and executive cognitive functions found in those patients, can cause increased psychiatric symptoms and psychosocial stress. Our results showed a strong increase of the proportion of suicides as well as the proportion of unknown causes of death. Results will be presented which indicate that suicides as well as other disorders related to increased psychiatric symptoms and psychosocial stress, such as heart disorders, might explain a large part of the increased SMR.

LONGITUDINAL STUDY OF FUNCTIONAL STATUS OF DEINSTITUTIONALIZED VETERANS—PRELIMINARY RESULTS

M. Losonczy,* S. Essock, R. Rosenheck, D. Smelson
Mental Illness Research Education and Clinical Center, Department of Veterans Affairs-New Jersey Healthcare System, Lyons, NJ, USA

Introduction: Despite large and rapid deinstitutionalization in the VA and public health care systems, there has been little systematic study of the quality of life of long-term hospitalized veterans. This study was undertaken to examine the effects of deinstitutionalization on the quality of life of veterans at several NY/NJ VA hospitals. Methods: Veterans with at least 90 consecutive psychiatric hospitalization days are rated for two years following discharge to the community. Functional and psychiatric status is assessed using a 16-item scale rated by their clinician. Results: Fifty-nine veterans have been rated. Eighty-eight percent of the deinstitutionalized veterans had at least one rating within six months of discharge. Symptom severity was moderate in this group (mean CGI=3.91). 10% were in nursing homes, while 62% were in supervised group homes. Employment of any type was low (10%). Most patients required a case manager (88%). Rehospitalization was low (10% within 30 days). Patient satisfaction with social setting was high (90%). Discussion: Despite concerns about adverse consequences of deinstitutionalization, patients remain in treatment, have low short-term relapse rates and remain generally satisfied with their quality of life. They do require case management, and improvements may be possible to provide greater autonomy in housing and employment.

PRODROMAL SYMPTOMS OF PSYCHOSIS AT AGE OF 15-16 YEARS IN A FINNISH GENERAL POPULATION SAMPLE

P. H. Maki,* H. Ebeling, I. Moilanen, A. Taanila, J. Miettunen, E. Lauronen, M. R. Jarvelin, J. Veijola
Psychiatry, University of Oulu, Oulu, Finland

Background. The possibilities of preventing schizophrenic psychoses have been investigated lately. Subjects with family history of psychosis and subjects with prodromal symptoms are at risk to develop schizophrenia. Methods: Members of the Northern Finland 1986 Birth Cohort Study (N= 9,215) were invited to participate in a field survey conducted during 2001-2002. The field study was extensive including 21 item PROD-screen questionnaire which is an instrument for screening prodromal psychotic symptoms indicating risk for psychotic conversion. The questionnaire includes a subscale of twelve specific symptoms for psychosis. Of the males 3,073 and 3,122 of the females completed the PROD-screen questionnaire. Results: Of the males 74 % had at least one PROD-screen symptom during the previous year. For females the respective figure was 87 %. Most common symptom was feeling euphoric or especially competent and important with prevalence of 42 % for males and 46 % for females. Two percent of the males and 6 percent of the females had had over ten of the 21 symptoms during the previous year. In females all PROD-screen symptoms were more common than in males, except for having difficulties in carrying out ordinary routine activities (1.9 % females vs. 2.1% males). 23 % of the males and 37 % of the females were screen positives when using the recommended screening cut-off point of 2/12 for specific symptoms. Conclusions: Prodromal symptoms of psychosis are prevalent in adolescence. Due to this it may be difficult to screen subjects at risk for developing schizophrenia with a questionnaire. Females had more commonly prodromal symptoms than males. This finding is in contradiction to the fact that the incidence of schizophrenia in adolescence and early adulthood is more common in males than in females.

DOES DUP HAVE AN INDEPENDENT EFFECT ON RATE OF AND TIME TO REMISSION AND RISK OF RELAPSE IN FIRST EPISODE PSYCHOSIS (FEP)?: A TWO YEAR SURVIVAL ANALYSIS

A. Malla,* R. Norman, R. Manchanda, J. Takhar, R. Harricharan
Psychiatry, McGill University, Montreal, QC, Canada

Duration of untreated psychosis (DUP) is reported to be related to outcome on some clinical and social indicators. Studies regarding independent influence of DUP on remission and relapse rates are particularly scant. A cohort (114) of consecutive previously untreated FEP patients from a defined catchment area, treated and followed within a comprehensive phase-specific treatment program for two years, was assessed on demographic, clinical and symptom measures using structured assessment schedules. Outcome was assessed on remission and relapse using weekly data generated from a combination of rating scales (SAPS & SANS) and Life Chart Schedule (WHO). The patient cohort was divided into short and long DUP groups using the median DUP for the entire sample (23.8 weeks) as the cut-off. Following a descriptive analysis comparing the short and long DUP groups on demographic, clinical and outcome (rate and time to remission, and rate and time to relapse) variables, a logistic regression analysis for estimation of rate, Poisson regression for estimating rate ratio, and survival analysis and proportional hazard ratio for time to remission and relapse were used for data analyses. Age, age of onset, pre-morbid adjustment, DUP and total duration of illness (both as continuous variables), and in the case of relapse, also time to remission were used as covariates. Results showed that there were no differences between the short and long DUP groups on any demographic variables but significant differences on pre-morbid adjustment, DUP and duration of total illness (DUI). Two year remission rates for short and long DUP groups, respectively, were 82.7% and 81.8%, mean time to remission 18.3 (SD 29.8) and 28.9 (SD 35.1), relapse rates 24.4% and 34.8% and mean time to relapse 81.9 (SD 28.8) and 70.4 (SD 31.6). There was no significant difference for rate of remission (adjusted OR 0.62, CI 0.16-2.32) or for rate ratio for remission (adjusted estimate 0.87, CI 0.47-1.6). While the short DUP group had lower time to remission, there was no difference in the adjusted Hazard ratio (0.87). For relapse, the adjusted OR for rate of relapse approached significance (OR 3.25, CI 0.96-11.01) as did the rate ratio (adjusted estimate 2.42, CI 0.94-6.22). Survival analysis showed the short DUP group to have longer time to relapse with the risk of relapse being higher for the long DUP group only during the first 40 weeks following remission (adjusted Hazard ratio 2.42, chi square 3.3, p<.07).

FERTILITY AND FECUNDITY RATES OF PATIENTS WITH SCHIZOPHRENIA IN CUIABA, BRAZIL: PRELIMINARY FINDINGS

J. Mari,* A. C. Terzian, J. McGrath, S. B. Andreolli
Department of Psychiatry, Federal University of Sao Paulo, Sao Paulo, Brazil

The aim of this study was to estimate reproductive rates from a representative sample of schizophrenic patients from Cuiaba, a city located in Western of Brazil. All patients attending mental health outpatient clinics of Cuiaba, in a period of three months, have received a semi-standardized questionnaire comprising questions on fecundity and fertility. The diagnoses were confirmed by means of a DSM-IV checklist. This data was compared with general population data of Cuiaba collected in the census of Brazil,2000(1). The survey has located 384 patients, 181 (47.1%) were males and 203 (52.9%) were females, with a mean age of 41.4 (SD=11.5) years old. The mean age at onset of illness was 26.2 years (SD=9.86) and there were no statistical gender differences (t= -0.6, df=375, p=0.5). 228 (59.4%) patients were ever married. The rates of marriage were significant higher for females (74.3%) than males (42.8%) (p<0,001). Marriage rate for the general population were respectively 48% for females and 42% for males. 234 patients (60.9%) reported being a parent and there were 791 offspring from patients with schizophrenia. The fertility rate for female patients (79.3%) was higher than the female general population (60.5%). The fecundity rate of the female patients (2.68) was also higher than the female general population (2.03). The fertility and fecundity rates of the schizophrenia female patients were found to be higher than the female general population. There may be social and cultural unknown explanations for such differences. (1)IBGE. Censo Brasileiro 2000, Brasilia. Available: http://www.ibge.gov.br/home/estatistica/populacao/censo2000/default_nupcialidade_fecundidade/shtm

UNWANTED PREGNANCY AND RISK FOR OFFSPRING SCHIZOPHRENIA: PSYCHOBIOLOGICAL OR SURROGATE GENETIC RISK FACTOR?

T. McNeil,* K. M. Henriksson, E. W. Schubert, M. Brossner, P. Schubert
Psychiatric Epidemiology, Lund University, Lund, Sweden

Unwanted pregnancy (UWP) has been found to increase risk for offspring schizophrenia, but being most characteristic of patients with a family history of schizophrenia, UWP may represent a surrogate for genetic factors rather than a negative perinatal psychobiological or psychosocial influence. Beginning before birth, we prospectively investigated whether UWP (i.e. a clearly ambivalent or negative attitude toward pregnancy during pregnancy) was (1) more characteristic of individuals at genetic risk for schizophrenia, compared with affective psychosis and normal-risk, (2) reflected early-life somatic abnormality and psychosocial stressors, and (3) predicted schizophrenia spectrum and affective disorders in young adulthood. This was studied in 44 individuals at genetic risk for schizophrenia, 44 at genetic risk for affective psychosis, and 104 at normal risk for psychosis, defined by presence or absence of a maternal psychosis history. Data were collected independently through standardized pregnancy interviews, well-baby clinic records, and follow-up examinations at about 22 yr of age. UWP was significantly more frequent in offspring at risk for schizophrenia (48%, p=.006) but not individuals at risk for affective psychosis (32%), as compared with normal-risk subjects (24%). In the total sample, UWP was significantly associated with maternal material, interpersonal and mental health problems during pregnancy (in both high- and normal-risk groups), but showed no significant relationships to problems in the offspring's psychosocial situation, behavior, language development, biological functioning or motor development during the first 4 yr of life. UWP predicted adult schizophrenia-spectrum disorder (p=.029, OR 3.94, CI 1.01, 14.67) especially in cases at risk for schizophrenia (OR 3.08, CI 0.49, 19.29), but not affective disorder in offspring (p=.330, OR 1.51, CI 0.66, 3.47) independent of schizophrenia-spectrum disorder. UWP is a risk factor for schizophrenia-spectrum, rather than affective, disorders, and may reflect genetic factors rather than independent, untoward psychobiological influence. Supported by the Stanley Medical Research Institute.

EXAMINING THE OUTCOME OF FIRST EPISODE PSYCHOSIS: A META-ANALYSIS OF PROSPECTIVE STUDIES

N. M. Menezes,* T. Arenovich, R. B. Zipursky
Department of Psychiatry, University of Toronto, Toronto, ON, Canada

This study aims to examine the literature on outcome from first episode psychosis (FEP) in order to calculate meta-analytic estimates of functional and symptomatic outcome and correlations with demographic/clinical variables. A structured MEDLINE literature search was carried out to identify all prospective studies between 1966 and 2004 examining outcome in non-affective FEP. One hundred and one studies met search criteria. Of these, 37 (36.6%) met inclusion criteria for the meta-analysis, representing 3292 patients, 63+/-21% of whom were male. The majority of studies reported on a diagnosis of schizophrenia. The mean age at entry was 27.3+/-3.9 years. The mean follow-up duration was 35.09+/-5.95 months. Seventy-six percent of patients experienced some degree of improvement in the follow-up period. There was a decrease in the proportion with very good outcome over time, though the proportion of patients with poor outcome (24.5+/-2.7%) was stable over time. There was a 44.9+/-5.7% rate of relapse over the mean follow-up period. Higher rates of employment/education were associated with a combination of pharmacotherapy and psychosocial therapy (49.5+/-4.9%) versus studies for which the therapy type was not specified (26.0+/-4.0%) (f=9.10, 1,11df, p=0.0117), and with having a non-epidemiologically representative sample (48.2+/-4.8%) versus an epidemiologically representative sample (24.6+/-3.8%) (f=8.78, 1,11 df, p=0.0129). Having a sample of inpatients was associated with a higher rate of improvement (49.2+/-3.4%) compared to a mixed sample of in- and outpatients (28.5+/-5.6%) (f=6.76, 1,7 df, p=0.0355). A higher rate of remission or good outcome was associated with a developing country of origin (54.9+/-9.3%) versus developed country of origin (39.4 +/- 3.5%) (f=15.83, 1,22 df, p=0.0006), and with a non-epidemiologically representative sample (49.3+/-8.6%) versus an epidemiologic sample (30.6+/-7.1%) (f=14.01, 1,9df, p=0.0046). The results suggest that the outcome from first episode psychosis may be more favourable than previously reported. Sampling and type of intervention may be more significant determinants of outcome than demographic factors. Significant heterogeneity in the definitions and methodology limit the meta-analytic technique. A multidimensional, globally used definition of outcome is required for future research directed at understanding the true outcome of schizophrenia.

HELP-SEEKING FOR PATIENTS' RELATIVES AFTER A FIRST EPISODE PSYCHOSIS

V. B. Monteriro,* J. Q. Santos, D. Martim, A. C. Chaves
Psychiatry, Federal University of Sao Paulo -UNIFESP-EPM, Sao Paulo, Brazil

Background:Untreated psychosis, after a first episode psychosis, can be delayed for a long time, as shown by some recent studies. Some patients can remain unattended, untreated, even when showing grave symptoms. Understanding the reasons for this delay until beginning treatment is a relevant issue for study. Objective: to understand why seeking adequate psychiatric treatment was delayed for at least 6 months, by patients' relatives. Method: qualitative analysis of semi-structured in-depth interviews with 15 relatives. Emphasis was given to the perception of early symptoms of psychosis, and the ensuing elaborations preceding the decision, and actually going to, a psychiatrist for specialized help and treatment. Interviews were recorded, transcribed, and had relevant parts coded and grouped, to form terms, concepts and categories. Setting: families of patients attending the First Psychotic Episode Program-PEP, of Federal University of Sao Paulo, were interviewed from June 2002, to July 2003. Results: the delay to initiate treatment was always a difficult and disturbing issue, both for patients, and their families. Relatives refer to 'mental illness' in prejudiced terms,defining 'madness' in different ways. Having no understanding of their ill member as a mental disease case, the relatives classified observed items as spiritual issue, drugs and nervous problems, all linked to specific psychic and social issues. After treatment at the PEP program, they absorbed the notion of mental disease, which was added to their former array of explanations about their relatives' behavior, now including several dimensions, biological, psychic, social, and supernatural. Negative conceptions they had before treatment also contributed for the delay in seeking a psychiatrist. Conclusions: the initial delay to begin treating the ill person was influenced by a) stereotyped misconceptions

employed by family members to understand their ill member's problems; b) wrong models they set up to understand their member behavior; c) prejudiced ideas concerning psychiatric treatment, and d) bad experiences with psychiatric services sought for. Cultural issues are present in all stances of this understanding process and could help deducing pain and grief.

PREGNANCY, DELIVERY, AND NEONATAL COMPLICATIONS IN A POPULATION COHORT OF WOMEN WITH SCHIZOPHRENIA AND MAJOR AFFECTIVE DISORDERS

V. A. Morgan,* A. Jablensky, S. Zubrick, C. Bower, L. Yellachich
University of Western Australia School of Psychiatry and Clinical Neurosciences, Perth, WA, Australia

This study ascertained the incidence of complications of pregnancy, labour and delivery, and the neonatal characteristics of infants born to women with schizophrenia, bipolar disorder or major depression, in a population-based cohort. Based on record linkage across a psychiatric case register and prospectively recorded obstetric data, the study comprised all women with schizophrenia or major affective disorders who had given birth to 3174 children during 1980-1992 in Western Australia. A comparison sample of 3129 births to women without a psychiatric diagnosis was randomly selected from all such women giving birth 1980-1992. Complications were scored using the McNeil-Sjöström scale. Odds ratios were calculated for specific reproductive events. Both schizophrenic and affective cases had increased risks of pregnancy, birth and neonatal complications, including placental abnormalities, antepartum haemorrhages, and fetal distress. Women with schizophrenia were significantly more likely to have placental abruption, to give birth to infants in the lowest weight/growth population decile, and to have children with cardiovascular congenital anomalies. Neonatal complications were significantly more likely to occur in winter births, while low birthweight had a peak in early spring. The incidence of complications other than low birthweight and congenital anomalies was higher in pregnancies following the onset of psychiatric illness than in pregnancies preceding the diagnosis. While genetic liability and gene-environment interactions may account for some of these outcomes, maternal risk factors, as well as biological and behavioral concomitants of severe mental illness, appear to be major determinants of increases in reproductive pathology in this cohort. Risk reduction in these vulnerable groups may be achievable through antenatal and postnatal interventions.

SOCIAL ISOLATION, ETHNICITY, AND PSYCHOSIS: FINDINGS FROM THE AESOP FIRST ONSET PSYCHOSIS STUDY

C. Morgan,* J. Kirkbride, R. Mallett, G. Hutchinson, P. Fearon, K. Morgan, P. Dazzan, T. Craig, G. Harrison, P. Jones, R. Murray, J. Leff
Division of Psychological Medicine, Institute of Psychiatry, London, United Kingdom

Introduction: Research has consistently suggested that the risk of schizophrenia and other psychoses is significantly higher in African-Caribbean and Black African populations in the UK, compared with the White population. This study sought to investigate whether social isolation is a risk factor for psychosis and, if so, whether this might at least partly account for the high rates of psychosis among the African-Caribbean and Black African populations in the UK. Method: Data were collected as part of the AESOP study, a three-centre population based incidence and case-control study of first episode psychosis. Data relating to sociodemographic characteristics, socio-economic status, social isolation and clinical presentation were collected using a number of validated instruments from all cases who consented to take part in the AESOP study and a group of unmatched, randomly selected community controls. Data were analysed using odds ratios and unconditional logistic regression. Results: A total of 381 cases with a first episode of psychosis and 411 controls were included in the analysis. A number of indicators of social isolation were associated with an increased risk of psychosis, including having no close confidants (OR 7.8; 95% CI 4.9, 12.5), never having had a long-term relationship (OR 4.0, 95% CI 2.9, 5.7), and being unemployed for more than a year (OR 2.0; 95% CI 1.5, 2.6). These associations remained after adjusting for sociodemographic characteristics (e.g. age and gender) and socio-economic status. An index of social isolation was constructed from these variables, and there was strong evidence that the risk of psychosis increased as levels of social isolation increased (Score test for trend: OR 2.0; 95% CI 1.7, 2.2). There was, moreover, evidence that African-Caribbeans, and to a lesser degree Black Africans, were more isolated than White subjects. Conclusion: The findings from this study provide strong evidence for an association between social isolation and the risk of psychosis. Establishing whether this association is one of cause or effect is far from straightforward. However, where possible, indicators of long-standing isolation were used, and the index of social isolation showed a strong dose-response relationship with psychosis. If this association is causal, the greater prevalence of isolation among African-Caribbeans and Black Africans in the UK may be one factor influencing the high rates of psychosis in these groups.

TOXOPLASMOSIS AND OTHER EARLY INFECTIONS IN RELATION TO SCHIZOPHRENIA RISK

P. B. Mortensen,* R. H. Yolken, B. Lindum, T. Sorensen, D. Hougaard, B. N. Pedersen
National Centre for Register-Based Research, University of Aarhus, Aarhus, Denmark

Infections during intrauterine life or infancy have been suggested to contribute to schizophrenia risk. Infections with Toxoplasma gondii have been implicated in the causation of some cases of schizophrenia. Few studies have combined individual serological data from infancy with data on adult onset mental disorders. The study was based on different population-based registers as well as the Danish PKU biobank and was approved by the Danish Data Protection Agency and Scientific Ethical Committee. The design of the study was a population-based case-control study. Cases of psychoses were identified using a national psychiatric case register. Matched controls were chosen in the biobank. Information regarding family history of mental disorders, sibship size, birth order, parental age, urbanicity of place of birth, as well as other potential risk factors was added from various population registers. The data presented here are from an analysis of 71 cases of schizophrenia (ICD-10 F20) compared to 684 controls. The data were analysed using logistic regression. All analyses of the 3.2 mm punches of the anonymized blood samples were done blindly to the case-control status. Analyses included total IgG, total IgM, IgG and IgM specific antibodies against Toxoplasma gondii, IgG against Herpes Simplex Virus (HSV) 1 and 2.Samples from individuals who were later diagnosed with schizophrenia

had significantly higher levels than controls with respect to IgG antibodies against Toxoplasma gondii (one-way analysis of variance p<0.003). When dichotomized at the 75th and 90th percentile, respectively, there was also a significantly elevated risk in individuals with higher levels of antibodies. After adjustment for gender, year of birth and place of birth and family history, however, the association was only marginally statistically significant for the 75th percentile dichotomy (OR=1.75 95% confidence limits 1.00-3.06, p=0.05), although all associations were of the same magnitude and direction. IgM against T. gondii was not elevated, suggesting that the child did not have acute toxoplasmosis. There were no significant findings in relation to HSV1, HSV2, total IgM or total IgG. Our data support a possible role for intrauterine infections with Toxoplasma as a risk factor for schizophrenia. The study was supported by the Stanley Medical Research Institute.

USE OF ANTIPSYCHOTIC DRUGS DURING PREGNANCY AND THE RISK OF ADVERSE BIRTH OUTCOMES: A POPULATION-BASED COHORT STUDY

E. M. Munk,* B. Norgaard, M. Gislum, P. B. Mortensen, H. T. Sorensen
Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

We examined the risk of adverse birth outcomes in women after exposure to antipsychotic drugs. We conducted a cohort study in four Danish counties (1.4 million people). We obtained data from a population-based prescription registry and the Danish Birth Registry from 1991 to 2003. Exposure to antipsychotics was categorized according to their mechanism of action: first-generation (typical) antipsychotics (FAPs) and second-generation (atypical) antipsychotics (SAPs). We estimated the risk of adverse birth outcomes according to exposure to only FAPs or SAPs, and after use of both drugs during pregnancy. To estimate the risk of congenital abnormalities (CAs) we included pregnancies exposed 30 days before conception or during the first trimester; 69 FAPs-exposed (3 CAs), 20 SAPs-exposed (0 CA), and 7 exposed to both FAPs and SAPs (1 CA). To estimate the risk of preterm birth and low birth weight we included pregnancies exposed during the entire pregnancy; 70 FAPs-exposed (5 preterm births, 7 low birth weight), 12 SAPs-exposed (1 preterm birth, 0 low birth weight), and 12 exposed to both FAPs and SAPs (2 preterm births, 2 low birth weight). Outcomes among exposed were compared with the total of 58,055 pregnancies of non-exposed. We used logistic regression models to estimate the risk of adverse birth outcomes, and to adjust for possible confounders(smoking, maternal age, and parity). The adjusted odds ratios (with 95% confidence intervals [CI]) for CAs, preterm birth and low birth weight after use of FAPs were 1.2 (95% CI 0.4-3.8), 1.1 (95% CI 0.5-2.8), and 2.2 (95% CI 0.9-5.7), respectively. Due to few events among SAPs-exposed we could only estimate the risk of preterm birth; adjusted odds ratio 1.3 (95% CI 0.2-10.5). The adjusted odds ratios for CAs, preterm birth and low birth weight after use of both FAPs and SAPs were 4.1 (95% CI 0.5-34.4), 2.8 (95% CI 0.6-13.0), and 1.8 (95% CI 0.2-19.3), respectively. Our findings may indicate an increased risk of adverse birth outcomes especially after exposure to both FAPs and SAPs, but our results are hampered by low statistical precision. Other studies indicate that schizophrenia itself may increase the risk of adverse birth outcomes; therefore, the clinical condition that determines drug-selection may be linked to the outcomes in our study (confounding by indication). The study was supported by an unrestricted grant from Lundbeck, DK. Dr Mortensen's work is supported by the Stanley Medical Research Institute.

THE MILITARY NEW-ONSET PSYCHOSIS PROJECT—A RESOURCE FOR THE STUDY OF GENE-ENVIRONMENT INTERACTIONS AMONG PERSONS WITH SEVERE MENTAL ILLNESS

D. W. Niebuhr,* R. H. Yolken, A. M. Millikan, D. N. Cowan, Y. Li
Division of Preventive Medicine, Walter Reed Army Institute of Research, Silver Spring, MD, USA

BACKGROUND: Schizophrenia (SCZ) and bipolar disorder (BPD) are complex diseases related to the interaction of genes and environment. There are few large populations where valid diagnosis and serologic data are collected over extended periods of time pre- and post-onset of illness. Such data are required to evaluate the interaction between genetic susceptibilities and exposure to environmental factors, such as infections occurring during defined periods of time. We are conducting multiple nested case-control studies to elucidate the roles of these interactions. METHODS: The Defense Medical Surveillance System routinely collects and maintains demographic and medical data and serum specimens on service members. We identified subjects hospitalized and subsequently discharged from the military with a diagnosis of SCZ (n=200) or BPD (n=200), and 3 matched controls per case. For each study subject we obtained the initial serum specimen and 2 additional samples from around the time of disease diagnosis. Each specimen from BPD study subjects was tested by solid phase immunoassay to detect antibodies to potentially neurotropic infectious agents. We examined for differences between cases and controls in the initial and subsequent sera, and for changes over time within the case and control populations. RESULTS: Initial analyses of 1861 samples (mean=2.3 sera/subject) from 200 BPD cases and 600 controls indicate that BPD is associated with changes or differences in antibody levels to human herpes virus type 6, human endogenous retrovirus K, T. gondii, and influenza viruses. Analyses of sera from SCZ cases and controls are underway. DISCUSSION: We found differences between BPD cases and controls for several agents, providing additional evidence that these agents or gene-agent interactions play a role in the etiology of BPD. Testing of sera from SCZ cases and controls will determine if similar interactions are operant in that disease as well. We will further explore both study populations using other methods of detection of infectious agents, genetic polymorphisms and expressions, and proteomic analysis. The hypotheses generated from this study will be tested in follow-on studies of SCZ and BPD with >1000 cases and >3000 controls for each illness. It is clear that the routinely collected data and serum specimens from military populations provide a unique and valuable resource for studying the etiology of serious mental illnesses.

AIDS/HIV RISK BEHAVIOUR KNOWLEDGE IN A SCHIZOPHRENIA POPULATION

D. Niehaus,* L. Koen, S. Van Vuuren, H. Lategan
Ngaphakathi Workgroup, University of Stellenbosch, Tygerberg, South Africa

Background: Several international studies have shown that schizophrenia sufferers as a group exhibited a much higher risk for HIV

disease. Patients with schizophrenia have been shown to exhibit lower levels of HIV/AIDS knowledge compared to control groups. The purpose of the study was (1) to assess whether the previously reported significantly lower levels of knowledge could be confirmed in a South African schizophrenia population and if so, (2) postulate how AIDS education strategies can be effectively individualized to address these. Methods: 43 subjects with schizophrenia and 43 controls were recruited. Each participant (schizophrenia group) was subjected to the standardized Diagnostic Interview for Genetic Studies whilst the AIDS Risk Behaviour (ARB) questionnaire was administered to both groups. Statistical analysis was performed using the SPSS software package. Results: Of the eleven risk-behaviour questions significant deficits could be demonstrated in the schizophrenia group on seven items. Among others they were more likely to believe that HIV risk was mostly confined to homosexuals and that washing yourself after sex could be regarded as a protective factor against contracting HIV. Conclusion: This was the first study on a South African schizophrenia population focusing specifically on HIV/AIDS knowledge and our results confirmed a clear overall knowledge deficit in this group in comparison to a control group. In follow-up a further 40 schizophrenia subjects will be recruited and factor analysis will be utilized to determine what if any contribution symptom-clusters make to knowledge-deficits.

FETAL GROWTH RESTRICTION AND SCHIZOPHRENIA—A SWEDISH TWIN STUDY

E. Nilsson,* G. Stalberg, P. Lichtenstein, S. Cnattingius, P. Otterblad Olausson, C. M. Hultman
Department of Medical Epidemiology and Biostatistics, The Karolinska Institutet, Stockholm, Sweden

Background; Obstetric complications increase the risk of schizophrenia. However, it is not known whether there is a causal relation or whether the association is mediated by genetic and/or shared environmental effects. Aims; To investigate the associations between birth weight, other birth characteristics and schizophrenia. Twin pairs discordant for schizophrenia will also control for unmeasured genetic and shared environmental effects. Method; Prospectively filed obstetric records for a cohort of 11,360 same-sexed twins born in Sweden were used. Within-twin-pair analyses were conducted on 90 pairs. Results; The results from the cohort study showed that low birth weight and reduced fetal growth was associated with later development of schizophrenia. The associations remained in the within-pair analyses. Conclusions; The association between low birth weight and schizophrenia is partly a function of reduced fetal growth and partly due to child specific characteristics. Fetal growth restriction seems to be associated with risk of schizophrenia independently of familial factors.

DURATION OF UNTREATED PSYCHOSIS PREDICTS PSYCHOTIC SYMPTOMS BUT NOT NEGATIVE SYMPTOMS

M. Nordentoft,* P. Jeppesen, L. Petersen, A. Thorup, P. Jorgensen
Psychiatric, Bispebjerg Hospital, Copenhagen, Denmark

Objective: Results of analyses of the predictive value of duration of untreated psychosis are conflicting. The ideal research design for testing the hypothesis of a positive effect of early detection and intervention is a randomised controlled trial, which cannot be conducted for ethical reasons. Studies using quasi-experimental design and natural studies indicate that early intervention may improve outcome in schizophrenia. Method: In the Danish OPUS-trial of first episode psychotic patients, duration of untreated psychosis was evaluated with IRAOS. 547 patients were interviewed at baseline and 77 percent and 66 percent were interviewed at one- and two-years follow-up, respectively. Patients with schizotypal disorder were excluded, thus 444 patients went into the analyses. Results: DUP mean was 119 weeks, median 47 weeks. In univariate and multivariate analyses DUP was associated with psychotic dimension, while premorbid adjustment (PAS) was associated with negative dimension. Conclusion: The finding that long DUP was not related to negative symptoms does not contradict the hypothesis of neurotoxicity, but it does not support it either.

RELATION BETWEEN NUMBER AND TYPE OF PATIENT NEEDS AND THEIR FAMILY BURDEN

S. Ochoa,* M. Dolz, M. Vilaplana, V. Villalta, J. Usall, J. Haro
Research Unit, Sant Joan de Deu SSM, Sant Boi, Spain

Objective: to relate number and needs of outpatients with schizophrenia to their family burden in a Spanish sample. Method: A random sample of 231 outpatients with schizophrenia (DSM IV criteria) from 5 mental health cacthement areas; were interviewed with a sociodemographic and clinical questionnaire and the Camberwell Assessment of Needs (CAN) rated by user. Their main carer were interview with a burden family scale (ECFOS-II), that evaluated objective and subjective burden. Results: One hundred fourty two carers were interview; 66% of them were women and principally they were their mothers. There is a positive correlation between number of needs detected by outpatients with schizophrenia and total objective and subjective family burden ($p<0.001$). Analysis of unmet needs detect a positive correlation with subjective family burden ($p<0.001$), but not with objective family burden. The presence of needs in the areas of daily activities, risk of commited suicide and problems with telephone are related to more burden family ($p>0.05$- 0.001). Conclusion: Level and type of patient unmet and total needs are related to the level of family burden. This results suggest that the family of patients with more needs have a high level of burden, so intervention will be address to patient and family. Bibliography: Magliano L, et al .The effect of social network on burden and pessimism in relatives of patients with schizophrenia. *Am J Orthopshychiatry*, 2003, 73 (3), 302-9 Bengtsson-Tops A. Mastery in patients with schizophrenia living in communty and its relationship to sociodemographic and clinical characteristics, and for care support, and social network. *J Psychiatr Ment Heath Nurs*, 2004, 11,(3), 298-304.

LACK OF EVIDENCE FOR ELEVATED OBSTETRIC COMPLICATIONS IN CHILDHOOD ONSET SCHIZOPHRENIA

A. E. Ordonez,* A. Bobb, D. Greenstein, N. Baker, A. Sporn, M. Lenane, D. Malaspina, J. L. Rapoport, N. Gogtay
Child Psychiatry Branch, NIMH, Bethesda, MD, USA

Objective: Pre-, peri- and postnatal obstetric complications (OC) have been found to be increased in adult patients with schizophrenia and have been linked to both greater severity and to earlier age of onset (either before age 18 or 22) in studies of adult patients. We

hypothesized that by extrapolation, patients with childhood onset schizophrenia (COS), with a very early onset and very severe form of the illness, would have had more numerous and/or more salient OC when compared to their healthy siblings. Methods: We compared the obstetric records of 60 COS children and 48 healthy siblings using the Columbia Obstetrics Complication Scale, a comprehensive measurement scale consisting of 37 variables having included a separate scale for fetal hypoxia. Results: Patients with COS did not have a higher incidence of OC than the healthy sibling control group with the exception of increased incidence of maternal vomiting. Conclusions: Obstetric complications are unlikely to play an important role in the etiopathogenesis of childhood onset schizophrenia.

STATUS OF FIRST EPISODE PSYCHOSIS PATIENTS PRESENTING FOR ROUTINE CARE IN A DEFINED CATCHMENT AREA

J. R. Payne,* A. Malla, R. Norman, D. Windel, N. Brown
Psychiatry, Douglas Hospital, Montreal, QC, Canada

Despite significant enthusiasm about setting up specialized services for patients with first episode psychosis (FEP), there is scant data about the status of FEP patients in routine care. The objective of this study is to examine the clinical and behavioral status of all FEP patients within a defined catchment area. Records of all admissions to hospitals within a defined catchment (population of 390,000) in London, Ontario, Canada for all patients diagnosed with a non-affective FEP over a 3 year period were reviewed. One hundred and forty-six patients were admitted during this period suggesting a treated yearly incidence of 12.5 per 100,000. The majority of subjects were male (63.7%), single (80.8%), unemployed (87.4%) received a primary diagnosis of schizophrenia spectrum psychosis (85%) and had a mean age of 31.3 years. At the time of their first admission to hospital, 88 (60.3%) patients were admitted involuntarily, 24 (18.8%) patients had attempted suicide, 23 (15.9%) patients had shown aggressive behavior, 46 (31.5%) patients demonstrated violence towards people, property or animals and 21 (14.4%) patients suffered injuries as a result of suicidal behavior or aggression from others. Finally, 50 (34.2%) patients had a history of legal involvement. At first admission, patients were hospitalized for a mean of 31 days (range: 1-731) and spent a mean of 2.93 days (range: 0-26) in the Intensive Care Unit. These results identify some of the clinical, behavioral and social characteristics of first episode psychosis patients and should provide some direction for development of new specialized services in responding to the needs of this population. They also provide baseline data for comparison with similar data after the establishment of a specialized early psychosis service in the same catchment area.

ARE THE URBAN-RURAL DIFFERENCES IN SCHIZOPHRENIA RISK DUE TO ENVIRONMENTAL FACTORS?

C. B. Pedersen,* P. B. Mortensen
National Centre for Register-Based Research, University of Aarhus, Aarhus, Denmark

Context: Many studies have demonstrated that urban birth or upbringing is associated with an increased risk of schizophrenia. Though unknown, the causes of these urban-rural differences have been hypothesised to include toxic exposures, diet, infections, or an artifact due to selective migration. Objective: To determine if the urban-rural differences in schizophrenia risk are due to environmental factors or an artifact due to selective migration. Design: Cohort study of incidence of schizophrenia. 3341 persons developed schizophrenia during 10.6 million person-years of follow-up from 1970 to 2001. Setting: Danish population register-based study. Participants: Using data from the Danish Civil Registration System, we established a population-based cohort of 809,816 people with older siblings including information on place of residence during upbringing and nearest older siblings place of birth. Schizophrenia in cohort members and mental illness in a parent or sibling were identified by linkage with the Danish Psychiatric Central Register. Main outcome measure: Incidence of schizophrenia in relation to urbanicity. We used nearest older siblings place of birth to evaluate if the effect of urbanicity operate prior to birth. If the urban-rural differences are due to environmental factors having a direct effect, this effect must operate during childs life, i.e., nearest older siblings place of birth should have no independent effect. Results: Nearest older siblings urbanicity at birth confounds and modifies the effect of urbanicity at birth and during upbringing; therefore the urban-rural differences in schizophrenia risk operate prior to childs birth. Among individuals who lived their first 15 years in the rural area, the risk was 1.73 (95% Confidence Interval: 1.22-2.45) if nearest older sibling was born in the capital compared to the rural area. Conclusions: The urban-rural differences in schizophrenia risk operate prior childs birth, meaning that some or all of the urban-rural differences are not caused by environmental factors having a direct effect on schizophrenia risk; therefore, some of these differences are an artifact due to selective migration.

THE CHARACTERISTICS OF HOMELESS INDIVIDUALS WITH SCHIZOPHRENIA IN RURAL CHINA

M. S. Ran,* E. Y. Chen, C. L. Chan, P. S. Yip, Y. Conwell, E. Caine
Hong Kong Jockey Club Centre for Suicide Research and Prevention, The University of Hong Kong, Hong Kong, China

Objective: Homeless individuals with schizophrenia may not be included in previous studies of suicide in China, given the methods used by such studies to establish cases for epidemiological research. The aim of this study has been to explore the frequency and characteristics of homeless persons among a previously identified cohort of persons with schizophrenia in rural China. Method: A pilot study for a planned 10-year follow-up investigation of suicidal behavior among a 1994 cohort (n=510) of persons with schizophrenia was conducted in a Chinese rural community. All the subjects were followed up using Patients Follow-up Schedule. Results: Forty-six subjects (9.0%) experienced a homeless period during the 10 years since accession into the initial study. Among these homeless subjects, 40 subjects (87.0%), including 22 men and 18 women, could not find home again. The average rate of homeless subjects who could not find home again was 0.63% per year in persons with schizophrenia. There was no significant difference between the rates for homelessness among men (9.2%) and women (6.6%) (X2=1.2, df=1, p=0.28). The mean age for homeless subjects (44.0+13.5 years) was similar to individuals who had killed themselves (42.3+14.4 years) (t=0.45, df=59, p=0.66), but significantly younger than the age of death from other causes (65.3+16.7 years) (t=6.99, df=115, p=0.00). Conclusion: Homelessness is an extreme form of social isolation, an often-recognized risk factor for suicide. This study shows that substantial numbers of people with schizophrenia (in itself a powerful risk factor for eventual suicide) experience periods of homelessness. Our results raise the concern that household-based community sampling

and registration system-based methods used to identify cases of suicide may miss homeless decedents.

ACTIVE, PREMORBID INTELLECTUAL DECLINE AND INTRA-INDIVIDUAL VARIABILITY IN INTELLECTUAL PERFORMANCE INCREASE RISK FOR SCHIZOPHRENIA

A. Reichenberg,* M. Weiser, M. Rapp, A. Caspi, H. Y. Knobler, G. Lubin, J. Rabinowitz, P. D. Harvey, M. Davidson

Psychiatry, Mount Sinai School of Medicine, New York, NY, USA

Context: Consistent evidence indicates that some, but not most, schizophrenia patients demonstrate below average intellctual ability before they manifest psychosis. However, it is not clear if this below-average IQ is stable or declining, and if those who's IQ falls within-normal-range nevertheless have cognitive abnormalities. Objectives: To examine if increased risk for schizophrenia is associated with a) declining intellectual performance from childhood through adolescence and b) intra-individual-variability in intellectual performance in individuals with normal IQ. Design: Historical cohort study of an entire population, using record linkage for psychiatric hospitalization during a 8 to 17 year follow-up period. Participants: Population-based cohort of 555,326 adolescents born in Israel. Data from mandatory assessment by the Draft Board were available on 4 intelligence sub-tests, as well as on reading and spelling abilities, and on behavioral and psychosocial variables. Cohort members were followed for psychiatric hospitalization through a National Psychiatric Hospitalization Case Registry. A regression-based approach was used to assess the discrepancy between actual IQ at age 17, and estimated IQ during childhood, based on the reading and spelling abilities. Variability was computed from the variance of the four intelligence tests' standardized scores. Results: Lower-than-predicted IQ at age 17 was strongly associated with increased risk for later hospitalization with schizophrenia. Specifically, individuals with the largest IQ declines were 6.5 times more likely to be hospitalized for schizophrenia (95%CI=4.1-10.4) compared with individuals with average change. There was a significant monotonic association between increased intra-individual-variability in intellectual performance and risk of schizophrenia in individuals with within-normal-range IQ (HR=1.6, 95%CI=1.4-1.9 over seven variability categories). Results held after controlling for potential confounders. Conclusions: Indirect evidence suggests that active intellectual deterioration from childhood through adolescence is associated with increased risk for schizophrenia. Despite within-normal-range premorbid IQ, apparently healthy adolescents who will later on manifest schizophrenia, nevertheless have cognitive abnormalities such as intellectual decline and increased variability across intellectual tasks.

DEMOGRAPHIC CHARACTERISTICS AND CLINICAL OUTCOMES AMONG FIRST EPISODE PSYCHOSIS PATIENTS: A PROSPECTIVE STUDY

P. D. Roy,* R. Norman, A. Malla, S. Archie, D. Windell, I. Furimsky, J. Hunt, H. Hobbs, R. B. Zipursky

Psychiatry, The Ottawa Hospital—General Campus, Ottawa, ON, Canada

The Ontario Working Group (OWG) on Early Intervention in Psychosis conducted a prospective, multi-site study of 200 patients presenting with a first episode of psychosis. The number of patients recruited at each site is as follows: Toronto (n = 84), London (n = 56), Hamilton (n = 34), and Ottawa (n = 26). Recruitment began in December 2001 and ended in November 2003. Follow-up assessments were completed at 6 and 12 months. The study objectives were as follows: 1) Who are the patients that are being referred? 2) What are the outcomes from treatment of a first episode psychotic episode? 3) What hospital resources are used over the early course of the illness? 4) How satisfied are patients and their families? and 5) How do the 4 programs differ in the above areas? Inclusion criteria consisted of: Males and females aged 16-50 years who were receiving treatment voluntarily, were capable of providing informed consent, and were experiencing a first episode of psychosis (i.e. at presentation met DSM-IV criteria for: schizophrenia, schizophreniform, schizoaffective disorder, brief psychotic disorder, delusional disorder, or psychosis NOS). The sample consisted of 156 males (78.0%) and 44 females (22.0%), with a mean age of 24.4 +/- 6.6 years. Thirty-one (15.6%) of the patients were Black, 121 (60.8%) were White, 24 (12.1%) were Asian, and 23 (11.6%) were classified as Other. Based upon SCID-IV assessments, 95 (48.2%) of the patients were diagnosed with schizophrenia, 33 (16.8%) with schizophreniform disorder, 20 (10.2%) with schizoaffective disorder, 6 (3.0%) with delusional disorder, 5 (2.5%) with brief psychotic disorder, and 38 (19.3%) with psychosis NOS. Mean scores for clinical scales were as follows: DUP = 1.08 +/- 1.90, CGI = 4.5 +/- 0.9, PANSS Total = 81.7 +/- 17.4. Outcome data will be presented.

DIMENSIONS OF PSYCHOTISM AND THEIR INTERACTION WITH DEPRESSIVE AND MANIC SYMPTOMS IN THE PATIENTS ATTENDING PRIMARY CARE: RESULTS OF THE RADEP STUDY

R. K. Salokangas,* S. Luutonen, M. Nieminen, H. Karlsson

Department of Psychiatry, University of Turku, Turku, Finland

The aim of the study was to analyse symptom dimensions of psychotism and their associations with occurrence of depressive and manic symptoms in primary care patients. A questionnaire including 22 questions about lifetime occurrence of psychotic symptoms extracted from the Composite International Diagnostic Interview (World Health Organisation 1990), the DEPS (Salokangas et al. 1995), and the Mood Disorder Questionnaire (Hirschfeld et al. 2000) was given to consecutive patients attending three local Health Care Centres in Southwest Finland. Psychotic symptoms were factored and rotated factor dimensions were analysed by patients' background, health history and concurrent occurrence of depressive and manic symptoms. Factor analysis produced seven factor dimensions: paranoid, thought disturbances, passivity experiences, visual, auditory and somatic hallucinations and infidelity experiences. Patients' background and health history associated differently with different factor dimensions. Additionally, manic symptoms associated with all dimensions of psychotism and depressive symptoms with paranoid and passivity experiences and with visual hallucinations. In passivity experiences, somatic hallucinations and infidelity experiences, there was an interaction between depressive and manic symptoms. We concluded that psychotism is composed of several independent symptom dimensions, which are associated differently with patients' background and health history. However, independently from patient's background and health history, occurrence of manic and depressive symptoms increases the risk of psychotism in general and

its sub-dimensions separately. Hirschfeld RMA, Williams JBW, Spizer RL, Calabrese JR et al. Development and validation of a screening instrument for bipolar spectrum disorder: The Mood Disorder Questionnaire. *Am J Psychiatry* 2000;157: 1873-5. Salokangas RKR, Poutanen O, Stengard E: Screening for depression in primary care. Development and validation of the Depression Scale, a screening instrument for depression. *Acta Psychiatr Scand* 1995;92:10-16. World Health Organisation. *Composite International Diagnostic Interview (CIDI)*. Version 1.0. World Health Organisation 1990.

THE ASSOCIATION BETWEEN NEUROBEHAVIORAL DEFICITS AND SCHIZOPHRENIA-SPECTRUM AND AFFECTIVE DISORDER IN ADULT OFFSPRING WITH HEIGHTENED RISK FOR PSYCHOSIS

E. Schubert,* T. F. McNeil
Psychiatric Epidemiology, University Hospital in Lund, Lund, Sweden

The authors investigated whether neuropsychological impairment and neurological abnormality are significantly related to schizophrenia-spectrum disorders and to affective disorders in young adults at risk for psychosis and normal risk, and whether the rate of accumulated signs of this disturbed neurodevelopment differs for groups at risk for schizophrenia vs. affective psychosis vs. normal risk. A 93%-effective (total n=166) follow-up of a longitudinally-studied sample investigated mental disturbance, neuropsychological performance and neurological abnormality at mean 22.4 yr of age, with complete data for 74 offspring of mothers with a history of psychosis (38 offspring with heightened risk for schizophrenia, and 36 with risk for affective psychosis), and 88 normal-risk offspring of mothers with no history of psychosis. Neurobehavioral deficits were related to schizophrenia-spectrum disorder in a different manner from that for affective disorders in the total sample and offspring at high-risk. Signs of neurodevelopmental disturbance were shown by 47% of offspring with heightened risk for schizophrenia, as compared with 14% at heightened risk for affective psychosis and 12% at normal risk. Schizophrenia-spectrum disorders may be part of a neurobehavioral syndrome and a consequence of disturbed neurodevelopment that belongs to a different neurobiological spectrum from that for affective disorders. Supported by the Stanley Medical Research Institute.

HYPOTHESIS: LONG-TERM EXPOSURE TO SOCIAL DEFEAT IS MAJOR RISK FACTOR FOR SCHIZOPHRENIA

J. Selten,* E. R. Cantor-Graae
Psychiatry, University Medical Center, Utrecht, Netherlands

It is proposed that the long-term exposure to social defeat, defined as a subordinate position or outsider status, leads to disturbed dopamine (DA) function in the brain and puts the individual at increased risk for schizophrenia. The hypothesis is derived from (1) Epidemiological findings of increased risks for (a) migrants*, particularly those from developing countries and those with black skin color; (b) subjects raised in urban areas, where levels of competition are high; (c) people with low IQ. (2) Animal experiments. An important experiment is the resident-intruder paradigm, whereby a male rat (intruder) is put into the cage of another male (resident). Repeated exposures to social defeat lead to sensitization, i.e., enhanced behavioral and DA response to DA agonists. (3) Research on schizophrenic patients which indicates that their mesolimbic DA system is sensitized. The hypothesis can be tested. Firstly, using PET one can compare amphetamine-induced DA release in defeated (e.g.long-term unemployed) and non-defeated individuals. Secondly, one can compare amphetamine-induced DA release in healthy migrants from a "superhigh" risk group to that in healthy natives. Thirdly, randomized studies of non-human primates could be used to examine whether exposed animals will develop greater subcortical DA activity. Finally, history carries out natural experiments. During the 1980s Ethiopian Jews migrated to Israel, where they are heavily discriminated against, primarily due to their black skin color. The hypothesis predicts that the risks in Jewish subgroups will be highest for Ethiopians. It is important to note that exposure to social defeat is neither a sufficient cause nor a specific risk factor for schizophrenia. It is also a risk factor for depression and addiction. * Cantor-Graae & Selten. Schizophrenia and migration: a meta-analysis and review. *Am J Psychiatry* (in press).

POPULATION VERSUS GENERAL PRACTITIONERS' PERCEPTION TOWARD SCHIZOPHRENIA IN QUEBEC

A. A. Sepehry,* A. Mancini-Marie, E. Stip
Psychiatry, Hopital Louis-H Lafontaine, Centre de Recherche Fernand Seguin, Universite de Montreal, Faculte de Medicine, Montreal, QC, Canada

Background: Negative attitudes towards schizophrenia have been reported in the literature and generally are attributed to insufficient educational programs aiming at raising the public's knowledge about schizophrenia and by large, mental illness. Conversely, high education has been associated with positive attitude toward mental illness. General practitioners' (GP) perception towards people with mental illness (e.g., schizophrenia patients) has repercussions on treatment approaches. The aim of this study was to investigate the difference between Quebec population (QP) and GPs perception and attitude toward people with schizophrenia. *Method:* A questionnaire was mailed out to practitioners. Computerized data collection was conducted at a research center in Montreal. These results were compared to replies of a questionnaire previously conducted with a sample of the QP (n=1001). *Results:* 963 GP responses were collected. First, on a question referring to the attitude in-response to having a neighbor with schizophrenia, GPs were significantly more compassionate by offering more help to the neighbor (GP 58% vs. QP 45%). Second, on a question pertaining to the seriousness of different illnesses (cancer, AIDS, depression, schizophrenia, cardiovascular disease and bipolar), 10% in each group considered schizophrenia to be the most serious illness. Third, what describes most their feelings towards schizophrenia? Compassion was the strongest feeling in both groups, but there was a significant difference between QP and GP (GP=72%, QP=67% p=0.005). Forth, regarding attitudes in-response to having a first relative (e.g., spouse) with schizophrenia. Our findings demonstrate that QP tend to be more open than GPs about the issue. *Conclusion:* Further sensitization of the QP and GPs are warranted. Results from GPs must be interpreted cautiously, since these results need to be further compared with other non-medical professionals (e.g., lawyer, police officer).

POST-TRAUMATIC STRESS DISORDER, SUBSTANCE MISUSE, AND AGE AT ONSET OF PSYCHOSIS IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

S. Sevy,* E. Honig, P. De Rosse, D. Robinson, E. Nunes, A. K. Malhotra
Psychiatry Research, The Zucker Hillside Hospital, Glen Oaks, NY, USA

Purpose of the study: The stress-diathesis model of schizophrenia suggests that early major stressors can precipitate the onset of schizophrenia. It is unclear, however, how early traumatic events may influence the onset of psychosis. We hypothesize that the onset of psychosis is triggered by the co-occurrence of post-traumatic disorder (PTSD) and substance misuse (abuse or dependence). Thus, the purpose of this study was to determine if schizophrenia or schizoaffective disorder patients with PTSD have higher rates of substance misuse (abuse or dependence) and earlier age at onset of psychosis compared to schizophrenia or schizoaffective disorder patients without PTSD. Methods: We conducted a retrospective review of data on 251 patients who met DSM-IV criteria for schizophrenia or schizoaffective disorder at the Zucker Hillside Hospital (Glen Oaks, NY). All diagnoses were assessed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID, version 2). Rates of substance abuse or dependence were compared between schizophrenia or schizoaffective disorder patients with and without PTSD. Age at onset of psychosis was compared between patients with PTSD onset preceding the onset of psychosis (PTSD-First,) and patients with PTSD onset following the onset of psychosis (PTSD-Second). T-Test and Fisher Exact Test procedures were conducted using the Statistical Package for the Social Sciences, version 11.5. Results: 32 out of 251 patients with schizophrenia or schizoaffective disorder had a co-occurring diagnosis of PTSD (6.3%). Compared to non-PTSD patients (n=219), the PTSD group had a higher proportion of females (50% vs. 26%) and higher rates for alcohol ($p<0.01$), cocaine, psychostimulant, and opiate ($p<0.05$) misuse, but not for cannabis and hallucinogens. There were no differences between PTSD-First (n = 18) and PTSD-Second (n= 14) groups for substance misuse, gender ratio, and age at onset of psychosis. Conclusion: Our findings suggest that PTSD in schizophrenia is more frequent in women, and is a risk factor for alcohol, cocaine, psychostimulant, and opiate misuse, but does not seem to precipitate the onset of psychosis.

POSTPARTUM PSYCHOSES IN BRITISH COLUMBIA: 1901–1950

G. N. Smith,* W. G. Honer
Psychiatry, University of British Columbia, Vancouver, BC, Canada

Postpartum psychosis (PPP) occurs in 1 to 2 women per 1000 deliveries and normally presents with prominent affective symptoms. Course of illness tends to be episodic with a relatively good prognosis. About 65% of cases relapse and a third may have residual deficits. A personal or family history of mania increases the risk for PPP. A precipitous drop in estrogen following parturition suggest a biological cause but other evidence indicates psychosocial stress may play a role. These findings suggest that PPP may result from an interaction between biological events interacting with environmental stressors in vulnerable women. Clinical records for every woman with a psychiatric hospital admission in British Columbia between 1901 and 1950 are preserved. Files for all patients with first-episode schizophrenia, schizoaffective disorder, manic depression, or depression were reviewed and DSM-IV diagnoses made. Three groups of women between 15 and 40 years were studied: 327 with PPP within one year of parturition, 314 with a youngest child 2 to 5 year old, and 977 with no children. Median hospital duration was 34 weeks and 48% were Canadian-born. Two thirds were discharged within BC, 25% died in hospital and 9% were deported or sent to another Province. Women with PPP had prominent affective symptoms and 72% had a DSM-IV mood disorder. The likelihood of receiving a diagnosis of schizophrenia increased with longer intervals between parturition and birth. Women admitted 3 to 12 months after parturition had the same rate of schizophrenia as women admitted with a non-PPP. Compared with the other groups, PPP patients had fewer admissions, and shorter hospitalizations. However, 31% spent more than one year in hospital, 20% died in hospital and 38% of those discharged to their community had further admissions. Course of illness in women who were raising young children was similar to that in women without children and worse than that of women with PPP. Those with either PPP or young children were more likely to be immigrants than women with no children. Consistent with previous reports, women with PPP had a better prognosis than other women with psychosis. However, the poorer prognosis and fewer affective symptoms in those with a delayed onset PPP may indicate distinct etiologies. The stress of having small children at home did not influence prognosis although the high number of immigrants in both this and the PPP group suggests an additive effect of these stressors.

THE MANY FACES OF THE PRODROME OF PSYCHOSIS: COMPARISON BETWEEN YOUNG PEOPLE AT ULTRA HIGH RISK (URH) OF PSYCHOSIS AND THOSE PRESENTING WITH NON-PSYCHOTIC DISORDERS

C. A. Stanford,* A. R. Yung, E. J. Killackey, E. M. Cosgrave, K. A. Godfrey, J. A. Buckby, P. D. McGorry
Psychiatry, ORYGEN Research Centre, University of Melbourne, Parkville, Melbourne, VIC, Australia

Background: Help seeking youth with psychotic-like experiences (attenuated or subthreshold psychotic symptoms and brief intermittent psychotic symptoms) are at ultra high risk of imminent development of a full psychotic disorder. For example, 35-40% of individuals presenting to a clinical service (the Personal Assessment and Crisis Evaluation, PACE Clinic) with psychotic-like experiences (PLE) had onset of a psychotic disorder within 12 months. PLEs have also been found incidentally in a proportion of young people presenting with other mental health problems. The aim of this presentation is to show data pertaining to the longitudinal outcome of these young people, in comparison to young people presenting for assistance with PLEs. Method: Young people aged 15-24 years presenting to two different clinics within ORYGEN Youth Health (OYH) were assessed for the presence of PLEs at baseline, 3 months and 6 month follow-up. One of these clinics (PACE) has been developed specifically for individuals presenting with symptoms indicating they are at UHR for psychosis. The other clinic (Youthscope) has been developed for young people presenting with non-psychotic disorders. In both clinics, PLEs were assessed using the Comprehensive Assessment of At Risk Mental State (CAARMS), an interviewer-rated instrument designed to assess attenuated and frank psychotic symptoms. Results: As expected, the proportion of young people

meeting CAARMS criteria for psychosis at 6 month follow-up was higher in the PACE group than the Youthscope group. It was notable that 11% of the Youthscope group met CAARMS criteria for psychosis at 6 month follow-up. Conclusion: A small proportion of young people presenting with non-psychotic disorders will make the transition to psychosis over time. This finding indicates the multidimensional nature of the prodrome of psychosis in help-seeking young people.

DIETARY FATTY ACID AND ANTIOXIDANT INTAKE IN COMMUNITY-DWELLING PATIENTS SUFFERING FROM SCHIZOPHRENIA

M. Strassnig,* J. S. Brar, R. Ganguli
University of Pittsburgh Medical Center, Western Psychiatric Institute and Clinic, Pittsburgh, PA, USA

Introduction: Brain phospholipids are uniquely rich in polyunsaturated fatty acids (PUFAs). Most PUFAs such as α-linolenic acid (18:3n-3), eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3), are essential and must be provided through the diet. PUFAs are also very sensitive to oxidative stress. A decreased essential fatty acid content has been observed in cell membranes of various tissue types of schizophrenia patients, including neural cell membranes. A number of mechanisms may account for these deficits, such as inadequate dietary supply of PUFAs or increased oxidation. It is known that patients with schizophrenia make poor dietary choices. However, whether their dietary fatty acid or antioxidant intake is insufficient and contributes to the observed deficiencies has not been assessed. Methods: After obtaining informed consent, a 24-hour diet recall was administered to elicit nutritional information in 146 outpatients with schizophrenia. Intake of fatty acids and antioxidants such as Vitamin A, C, and E was calculated and compared to US population standards according to the National Health And Nutrition Examination Survey Cycle III (NHANES III) results. Results: Saturated and polyunsaturated fatty acid (PUFA) intake was significantly higher in schizophrenia patients than in controls ($p \leq 0.05$; $p \leq 0.005$ respectively). No differences were found with regard to dietary intake of α-linolenic acid (18:3n-3), eicosapentaenoic acid (20:5n-3) and docosahexaenoic acid (22:6n-3). Similarly, antioxidant intake was not significantly different between schizophrenia patients and controls. Conclusion: The observed cell membrane deficits in PUFA and essential fatty acid content do not appear to derive from decreased dietary supply. Rather, intrinsic membrane phospholipid metabolism abnormalities may be causative. The increased saturated fat intake in schizophrenia patients may contribute to the development of serious medical comorbidities; and further advance the risk for cumbersome metabolic side effects introduced by antipsychotic treatment.

DEVIATIONS OF DEVELOPMENTAL MILESTONES IN PRESCHIZOPHRENIC CHILDREN: A STUDY WITH MOTHER AND CHILD HEALTH HANDBOOK

S. Takagai,* K. J. Tsuchiya, M. Kawai, N. Mori, N. Takei
Psychiatry and Neurology, Hamamatsu University School of Medicine, Hamamatsu, Japan

Background: Previous studies have reported that some deviations from normal early development exist in individuals who later develop schizophrenia. However, the question remains unanswered of what is the exact nature of these deviations. Methods: We obtained contemporaneously recorded, special notes of "the Mother and Child Health Handbook (MCHH)" for 44 individuals with DSM-IV schizophrenia. We also obtained MCHHs from 93 unrelated healthy controls. With the use of data from the MCHH, we investigated various domains of development such as motor, and sensory and linguistic attainments early in life for the patients and the control groups: that is, first appearance of sitting stably, first walking without/with support, first signs of the sense of sight / hearing, and beginning of prattle (speaking one word, two words, and own name). Results: The proportion of "delayed stable sitting (over 8 months of age)" and "late walking with support (> 12 months)" was significantly higher in the patients than in the controls (p=0.01, OR= 2.9, 95% CI: 1.3-6.6; p=0.05, OR=3.7, 95% CI: 1.0-14, respectively). The rate of "delayed response to sounds (> 3 months)" was also significantly higher in patients compared to that of controls (p=0.006, OR=9.4, 95%CI: 1.9-46). The proportion of late start of speaking "one word (> 12 months)" and "two words (> 24 months)" was higher, but at a trend level, in patients than in controls (p=0.07, OR=2.1, 95%CI: 0.9-4.7; p=0.09, OR=2.4, 95% CI: 0.9-6.8, respectively). Conclusions: These findings suggest that preschizophrenic children have a wide range of impaired developments including motor, sensory, and, to a lesser degree, linguistic functions. Although pathophysiological correlates underlying these subtly impaired developments have yet to be elucidated, some tools to detect individuals who are liable to develop schizophrenia at an early stage in order to preclude them from developing the disorder are required.

FERTILITY AND FECUNDITY ESTIMATES FROM AN OUTPATIENT CLINIC FOR PATIENTS WITH SCHIZOPHRENIA IN BRAZIL

A. C. Terzian,* D. Razzouk, J. J. Mari, R. A. Bressan
Medical Sciences Faculty, Federal University Mato Grosso, Cuiaba, Mato Grosso, Brazil

The aim of this study was to determine reproductive rates among patients with schizophrenia from an outpatient clinic in the Federal University of Sao Paulo (Unifesp) in Brazil, and to explore the interactions with demographic characteristics and age at onset of illness. All patients from the outpatient clinic for schizophrenia at Unifesp have received a semi-standardized questionnaire covering questions on fertility and fecundity. Data of Brazilian census had been used for comparison(1). 167 patients fulfilled the questionnaires (61.1% males and 28.9% females), 33 (20%) were ever married and 32 (19.4%) reported being a parent. The mean number of children for all patients was 0.33. In Brazil, the marriage rate for the general population is 45.2%, whereas the fertility for women is 61.5% and the mean number of offspring is 2.28 children. The mean age at onset of illness was significantly higher for parents (28.8 y) than for childless patients (21 y) (t=6.57, df=161, p<0.001). 71.9% of parent patients were ever married. 60% of parent patients had had children after onset of illness. There were no significant differences between the male and female patients in the fertility and fecundity rates when multivariate analysis was performed using variables as marital status and age at onset of illness. There was an association between reduced fertility and early age at onset of illness. Although there was a reduction in reproductive rates when compared to normal population, it is noteworthy that an important number of patients with schizophrenia in Brazil have children. It is paramount to develop services able to attend specific issues related to schizophrenia in developing countries where, resources are scarce and there is no policy for dealing with such demand. (1)IBGE. Censo Brasileiro 2000, Brasilia.

FLUCTUATION IN SELF-ESTEEM AS A MEDIATOR IN THE DEVELOPMENT OF PARANOID BELIEFS

V. Thewissen,* I. Myin-Germeys, R. Bentall, R. de Graaf, W. Vollebergh, J. van Os

Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht University, Maastricht, Netherlands

Studies which have investigated the association between paranoid delusions and self-esteem show inconsistent results. Some studies show an association between paranoid delusions and low self-esteem, while other studies find an association with high self-esteem. A possible explanation for this incongruity is that self-esteem is fluctuating in paranoid patients. A sensitive approach to elucidate the association between fluctuation in self-esteem and paranoid ideation is to study psychosis-like experiences in the general population. In the current study, therefore, the association between fluctuation in self-esteem and psychosis-like experiences was investigated in a general population cohort of 7076 individuals. All individuals were interviewed with the Composite International Diagnostic Interview at baseline (T0) and one (T1) and three (T2) years later (the NEMESIS study). They also completed the Rosenberg Self-Esteem Scale at T0, T1 and T2. Fluctuation in self-esteem was defined as the standard deviation of each participant over the three self-esteem assessments. Paranoid symptoms were defined as the mean of paranoid symptoms over T1 and T2. Logistic regression analyses revealed that fluctuations in self-esteem were strongly associated with the development of paranoid symptoms at T1 and/or T2 (OR 1.42 95% CI 1.23-1.63). This association remained after adjustment for age, sex, education, presence of any baseline DSM-III-R psychiatric disorder, childhood abuse, experience of discrimination, urbanicity, lifetime drug use, single marital status, unemployment, ethnic group, baseline depression, baseline neuroticism, baseline self-esteem, and standard deviation of depression and neuroticism (OR 1.33 95% CI 1.07-1.67). Furthermore, no significant association was found between fluctuations in self-esteem and positive psychotic symptoms in general (excluding paranoid symptoms) at T1 and/or T2 (OR 1.11 95% CI 0.96-1.27) after adjustment for all of the abovementioned confounders. These data suggest that fluctuations in self-esteem are specifically associated with the development of paranoid symptoms, and not with positive symptoms in general. These results are in line with a psychological model suggesting that paranoid beliefs have a defensive function and arise partly as a consequence of dysfunctional efforts to regulate self-esteem.

INFLUENCE OF DURATION OF UNTREATED PSYCHOSIS ON TREATMENT RESPONSE IN SCHIZOPHRENIA: A REPORT FROM INDIA

J. Thirthalli,* M. Philip, T. S. Srinivas, B. N. Gangadhar, D. K. Subbakrishna

Department of Psychiatry, National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore, Karnataka, India

Duration of untreated psychosis (DUP) has been shown to be associated with poorer outcome of schizophrenia. Almost all the reports are from the developed countries. Outcome of schizophrenia is better in India than in the developed countries, but DUP is unlikely to be shorter in India. We examined the influence of DUP on the treatment response in never-treated schizophrenia. Seventy-six patients with never-treated schizophrenia, who presented to National Institute of Mental Health & Neurosciences, Bangalore formed the sample for the study. The diagnosis of schizophrenia was established independently by two psychiatrists using ICD-10 DCR. Patients with comorbid affective and substance use disorders were excluded. The patients were treated with either risperidone (4-8mg/day) or olanzapine (5-20mg/day). Patients and the caretakers were interviewed to assess the month and year of onset of different symptoms of schizophrenia using a semi-structured schedule. Psychopathology was assessed using PANSS at baseline and at weekly intervals thereafter by a rater blind to the status of duration of symptoms. Both PANSS and the onset schedule had good inter-rater reliability. Sixty-three (83%) patients could be assessed at the end of fourth week of treatment and these formed the sample for further analysis [30 males; Mean±SD age: 31.58±8.5 years]. There was no significant difference between the dropped out patients (n=13; 17%) and the followed up patients in any demographic and clinical variables. Both duration since the onset of non-specific changes in behaviour (duration of illness-DUI; mean±SD=28.0±25.9 months) and duration since the onset of any of the psychotic symptoms (duration of psychosis-DUP; mean±SD=22.0±22.6months) had highly significant negative correlations with the percentage of improvement in psychopathology at the end of four weeks (DUI: r=-0.410; p=0.005; DUP: r=-0.533; p<0.001). Total PANSS score at baseline had a positive correlation with percentage of improvement (r=0.315; p=0.015). No other variables including age, age at onset, gender, education and the type and dose of medications had significant association with improvement in psychopathology. Longer duration of untreated psychosis is associated with poorer acute treatment response schizophrenia. The duration of untreated psychosis in India is comparable to that in the developed countries. DUP seems to have similar effect on the outcome of schizophrenia even in a developing country like India.

A PROSPECTIVE STUDY OF ADOLESCENT CANNABIS USE AND EARLY ADULTHOOD PSYCHOTIC SYMPTOMS

J. L. Thompson,* M. F. Pogue-Geile, M. Stouthamer-Loeber, R. Stallings, R. Loeber

Psychology, University of Pittsburgh, Pittsburgh, PA, USA

Several recent prospective studies suggest that cannabis use may increase risk for psychosis. To explore this question further, the current investigation examined data from 777 male participants of the population-based longitudinal Pittsburgh Youth Study to assess the association between cannabis use as reported at annual evaluations from ages 13 to 18 and psychotic symptoms as assessed by the Diagnostic Interview Schedule at a mean age of 22. Eighteen boys reported at least one psychotic symptom that persisted for at least one month (psychosis group), 24 boys met criteria for a DSM-IV depressive and/or anxiety disorder (depression/anxiety group), and 62 met criteria for antisocial personality disorder (APD); the latter two groups were used to address questions of specificity. These groups were compared to the 658 boys not reporting any psychotic symptoms and not meeting criteria for an anxiety or depressive disorder, or APD (control group). Total frequency of cannabis use from ages 13 through 15 (early adolescence) did not discriminate the psychosis and control groups; however, total cannabis use from ages 16 through 18 (late adolescence) was increased among those of the psychosis group compared to controls ($p = .03$, one-tailed). Likewise, whereas the psychosis and depression/anxiety groups did not differ on early adolescent cannabis use, late adolescent use was increased among those of the psychosis group compared to the depression/anxiety group ($p < .05$, two-tailed). Early adolescent cannabis use was

increased among those diagnosed with APD compared to those of the psychosis group ($p < .05$, two-tailed), whereas these groups did not differ on use during late adolescence. Cannabis use across adolescence did not differ between the depression/anxiety and control groups. As expected, the APD group reported more cannabis use than controls during both early ($p < .001$) and late adolescence ($p < .001$). These results suggest that late adolescent cannabis use may be specifically related to early adulthood psychosis compared to nonpsychotic depressive and/or anxiety disorders. Attempts to control for age at first psychotic symptom were limited due to small numbers; thus these results cannot rule out the possibility that the experience of psychotic symptoms led to increased cannabis use in later adolescence in the psychosis group. Alternatively, these findings may reflect that cannabis use increases psychosis risk in vulnerable individuals.

TOXOPLASMOSIS AND SCHIZOPHRENIA: IS THE CAT IN THE HAT?

E. F. Torrey,* R. H. Yolken
Stanley Medical Research Institute, Bethesda, MD, USA

An 1896 editorial in *Scientific American* asked: "Is insanity due to a microbe?" A century later, evidence is emerging that, at least for some patients, the answer is yes. Recent studies have linked several infectious agents to schizophrenia, including influenza, rubella, HSV-2, enteroviruses, and endogenous retroviruses. *Toxoplasma gondii* is an intracellular parasite commonly found in cats and other felines. Many mammals, including humans, are intermediate hosts. Humans may become infected congenitally or by exposure to cat feces, undercooked meat, or contaminated water. *T. gondii* is known to be neurotrophic, to specifically affect glia, and to alter dopamine and other neurotransmitters, and its growth in cultures may be inhibited by antipsychotic drugs. In animals, *T.gondii* may alter behavior, and in acute cases in humans it may cause delusions and hallucinations. Since 1953, 20 studies have examined antibodies to *T. gondii* in individuals with schizophrenia. In 19 of the studies, patients had more antibodies than controls did, the difference being statistically significant in 12 studies. Most striking were increased *T. gondii* antibodies in the sera and CSF of antipsychotic-naive, first-episode patients compared to controls, significant for both serum (n of 36; $p<0.007$) and CSF (n of 34; $p<0.001$). Also of interest are two studies of adults with schizophrenia or bipolar disorder that reported that they had had more exposure than controls to cats in childhood (n of 165, $p=0.02$; n of 262, $p<0.007$). *T. gondii* would thus appear to be a promising infectious agent for further schizophrenia studies. Ongoing studies include four treatment trials using anti-toxoplasmosis drugs as adjuncts for treating schizophrenia and a neuropathological study to ascertain the precise location of *T. gondii* in the human brain.

HOW TO SCREEN PAYCHOSES IN GENERAL POPULATION?

J. K. Ukkola,* J. M. Suvisaari, S. Saarni, S. Pirkola, J. Haukka, J. Lonnqvist
Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland

Background: Based on the Health 2000, a nationwide health survey, we seek to estimate lifetime prevalence of psychotic disorders in Finland. Methods: A nationally representative two-stage cluster sample of 8028 persons (30 years or over) was screened for psychosis using information from the health examination, which included the CIDI interview, and from nationwide health care registers. Screening was based on self-reported psychotic disorder, psychotic disorder diagnosed by a general practitioner in the health examination, psychotic symptoms in the CIDI, and hospitalization because of psychotic disorder according to the Finnish Hospital Discharge Register. Those with a suspected psychotic disorder were assessed using the SCID-I interview. Consensus diagnoses are made according to DSM-IV criteria using information from medical records, available also for those who did not participate in the health examination, and SCID-I interview. A weighting adjustment was applied for the analyses using the SUDAAN statistical survey package. Results: 1.01% of the study population had a self-reported psychotic disorder and 0.65% received a diagnosis of psychotic disorder in the health examination. 2.94% had a hospitalization for psychotic disorder including 0.26% substance-induced psychosis or psychosis due to general medical disorder. 3.30% had a psychotic disorder based on any of these criteria. In addition, 1.91 % received a diagnosis of possible psychotic disorder in the CIDI interview. Altogether, 4.47% had a suspected psychotic disorder when CIDI-diagnoses were included. 14.9% of those who fulfilled the CIDI psychotic symptom screen had a hospitalization for psychotic disorder, whereas only 26.1% of individuals with hospitalization fulfilled the CIDI symptom screen, the rest did not participate in the CIDI interview or did not report their symptoms and hospitalizations. 704 individuals were selected for the SCID-I interview. Consensus diagnoses will be completed by January 2005. Conclusion: Hospital discharge register information is essential to accurately screen psychoses in general population. The prevalence of psychotic disorders in the general population seems to be higher than previously established.

EVIDENCE THAT THE URBAN ENVIRONMENT IMPACTS ON PRE-EXISTING PSYCHOSIS LIABILITY IN ADOLESCENTS WITH ONSET OF PSYCHOTIC SYMPTOMS

J. Van Os,* J. Spauwen, R. Lieb, H. U. Wittchen, L. Krabbendam
Psychiatry & Neuropsychology, Maastricht University, Maastricht, Limburg, Netherlands

Background. Urban birth and upbringing are associated with later risk for schizophrenia. Previous work has suggested that the urban environment impacts on this risk function by facilitating the expression of a pre-existing liability for psychosis, but direct confirmation has been lacking. Objective. To examine synergism between a personal indicator of liability for psychosis and the urban environment, in a sample of adolescents growing up in differentially urbanised environments. Design. A cohort of 1068 adolescents from the EDSP study aged 14-17 years (mean: 15.1 years), growing up in contrasting urban and non-urban environments, completed a self-report measure of psychosis proneness (SCL-90-R psychosis scale) at baseline and at first follow-up around one year post-baseline (T1), and were interviewed by trained psychologists for the presence of psychotic symptoms at the second follow-up on average 3.5 years post baseline (T2). Results. The rate of psychotic symptoms in those exposed to neither psychosis liability nor urbanicity was 13.1%, 12.6% in those exposed to urbanicity alone, 16.3% in those exposed to psychosis liability alone and 31.8% in those exposed to both psychosis liability and urbanicity. The odds ratio (OR) for the combined exposure, adjusted for age, sex, SES, drugs use and family history, was 3.09 (95% CI, 1.88,

5.06), significantly greater than expected if urbanicity and psychosis liability acted independently (expected OR: 1.17, difference with observed OR: ?2=5.5, P=0.019). Conclusion. These findings add credence to the suggestion that a powerful environmental moderator of genetic risk for psychosis is more prevalent in urban environments.

Rates of psychotic symptoms according to the 4 exposure states formed by urbanicity (urban vs. rural) and psychosis liability (high vs. low)

PRESCRIPTIONS UNDER INFLUENCE: IMPACT OF VISITS FROM MEDICAL REPRESENTATIVES ON ANTIPSYCHOTIC PRESCRIPTION BY GENERAL PRACTITIONERS

H. Verdoux,* A. Cougnard, S. Grolleau, R. Besson, F. Delcroix, B. Begaud
EA 3676, Bordeaux 2 University, Bordeaux, France

Objective: To explore the factors associated with prescription of antipsychotic drugs in general practice Method: Survey questionnaires were mailed to all general practitioners (GPs) of South-Western France (n= 3829). As part of this questionnaire exploring practice in patients with early psychosis, GPs were asked to anonymously fill out questions regarding renewal and initiation of antipsychotic drugs marketed in France (amisulpride, risperidone, olanzapine). Factors independently associated with initiation of treatment were explored using logistic regressions. Results: The response rate to the survey was 23.4%. Over the last month, most GPs renewed a prescription of antipsychotic drug (82%), and one of three initiated an antipsychotic drug treatment (33%). After adjustment for age, gender, level of urbanicity at place of practice, the strongest predictor of initiation of antipsychotic treatment was visit of a pharmaceutical company representative promoting an antipsychotic over the last month (OR=3.1; 95%CI 2.3-4.2). Of the prescribers, 60% reported such a visit compared to 32% of non-prescribers. The other independent predictors were attending continuing medical education on schizophrenia over the last year (OR=1.7, 95%CI 1.1-2.5) and psychiatric hospital experience during medical training (OR=1.7, 95%CI 1.2-2.3). The associations were not modified after further adjustment for having diagnosed or hospitalized subjects with possible early psychosis over the last year. Conclusion: The present study shows that initiation of antipsychotic drug is frequent in general practice, and confirms the marked influence of drug promotion on prescribing behavior. The introduction of antipsychotic drugs with less acute extrapyramidal side-effects may have favored antipsychotic promotion strategies targeting GPs and hence extension of prescribing practice in primary care. Despite a lower incidence of extrapyramidal side-effects, antipsychotic drugs may induce severe metabolic side-effects. It is thus necessary to explore at the population level the consequences of a widespread use of antipsychotics in primary care.

PREMORBID DYSFUNCTION AND DEVELOPMENTAL DEVIANCE IN SCHIZOPHRENIC PROBANDS AND THEIR UNAFFECTED SIBLINGS: THE EFFECTS OF PRENATAL STRESS

M. Walshe,* E. Bramon, C. McDonald, A. Fern, M. Cannon, R. M. Murray
P063, Institute of Psychiatry, London, United Kingdom

To examine the relationship between prenatal stress and abnormal childhood features in schizophrenia using data collected on patients with schizophrenia and their unaffected siblings from the Maudsley Family Study. Data on prenatal stress and premorbid childhood characteristics were obtained by maternal interview for 63 schizophrenic patients and 59 of their unaffected siblings. The List of Threatening Experiences (LTE-Q) was used to help mothers recall stressful life events during pregnancy. A question was added to the maternal interview schedule regarding overall stress levels during the pregnancy. Data on premorbid social adjustment (PSA) and premorbid schizoid-schizotypal traits (PSST) were obtained by maternal interview using a modified version of the Cannon-Spoor Scale. Data on childhood milestone development were also collected by maternal interview using the Developmental Scale (DS). Analysis was performed using logistic and linear multiple regression, controlling for age and gender. The two groups differed significantly for PSA ($F=11.7$, $df=1$, $p<0.001$) and PSST scores ($F=18.7$, $df=1$, $p<0.001$); a trend was found for developmental deviance in the proband group ($\chi^2=2.8$, $df=1$, $p=0.09$). A trend was also found for mothers to recall the pregnancy as more stressful ($\chi^2=3.5$, $df=1$, $p=0.06$) for patients than for unaffected siblings. Exposure to prenatal stress alone was not associated with the premorbid function variables but proband status was significantly associated with PSA2 ($B=-0.2$, $p=0.05$) and PSST ($B=-0.3$, $p=0.02$) scores. Probands exposed to prenatal stress had significantly higher PSA1 scores ($B=-0.4$, $p=0.03$). Our results suggest that for schizophrenia patients, there is a relationship between exposure to prenatal stress and abnormalities in premorbid social interaction but not developmental deviance.

URBANICITY AND PSYCHOSIS: A POPULATION-BASED LONGITUDINAL STUDY

M. Weiser,* A. Reichenberg, J. Rabinowitz, D. Nahon, E. Kravitz, G. Lubin, H. Y. Knobler, M. Davidson
Department of Psychiatry, Sheba Medical Center, Tel-Hashomer, Israel

Objective: The association between urban dwelling and increased prevalence of psychotic disorders has been consistently replicated; the underlying social and biological reasons for this phenomenon remain obscure. Increased tolerability for aberrant behavioral in rural areas and hence under-diagnosis, social isolation, migrant status and socio-economic status (SES) in cities have been hypothesized as plausible causes for this association. Method: Subjects were a population-based cohort of 378,347 Israeli-born male adolescents, assessed by the Israeli draft board at age 16-17. Data on population density (in persons/km2), based on address, was obtained from the Israeli Central Bureau of Statistics. We first examined the effect of population density on the risk of being diagnosed with a psychotic disorder in the screening performed on all male adolescents by the Israeli Draft Board, and then examined the effect of population density on the risk of being diagnosed with a psychotic disorder using the Israeli National Psychiatric Hospitalization Case Registry. Cox

regression analysis assessed the effect of urbanicity on hospitalization for psychosis, including social functioning and SES as covariates. Results: Increased population density was associated with a diagnosis of psychotic disorder both in the draft board screening (OR=3.991, 95% CI: 3.395-4.691); increased population density was also associated with increased risk for later hospitalization for psychotic disorder (HR=1.164, 95% CI: 1.055-1.284). When examining risk for hospitalization for psychosis while controlling for social functioning, the effect of urbanicity remained significantly increased (adjusted HR=1.142, 95%CI: 1.029-1.268). Conclusions: The association between urbanicity, measured as population density, and increased risk for psychotic disorders is probably not caused by higher threshold for aberrant behavior in rural areas leading to lower rates of hospitalization in rural areas, nor by social isolation or migrant status in cities. Thus, other social or biological causes must be investigated.

A NATURALISTIC OBSERVATIONAL STUDY OF FIRST EPISODE PSYCHOSIS PATIENTS OVER 12 MONTHS

A. Wheeler,* M. Ang, G. Robinson
Waitemata DHB, Auckland, New Zealand

To explore outcome over 12 months with respect to functioning, treatment adherence, compulsory status and relapse rates for people experiencing a first episode of psychosis(FEP). The study population includes all FEP patients presenting to Waitemata DHB (pop 450,000) who started treatment with an atypical antipsychotic (AP) between 2002-2004. Demographic and clinical data were obtained from the file at baseline (T0) and 12 months (T3) including diagnosis, GAF, CGI, medication, legal status and relapses. Patients who consented within 12 weeks of starting treatment had additional information collected at 3 and 6 months including attitude to medication, side-effects, QOL, substance use and a cognitive assessment. Baseline (T0): 59 FEP patients presented and started on AP treatment in the first year of the study. 73% were male, median age was 21 years and median duration of untreated psychosis was 7 months (range 1-60). At first presentation 49% were assessed under compulsory status and 69% presented to a crisis team or required admission. Median score of severity of illness (CGI-S) was 5="markedly ill". 12-months (T3): Follow-up information was available for 53 patients. At 12-months, 30% were not taking AP treatment and just over half had remained on AP treatment continuously. A significant change in CGI-S was found at the two time points (Mann-Whitney U p=0.000). Median CGI-S score was 2="borderline mentally ill" and 88% of FEP patients showed some improvement (6% no change, 6% minimally/moderately worse). Over their first year 18% of patients had one relapse and at 12-months there was a significant reduction in treatment under compulsory status (13%). Initial service contact for the majority of FEP patients appears to be an acute crisis rather than planned presentation. About a third of FEP patients took APs for less than 6 months and just less than a third were taking no treatment 12 months after their first episode. Additionally 18% of FEP patients had a subsequent relapse requiring admission or crisis/respite care. These results suggest that the year following a first psychotic episode may be a 'critical period' when patients are at high risk of stopping medication and relapsing and therefore intensive monitoring and follow-up may be required. The study team acknowledge the clients and their families who experienced a first episode of psychosis, CRRC and Early Psychosis Intervention staff, and an unrestricted research grant from AstraZeneca NZ Ltd.

GENDER DIFFERENCES IN NEUROLOGICAL SOFT SIGNS IN THE FIRST-ONSET OF PSYCHOSES

J. Zanelli,* P. Dazzan, T. Lloyd, K. Morgan, C. Morgan, P. Fearon, K. Orr, G. Hutchinson, J. Holloway, R. Mallett, J. Leff, P. Jones, R. Murray
Division of Psychological Medicine, Institute of Psychiatry, London, United Kingdom

A higher prevalence of neurological soft signs (NSS) is typically observed in patients with psychosis. It remains unclear whether there is a difference in NSS scores between males and females. We examined gender differences in NSS in a large epidemiological sample of 313 first episode psychosis patients (53% females; mean age 31 years; S. D.11; 47% schizophrenia, 18% mania, 18% depression, 17% other psychosis), and 141 healthy controls (48% females; mean age 33 years; S.D. 10). An expanded version of the Neurological Evaluation Scale was employed, which is composed of four subscales: Primary, Sensory Integration, Motor Coordination and Motor Sequencing. Females with psychosis had significantly higher scores of Primary signs (Mean 3.83; S.D. 4.15) than males with psychosis (Mean 2.99; S.D. 3.16). Age was positively associated with NSS scores. However, scores of Primary signs in females with psychosis remained significantly higher even after having adjusted for age ($p < 0.039$). There was no difference in NSS scores between female and male controls. Significantly higher scores for Primary signs in females with psychosis may reflect gender differences in the pathogenesis underlying NSS. These may be related to differences in genes, hormones and brain development.

CANNABIS USE IN THE YEAR PRIOR TO DIAGNOSIS OF SCHIZOPHRENIA, MANIA, AND OTHER PSYCHIATRIC DISORDERS IN SOUTH LONDON FROM 1965 TO 1999

J. Boydell,* E. Giouroukou, N. Kennedy, P. Fearon, R. Murray
Psychological Medicine, Institute of Psychiatry, London, United Kingdom

Background: The role of cannabis in the aetiology of psychotic disorders is controversial. We have previously found a doubling in incidence of schizophrenia, and a smaller increase in incidence of mania in South-East London over a thirty year time period. This study aimed to investigate whether cannabis use might have contributed to these increases. Aims: To identify and compare any change over time in cannabis use in those first presenting with schizophrenia, mania and other psychiatric disorders in South-East London from 1965 to 1999. Method: The rate of cannabis use in the year prior to first ever presentation with schizophrenia, mania and a random selection of other psychiatric disorders(mainly depression,anxiety and personality disorders)was measured, in seven time periods. Poisson regression modelling was used to determine whether cannabis use changed over time after controlling for age, sex and ethnicity. Results: There was a continuous and statistically significant increase in the incidence of cannabis use in schizophrenia (RDC rate ratio linear trend over 7 time periods: 2.45; 95% CI: 2.2, 2.7) and a trend towards increase in mania (rate ratio linear trend 1.31 95%CI 0.99, 1.7). No statistically significant increase in cannabis use was detected in those with other psychiatric disorders (rate ratio linear trend 0.93:95%CI: 0.8,1.1). All rate ratios were adjusted for age, sex and ethnicity if these improved the fit of the model. Conclusion: The rate of cannabis

use in the year prior to presentation with schizophrenia, in South-East London has disproportionately increased compared to the rate of use in other psychiatric disorders. This provides indirect evidence for an aetiological role for cannabis in the development of schizophrenia.

INCIDENCE RATE RATIOS (IRR) AND 95% CONFIDENCE INTERVALS FOR CANNABIS USE BY DIAGNOSTIC GROUP

***female = 2, male=1**
****ethnic minority = 2, ethnic majority=1**

CANNABIS AND THE COURSE OF SCHIZOPHRENIA

D. van Dijk,* S. de Metz, C. M. Jonkman, W. van den Brink, R. S. Kahn
Dijk en Duin, Castricum, Netherlands

Substance abuse among people with schizophrenia is high by comparison with the general population and is estimated to be 30-50 percent. Cannabis seems to be the substance of choice in this group of patients. Results of previous studies about causes of abuse and its effects on schizophrenia are inconsistent. In order to investigate the effects of the use of cannabis on the course of schizophrenia a cohort study is performed in a Dutch catchment area. After diagnosis was confirmed by a CASH interview, subjects were enrolled into our cohort. Symptomatology, medication, substance abuse, reasons for use and neuropsychological outcome measures were assessed in 176 patients. Baseline results will be presented. During the month before inclusion, 42 percent of the patients used cannabis. Most of the users were male and younger than 30 years of age. Our study suggests that cannabis use might be associated with an earlier onset of the disease. Most of the patients that used cannabis reported compelling reasons for use and experienced a relief of disease related stress by using cannabis. Furthermore they mentioned a tempering effect with regards to the side effects of antipsychotic medication, when using cannabis. Treatment with typical antipsychotics tends to correlate with the use of cannabis. A significant correlation with the use of other street drugs and alcohol was also found. No difference was seen comparing users and non-users with respect to psychopathology or neuropsychological parameters which is in contrast with our hypothesis. Cannabis seems to be associated with earlier onset of the disease and is perceived by patients as self-medication.

4. Neuroanatomy, Animal

EXPRESSION OF DISRUPTED IN SCHIZOPHRENIA 1 (DISC1) PROTEIN IN MOUSE BRAIN

E. Armstrong,* I. L. Schurov, N. J. Brandon, P. J. Whiting
Merck Sharp & Dohme, Harlow, United Kingdom

Disrupted in Schizophrenia 1 (DISC1) was identified as a schizophrenia susceptibility gene that associated with major psychiatric illness in a large Scottish family (Millar et al., 2000). Further studies have linked genetic markers within the DISC1 gene to schizophrenia in a Finnish cohort (Hennah et al., 2003) and in Taiwanese families (Hwu et al., 2003), suggesting that DISC1 may be a general risk factor for schizophrenia. Here, we have studied the expression pattern of DISC1 in postnatal and adult mouse brain using immunohistochemistry and quantitative western blot. In addition we have investigated the specific cell types which express DISC1 in mouse brain using double immunofluorescent staining. DISC1 appears to be broadly expressed in several regions of the brain, but especially in the cortex, hippocampus, hypothalamus, cerebellum and brain stem. Moreover, in the regions where DISC1 is expressed, the intracellular distribution is uneven and clustered. DISC1 exists in a number of isoforms including doublets of approximately 75kDa and 100kDa. Quantitation of the immunoblots clearly shows the unique profile of these isoforms during mouse postnatal development. The expression of the 75kDa and 100kDa isoforms are upregulated at PD25 and PD35 respectively and both remain at a relatively high level through to 6 months of age. These results suggest that DISC1 may play a pivotal role in brain development, in accordance with the neurodevelopmental hypothesis of the aetiology of schizophrenia. Millar, J. K. et al., *Human Molecular Genetics* 2000, 9:1415-1423 Hennah, W. et al., *Human Molecular Genetics* 2003, 12: 13151-13159 Hwa H.G. et al., *Molecular Psychiatry* 2003, 8: 445-452.

THE EFFECT OF RISPERIDONE ON SPATIAL MEMORY IN RATS WITH HIPPOCAMPAL DAMAGE

M. E. Bardgett,* H. N. Foozer, K. S. Wasen, J. R. Borden, M. S. Griffith
Psychology, Northern Kentucky University, Highland Heights, KY, USA

Abnormalities in hippocampal structure or function have been commonly reported in some individuals with schizophrenia, and these abnormalities have been associated with memory deficits. We have recently reported that risperidone, an atypical antipsychotic drug with demonstrable cognitive enhancing properties, modestly improves memory in rats with hippocampal damage. The purpose of this research was to determine if other doses of risperidone, as well as clozapine, could improve memory in rats with hippocampal damage. Adult male Long-Evans rats were pre-trained in a delayed spatial alternation (DSA) task prior to lesion surgery. Stereotaxic surgery was performed on all rats and half of them received direct infusions of the excitotoxin, NMDA, into the dorsal hippocampus. Infusions of NMDA decreased hippocampal area by 50%. One week after surgery, animals in the control and NMDA lesion groups began receiving daily injections of saline, risperidone (0.1, 0.2, or 0.4 mg/kg) or clozapine (3.0 mg/kg) (n = 5-8 per group). One month after the initiation of drug treatment, animals were tested in the DSA task for two weeks and in the Morris swim maze for one week. While hippocampal damage significantly impaired performance in each memory paradigm, none of the risperidone doses nor clozapine significantly improved memory in the lesioned animals. Unlike our initial work, these data suggest that risperidone does not modestly improve memory in rats with hippocampal damage. This discrepancy between studies may be attributable to differences in rat strain or the inclusion of a pre-training regimen. Nonetheless, continued research with animal models of hippocampal damage may useful in identifying new pharmacological approaches that specifically target memory impairments produced by hippocampal dysfunction. This work was supported by grants from Janssen Pharmaceutica Products L.P., and the KY-Idea Networks of Biomedical Research Excellence Program, grant number P20-RR16481.

REGULATION OF OREXIN/HYPOCRETIN NEURON ACTIVITY BY DOPAMINE AGONISTS: INVOLVEMENT OF THE DOPAMINERGIC INNERVATION OF THE LATERAL HYPOTHALAMUS?

M. Bubser,* L. L. Jackson, J. R. Fadel, J. H. Meador-Woodruff, A. Y. Deutch
Department of Psychiatry, Vanderbilt University Medical Center, Nashville, TN, USA

Orexin neurons are found only in the lateral hypothalamus/perifornical area (LH/PFA) from where they project widely throughout the brain. Among these projections is one to the midbrain dopamine (DA) neurons that project to corticolimbic sites. It is not known if DA neurons in turn innervate and/or regulate orexin neurons. We examined if the LH/PFA receives a DA innervation, determined the source of any DA afferents, and determined if LH/PFA cells express any DA (D1-5) receptors. Immunostaining for DA revealed a moderately dense DA innervation of the LH/PFA that consisted of thin, varicose fibers that emanated from both the median forebrain bundle and midline hypothalamic DA cells. Both dopaminergic (tyrosine hydroxylase+-dopamine-β-hydroxylase [DBH]-) and noradrenergic (DBH+) axons were seen in close proximity to orexin cells. Injections of Fluoro-gold into the LH/PFA revealed that cells in the ventral tegmental area contribute to the DA innervation of the LH/PFA. D2 receptor mRNA was rarely expressed by LH/PFA cells; none of the other DA receptor transcripts was expressed in the LH/PFA. We subsequently examined if DA receptor agonists activate orexin neurons, as reflected by induction of Fos. Mixed (apomorphine) and selective D1 (A-77637)- and D2 (quinpirole)-like DA receptor agonists induced Fos in orexin cells, with a greater effect on orexin neurons medial to the fornix. The activation of medial orexin neurons by apomorphine was not significantly attenuated by pretreatment with D1-like (SCH 23390) or D2-like (haloperidol) DA receptor antagonists, suggesting that DA agonist-induced activation of orexin cells may occur transsynaptically. However, excitotoxic lesions of the nucleus accumbens, which was previously shown to modulate the activity of lateral orexin neurons, did not dampen apomorphine-induced activation of orexin cells. Taken together, the current findings strengthen the notion of functional differences between medial and lateral orexin neurons, with the medial and lateral cell population being more responsive to DA receptor agonists/psychostimulants and certain antipsychotic drugs, respectively. Our data also suggest that DA agonists activate orexin cells in an indirect manner. It is suggested that the alteration of orexin cell activity may contribute to the effects on dopaminergic and antipsychotic drugs. Supported by

MH 45124 (AYD), MH 57995 (AYD) and MH 53327 (JHMW) and Meharry-Vanderbilt Alliance Training grant T32 MH65782 (LLJ).

INTRINSIC SENSORY DEPRIVATION INDUCED BY NEONATAL CAPSAICIN TREATMENT INDUCES CHANGES IN ADULT RAT BRAIN AND BEHAVIOUR RELEVANT TO SCHIZOPHRENIA

L. A. Chahl,* P. Newson, A. Lynch-Frame, R. Roach, S. Bennett, V. J. Carr
School of Biomedical Sciences, University of Newcastle, Newcastle, NSW, Australia

It has been proposed that schizophrenia might result from intrinsic sensory deprivation (Chahl, unpublished) leading to reduced synaptogenesis during development, reduced neuropil and increased neuronal density, such as has been found in the prefrontal cortex of subjects with schizophrenia [1]. In support of this proposal is evidence that deficits in pain sensation are present in subjects with schizophrenia [2]. Vascular responsiveness is also altered in schizophrenia as shown by reduced niacin skin flare [3] suggesting that capsaicin sensitive primary afferent neurons mediating axon reflex flare might be abnormal in schizophrenia. Capsaicin acts on vanilloid (TRPV-1) receptors located on neuropeptide-containing unmyelinated primary afferent neurons involved in pain, axon reflex flare and neurogenic inflammation. If given to neonatal rats, capsaicin produces life-long loss of these neurons. In the present study rats under ice anaesthesia were treated on post-natal day 2 with capsaicin, 50 mg/kg subcutaneously (sc), or vehicle. Capsaicin treated rats developed normally except for excessive face grooming in some animals and slightly, but not significantly, lower body weight than controls. At 8 weeks of age the capsaicin treated animals were hyperactive compared with controls, exhibiting significant increases in locomotor activity and other behaviours such as rearing and grooming. The hyperactivity was abolished by haloperidol, 1mg/kg sc. At 8 weeks of age the average brain weight of capsaicin treated rats was significantly less ($p<0.05$, Students t test) than that of controls (control mean ± sem 1.89 ± 0.04g, N=9; treated 1.78 ± 0.02g, N=10). Measurements of coronal sections at several brain levels showed significant reductions in cross-sectional area ($p<0.01$, ANOVA) and cortical thickness ($p<0.05$). Hippocampal area at -3.60mm Bregma, and corpus callosum thickness at 1.20mm Bregma were also significantly reduced ($p<0.05$). Neuronal counting following Nissl staining showed significantly increased neuronal density in the cingulate cortex (control 2056 ± 78; treated 2416 ± 13 per 10-4 mm2; $p<0.05$, t test). Thus intrinsic sensory deprivation induced by neonatal capsaicin treatment produces behavioural and brain changes in young adult rats of relevance to schizophrenia. 1. Selemon, LD, Goldman-Rakic, PS (1999) *Biol Psychiatry*, 45, 17-25. 2. Blumensohn, R (2002) *J Nervous Mental Disorders*, 190, 481-483. 3. Messamore et al (2003) *Schizophrenia Res*, 62, 251-258.

EFFECTS OF PRENATAL TREATMENT WITH A DNA METHYLATING AGENT ON BRAIN ANATOMY AND BEHAVIOR IN ADULT RATS

K. A. Davoli,* H. F. Herman, E. Thiels, A. A. Grace
Center for Neuroscience (Neurobiology), University of Pittsburgh, Pittsburgh, PA, USA

We found previously that treating rats with the DNA methylating agent methylazoxymethanol acetate (MAM) on prenatal day 17 yields anatomical alterations and sensorimotor gating deficits in the adult animal analogous to those observed in human schizophrenia patients. Here, we examined the effect of MAM on (1) gross brain anatomy and (2) performance on a hippocampus- and prefrontal cortex-dependent behavioral task. We observed significant brain hypotrophy that was reflected in a decreased cortical coverage of the dorsal brain surface as well as neuronal disarray in the pyramidal cell layer of the dorsal hippocampus in MAM-treated rats. Lateral ventriculomegaly was also apparent. These observations are characteristic of the effects of other neurodevelopmental manipulations and are arguably isomorphic with human schizophrenia. To investigate whether these anatomical alterations might parallel behavioral deficits, we used an 8-arm radial maze task for which good performance requires proper hippocampal and prefrontal cortical function. MAM-treated rats were slow to learn the task compared to controls, and their performance was susceptible to distraction. Taken together with our previous findings, these results suggest that MAM-treated rats may prove to be useful for replicating relevant aspects of the brain state of human schizophrenia patients in rodents as a step towards a better understanding of this complex disorder and to develop more effective treatments. Support Contributed By: NIMH #MH 57440, NIH #T32 NS007433-06, a University of Pittsburgh O. E. L. Small Grant, and the Center for the Neural Basis of Cognition.

ABNORMALLY ENHANCED SYNAPTIC PLASTICITY IN THE PREFRONTAL CORTEX OF THE NEURODEVELOPMENTAL DISRUPTION RODENT MODEL OF SCHIZOPHRENIA: RELATION TO STRESS VULNERABILITY

Y. Goto,* A. A. Grace
Departments of Neuroscience, Psychiatry, and Psychology, University of Pittsburgh, Pittsburgh, PA, USA

Accumulating evidence suggests that the pathophysiology of schizophrenia involves neurodevelopmental deficits as well as dopamine (DA) and glutamate (GLU) dysfunctions in the prefrontal cortex (PFC). Disruption of neurogenesis by prenatal treatment with methylazoxymethanol acetate (MAM) in rodents has been shown to induce anatomical and behavioral deficits analogous to those observed in schizophrenia patients. In this study, we investigated the alterations in synaptic plasticity induction mediated by DA-GLU interaction at hippocampal (HPC) inputs into the PFC of MAM-treated animals. In vivo electrophysiological recordings were obtained from the PFC of adult animals that received either MAM or saline at gestational day 14. High frequency tetanic stimulation was given to the HPC that has been shown to induce DA-dependent long term potentiation (LTP) in the PFC. High frequency stimulation in the HPC induced LTP in the PFC of both MAM (n=8) and control (saline-treated; n=7) animals. However, LTP in MAM animals was significantly larger in amplitude than that in control animals, suggesting that synaptic plasticity was abnormally augmented in the PFC of MAM animals compared to the normal condition. In addition, the effects of acute stress exposure on synaptic plasticity in the PFC was also investigated by placing MAM and saline-treated animals in a cold room at 4 degrees C for 10, 30, and 120 minutes. Preliminary results showed that 10 minutes of stress exposure increased the magnitude of LTP induction in control animals compared to the non-stress exposed condition (n=5), although LTP induction was moderately impaired by 30 minutes (n=4), and more robustly disrupted by 120 minutes, of stress exposures (n=4). On the other hand, 10 minutes of stress exposures moderately disrupted LTP induction in MAM animals (n=4). Impair-

ment of LTP induction with 30 minutes of stress exposures in MAM animals (n=4) was already comparable to that induced with 120 minutes of stress exposures in control animals. These results suggest that interference of early cortical development induces altered DA-GLU interactions in the PFC, causing abnormal enhancement of plasticity; as a result, information processing in this region becomes more vulnerable to stress. Support Contributed By: USPHS MH57440, DA15408, and NARSAD.

THE ROLE OF PREFRONTAL CORTICAL NMDA RECEPTORS IN WORKING MEMORY

R. Greene,* J. M. Finlay
Psychiatry, UTSW, Dallas, TX, USA

Deficits in working memory have been observed in association with both schizophrenia and, in healthy volunteers, exposure to NMDA receptor antagonists such as PCP or ketamine. However, the localization of the responsible NMDAR deficit is not well characterized. We have developed a technique to induce a localized gene deletion of the essential NR1 subunit of the NMDAR using a floxed NR1 knock in a mutant in conjunction with an adeno viral vector mediated delivery of Cre-recombinase. This technique allows molecular, temporal and anatomical specificity of the lesion. Mutant mice (containing the fNR1 knock in) are trained on an alternating T-maze task requiring working memory for successful performance. Bilateral injections of 1.0 uL of AAV-Cre (~10exp8 titer) are made into the prefrontal cortical region and after 10 days recovery, the mice are tested on the maze. Following test completion, the mice are assessed for both Cre recombinase immunohistochemistry and for mRNA NR1 message. Our preliminary findings show the feasibility of inducing a localized gene deletion of the NR1 gene in the PFC and behavioral testing is now in progress.

PERINATAL ADMINISTRATION OF STRESS-SENSITIVE NEUROSTEROID ALTERS RAT CORTICAL DEVELOPMENT

A. Grobin,* S. S. Gizerian, J. H. Gilmore, J. A. Lieberman
Psychiatry, University of North Carolina, Chapel Hill, NC, USA

Non-specific stress in the environment is thought to play a critical role in the development of schizophrenia vulnerable phenotype: the most prevalent associated factor is prolonged labor. Stress increases neurosteroid levels, and neurosteroids are potent endogenous modulators of $GABA_A$ receptor function. Since $GABA_A$ receptors are thought to be involved in the migration and axon pathfinding of developing neurons, it is possible that aberrant neurosteroid level regulation plays a role in creating a schizophrenia vulnerable phenotype. To determine if infection could alter neurosteroid levels during development, pregnant rats were administered LPS and allowed to deliver. Four week old male rat brains exposed to LPS in utero has elevated neurosteroid levels (3.0± 0.4 ng/g vs 1.7 ±0.3 for litter mates). To investigate potential consequences of altered neurosteroid levels, BrdU labeling of E17 mitotic cells was used to determine the effects of neurosteroid administration on lamination of the parvalbumin-positive neuron population in P21 animals. Immunohistochemical staining and analysis of variance revealed that allopregnanolone administration (10 mg/kg, i.p.) during the first week of life alters the localization of the E17-born cells in the prefrontal cortex ($F=6.743$, $p<0.01$, n= 9-13 animals/group) without altering the number of BrdU-positive cells ($F=0.8263$, p=n.s.) or the volume of the cortex ($F=0.025$, p=n.s.). The localization of the parvalbumin-positive subpopulation of BrdU-labeled cells was not changed ($F=0.4937$, p= n.s., n= 9-13 animals/group). Moreover, neither the number or density of TH+ fibers in the PFC was altered by neonatal neurosteroid administration. Neurosteroid levels may affect the velocity of neuronal migration though the developing cortex, with implications for later developmental processes, including the laminar placement of specific cell populations. Neurosteroid levels may be important in the late events of normal CNS development, including lamination, and could therefore play a role in abnormal development.

DECREASED THALAMIC NEURONAL NUMBER AND CORTICAL VOLUME IN A PRIMATE MODEL OF SCHIZOPHRENIA

L. D. Selemon,* L. Wang, M. B. Nebel, J. G. Csernansky, P. S. Goldman-Rakic, P. Rakic
Dept. Neurobiol., Yale Univ. Sch. Med., New Haven, CT, USA

Thalamic neuronal number and cortical volume were examined in macaques that had been exposed to x-irradiation during the first trimester of gestation to explore whether prenatal disruption of thalamic neurogenesis could produce schizophrenia-like pathology. In vivo high resolution, magnetic resonance scans (0.7mm slices with 0.625mm x 0.625mm voxel dimensions) were acquired on a 1.5 Tesla LX GE Advantage scanner from 3 early fetally irradiated monkeys (eFIMs), 3 midgestationally irradiated monkeys (mFIMs) for comparison and 7 non-irradiated controls (CONs). The frontal lobe was separated from the posterior lobes using anatomical landmarks. The images were manually segmented into cortical gray matter and cortical white matter. Frontal lobe cortical gray matter volume (FGMV), frontal lobe white matter volume (FWMV), posterior lobe (parietal, temporal, occipital) cortical gray matter volume (PGMV), and posterior lobe cortical white matter volume (PWMV) were measured by extracting cortical gray and white voxels using a surface-based method. In these same 3 adult eFIMS, 2 infant eFIMs, 1 adult and 4 infant mFIMs, and 4 adult and 2 infant CONs, postmortem stereologic cell counting was performed on a series of 40-um thick, Nissl-stained sections using the optical disector method to determine total neuronal number in the whole thalamus, mediodorsal (MD), pulvinar (PUL), and anterior (A) nuclei. In the eFIMs, total neuronal number was reduced in MD (32%), and there was a trend reduction in the whole thalamus (18%). Reductions in the PUL (8%), and A (10%) in the eFIMS were not significant. Thalamic neuronal number did not differ from CONs in the mFIMs. Significant reductions in FGMV (28%) and PGMV (22%) were found in the mFIMs whereas the reductions of FGMV (13%) and PGMV (17%) in the eFIMS did not reach statistical significance in this small sample. Greater reductions in FWMV (26% for eFIMS; 29% for mFIMs) and PWMV (36% for eFIMs; 38% for mFIMs) were observed in both groups. The pattern of pathology observed in early gestationally irradiated monkeys, i.e., reduction in MD neuronal number in conjunction with a modest, non-significant reduction in cortical gray matter volume, is similar to the neuropathology described in schizophrenia patients. In contrast, exposure to irradiation in midgestation, during the period of neocortical neurogenesis, produced more prominent pathology in the cortex with sparing of the thalamus. Supported by MH59329 (LS) and MH71616 (JC).

5. Neuropathology, Biochemistry

TOTAL AND SER-9-PHOSPHORYLATED GSK-3BETA IN SCHIZOPHRENIA AND ITS TREATMENT

G. Agam,* N. Kozlovsky, C. Nadri, R. H. Belmaker
Ben-Gurion University of the Negev, Beer-Sheva, Israel

A burst of high impact studies during the last months suggests the involvement of phosphorylation-deactivation of glycogen synthase kinase (GSK)-3β on its Ser-9 residue in antipsychotics and psychotomimetics action. Glycogen synthase kinase (GSK)-3β is highly abundant in brain and is a negative regulator of signaling cascades (e.g. phosphatidylinositol-3-kinase/AKT & Wnt). Components of these cascades are altered in schizophrenia. Using Western blotting we found ~40% lower activity and protein levels of GSK-3β in postmortem frontal cortex of schizophrenia patients; occipital cortex GSK-3β in schizophrenia patients is not reduced, suggesting regional specificity. Low GSK-3β protein levels in schizophrenia patients frontal cortex were replicated by others. We have recently found that CSF GSK-3β protein levels in schizophrenia patients are also 28% lower vs control subjects. In the schizophrenia-related neonatal ventral hippocampal lesion rat model frontal cortex GSK-3β protein levels in the lesioned rats were found significantly lower than in sham rats, favoring perinatal insult as a cause of low GSK-3β in schizophrenia. Rat frontal cortex total GSK-3β protein levels and GSK-3 activity are not altered following chronic administration of the mood stabilizers lithium or valproate or the neuroleptic drugs haloperidol or clozapine. Since the levels of kinases, in general, and GSK-3, in particular, are regulated not only at the transcription level but also by phosphorylation, and taken recent growing interest in P-Ser-9 GSK-3β in psychiatry we conducted a study to evaluate the in vivo effect of these psychotropic drugs on frontal cortex protein levels of the P-Ser-9 form of GSK-3β. Chronic administration of haloperidol to rats (21dX10mg/kg i.p.) resulted in a significant reduction in frontal cortex P-Ser-9 GSK-3β protein levels, while chronic administration of clozapine (25g/l) or of valproate (12g/l supplemented with 300mg/l saccharin) in drinking water (21d) caused significant elevation. Mice treated chronically with lithium (33dX2.5g/kg) exhibited the most prominent elevation in P-Ser-9-GSK-3β. The results support the notion that GSK-3β may be a common target for mood stabilizers and neuroleptics. Further studies will be aimed at determining whether nonspecific neonatal damage or only specific factors affect total or P-Ser-9 GSK-3β.

LASER CAPTURE MICRODISSECTION REVEALS DEFICIENT HIPPOCAMPAL NEURON EXPRESSION OF PROTEASOME, UBIQUITIN, AND MITOCHONDRIAL GENES IN MULTIPLE SCHIZOPHRENIA COHORTS

C. A. Altar,* L. W. Jurata, A. L. Lemire, M. J. Webster, J. A. Brockman
Research, Psychiatric Genomics, Gaithersburgh, MD, USA

Laser-captured hippocampal dentate granule neurons from 2 groups of schizophrenic and control cases were examined for alterations in gene expression using cDNA microarrays and RT-PCR to confirm changes. Compared with 24 control cases, the 22 schizophrenic patients in both groups revealed decreases in clusters of 243 genes that encode for protein turnover (proteasome subunits and ubiquitin), mitochondrial oxidative energy metabolism (isocitrate, lactate, malate, NADH and succinate dehydrogenases; cytochrome C oxidase and ATP synthase) and genes associated with neurite outgrowth, cytoskeletal proteins, and synapse plasticity. These changes were not obtained in 9-10 cases with bipolar disorder or major depressive disorder, or in dentate neurons of rats treated chronically for 3 weeks with 30 mg/kg/day clozapine, which was most commonly taken by the patients. The changes were not associated with patient demographics including age, sex, brain weight, body weight, post-mortem interval, or smoking or drug histories. Brain pH contributed to the variance of some of the genes but was mostly independent of a much larger disease effect. Interestingly, many of the genes whose expression varied with pH are themselves involved in hydrogen ion transport, suggesting a physiological basis for this relationship and for the 0.1 pH unit decrease measured in 115 schizophrenic brains versus 90 control brains. The decreases in hippocampal neuron gene expression are consistent with imaging, mRNA, and protein studies of the frontal cortex in schizophrenia, and suggest that a metabolic deficit of hippocampal neurons may characterize schizophrenia. We will describe our selection and use of 16 gene subsets to screen novel antipsychotic drugs by their ability to reverse these mRNA changes.

Statistically Significant Groupings of Gene Changes into Functional Pathways Based on Binomial Probability Test and Fisher Exact Test Used in the EASE analyses.

NA = Grouping category is not available for that analysis. Binomial score is derived from software developed at Psychiatric Genomics.

DOPAMINE-INTERACTING MOLECULES ARE ALTERED IN SCHIZOPHRENIC PREFRONTAL CORTEX

K. L. Baracskay,* V. Haroutunian, K. Davis, J. H. Meador-Woodruff
Psychiatry, University of Michigan, Ann Arbor, MI, USA

Considerable evidence suggests schizophrenic patients exhibit neuropathology in neurotransmitter systems, particularly dopamine, glutamate and serotonin. Alterations in several recently identified molecules that mediate dopaminergic signal transduction have been found in schizophrenia, supporting the hypothesis of altered dopaminergic neurotransmission. To further explore these findings, we measured transcript expression of three proteins involved in the dopamine signaling cascade in postmortem prefrontal cortex of schizophrenic and control patients. The mRNA of DARPP-32, a downstream effector of dopaminergic, serotonergic and glutamatergic neurotransmission, was similar in both groups. Transcript levels of spinophilin, a protein enriched in dendritic spines that modulates excitatory neurotransmission, were similar in Brodmann area (BA) 32 of control and schizophrenic patients. In contrast, spinophilin mRNA was increased (~22%) in schizophrenic BA9 compared to

control. Calcyon mRNA, encoding a protein which potentiates crosstalk between D1 dopamine receptors and Gq/11 receptors, was increased in schizophrenic prefrontal cortex (both BA9 and BA32) by ~25%. The alterations in spinophilin and calcyon mRNA levels in schizophrenic prefrontal cortex provide further evidence of altered dopaminergic neurotransmission in the pathophysiology of schizophrenia. Supported by MH53327.

NEUROCHEMICAL MARKERS FOR SCHIZOPHRENIA, BIPOLAR DISORDER, AND MAJOR DEPRESSION IN POSTMORTEM BRAINS

B. M. Barci,* E. F. Torrey, M. J. Webster, J. J. Bartko, J. H. Meador-Woodruff, M. B. Knable
The Stanley Medical Research Institute, Bethesda, MD, USA

Background: Previous studies of postmortem neurochemical markers in severe psychiatric disorders have been carried out on different brain collections, making it difficult to compare results. Methods: One hundred RNA, protein, and other neurochemical markers were assessed in a single set of 60 postmortem brains (15 each with schizophrenia, bipolar disorder, major depression without psychosis, and unaffected controls) in relationship to 7 neurochemical systems. Quantitative measures of continuous variables for prefrontal, hippocampus, anterior cingulate, and/or superior temporal cortex were analyzed from published and unpublished studies by 56 research groups. Results: Before correcting for multiple comparisons, 23 percent (23/100) of markers were abnormal in ? 1 region, with most indicating decreased expression. The largest percentage were associated with the developmental/synaptic (10/22) and GABA (3/7) systems. Bipolar disorder (20) and schizophrenia (19) had the most abnormalities, with a 65 percent overlap. When all brain areas were considered together and corrected for multiple comparisons, reelin, parvalbumin, and GAD67 were the most abnormal. Conclusions: Confirming other studies, the GABA and developmental/synaptic neurochemical systems are promising areas for research on schizophrenia and bipolar disorder. Such research should include tissue from both diseases and additional brain areas should be assessed.

Significant Neurochemical Markers Following Dunn-Sidak Correction for Multiple Comparisons

*** total number of parvalbumin positive cells**
**** parvalbumin positive cells corrected for volume of tissue section**

NEUREGULIN SIGNALING ABNORMALITIES IN SCHIZOPHENIA

J. D. Buxbaum,* K. Davis, J. Gorman, V. Haroutunian, Y. Jiang, P. Katsel, M. O'Donovan
Psychiatry, Mount Sinai School of Medicine, New York, NY, USA

Oligodendrocyte abnormalities have been implicated in schizophrenia through genetic, microarray, and imaging studies. The cause of the oligodendrocyte abnormalities can involve alterations in neuregulin signaling, as evidenced by association of variants in the neuregulin (NRG1) gene with schizophrenia, and alterations in expression of the neuregulin receptor ErbB3 observed in multiple, postmortem microarray analyses. ErbB3 has impaired tyrosine kinase activity and therefore cannot activate intracellular signaling cascades on its own. For this reason, appropriate signaling through ErbB3 requires the formation of heterodimers with the neuregulin co-receptors ErbB2 or ErbB4. ErbB4, which is also known as HER4, is unique among the neuregulin co-receptors in that it can undergo regulated proteolysis at or within the transmembrane. In this process, ErbB4 is cleaved by the gamma-secretase protease complex, comprised of aph-1, pen-2, nicastrin, and presenilin (the latter genetically implicated in Alzheimer disease). Cleavage of ErbB4 liberates a cytoplasmic peptide, which can then act as a cytoplasmic and/or nuclear signal. As cleavage is activated by binding of extracellular ligands to ErbB4, this provides a unique method to transduce signals from outside the cell to the cytoplasm and nucleus. Given that neuregulin signaling in oligodendroctyes directly controls myelination, and modulates the expression of myelin-related genes, it is interesting to dissect the signaling pathway of neuregulin. We have carried out yeast two-hybrid analysis with the cytoplasmic domain of ErbB4 and identified a transcription factor and a scaffolding protein. The scaffolding protein likely maintains a signaling complex at the cell surface, which regulates the cellular response to neuregulin. We are now studying the potential role for the transcription factor in neuregulin-mediated gene expression. Furthermore, we are examining the expression of the signaling complex in postmortem brain tissue in controls and schizophrenic subjects. Finally, we are testing for genetic association of these genes in a case-control cohort to determine whether these genes represent genetic susceptibility genes for schizophrenia.

PROTEOME ANALYSIS OF THE ANTERIOR CINGULATE CORTEX IN MAJOR PSYCHIATRIC DISORDERS

D. R. Cotter,* C. L. Beasley, K. P. Pennington, R. Wait, M. J. Dunn
Psychiatry, Royal College of Surgeons in Ireland, Dublin, Ireland

Background: Marked alterations in neuronal and glial size and density have been observed in the anterior cingulate cortex (ACC) in schizophrenia, major depressive disorder (MDD) and bipolar disorder (BPD). The basis for these morphological changes are not known. Recent microarray and proteomic investigations have suggested that metabolic and mitochondrial function is dysregulated in schizophrenia. We have undertaken a proteomic analysis of the anterior cingulate cortex in these disorders in an attempt to further characterise the protein changes which are associated with cytoarchitectural alterations in this brain region. Methods: Two dimensional electrophoresis (2DGE) and mass spectrometry were used in this study to compare and identify disease-specific protein changes in schizophrenia, MDD and BPD in the ACC. We applied immobilised pH gradients (IPG) 4-7 and 6-9 to the Stanley Foundation Brain Consortium brain series (comprising 15 subjects per group from each of MDD, BPD and schizophrenia). Gel image analysis was undertaken using Progenesis 2003.1 (Nonlinear Dynamics). Data was analysed by ANCOVA. Results: 33 spots were differentially expressed in one or more disease group. Proteins present within 23 of these spots were identified. These represented 17 distinct proteins; aconitate hydratase, malate dehydrogenase, fructose bisphosphate aldolase A, Glyceraldehyde-3-phosphate dehydrogenase, ATP synthase, succinyl CoA

ketoacid transferase, carbonyl reductase, carbonic anhydrase, beta tubulin, dihydropyrimidinase related protein-2, neuronal protein 25, glutamate dehydrogenase, glutamine synthetase, sorcin, vacuolar ATP synthase, creatine kinase and guanine nucleotide binding protein G(I). Conclusion: Our findings concur with recent studies demonstrating altered metabolism in schizophrenia. We also observed similar changes in bipolar disorder and major depressive disorder. While our findings in part replicate previous observations, we have also identified novel proteins; their potential role in the pathophysiology of these major psychiatric disorders will be explored further. Acknowledgement: Research supported by the Stanley Medical Research Institute and the Wellcome Trust.

QUALITATIVE AND QUANTITATIVE CHARACTERIZATION OF PHOSPHATIDYLETHANOLAMINE ON HUMAN ERYTHROCYTES MEMBRANE: A PRELIMINARY METHOD TO A FURTHER EXPLORATION OF MEMBRANE HYPOTHESIS IN SCHIZOPHRENIA

F. Ferreri,* H. Trespalacios, C. Tessier, C. Wolf, P. Nuss
Inserm U538, Paris VI University, Paris, France

The aim of our research is get more precise knowledge of the repartition of phosphatidylethanolamine (PE) on the 2 membrane leaflets in normal subjects to get a reference level. Membrane hypothesis in schizophrenia postulates the existence of an abnormal phospholipids (PL) ratio in erythrocytes and brain cells membranes in schizophrenic patients compared to normal controls. For instance the sPLA2 overactivity in the serum of schizophrenic patients had been implied in this process. Other authors suggest an increased turn-over of phospholipids in the membrane of schizophrenic patients. Another perspective may look more in detail into the membrane structure to understand the general findings concerning these lipid abnormalities. The membrane structure is not homogenous neither in its PL composition between the inner and the outer leaflet nor in its longitudinal composition (segments of membrane expresses specific characteristic, in particular a detergent resistance due to a specific PL arrangement). PE has been chosen because it has a key role among the PL implicated in the membrane hypothesis in schizophrenia. Erythrocytes from normal subjects have been labelled with TNBS (trinitrobenzensulfonic acid) a colorimetric probe able to specifically label the externally located PE of the erythrocytes membrane. The experimental condition have been chosen in order to get a non permeating labelling. Once this outer PE labelling done, an extraction of all of the membrane PL was processed. Labelled PE (external) and non-labelled PE was separated by thin layer chromatography (TLC). After recuperation of the 2 distinct PE spots on the TLC plate, and isolation of PE, the measure of the total PE amount and the nature and the amount of their constitutive fatty acids was assessed by mass spectrometry. This method was proven to be a reliable and sensitive way to determine the amount and the localisation of phosphatidylethanolamine in the erythrocytes bilayer membranes. This method confirmed previous findings with other methods concerning the asymmetrical PE partition between the inner and the outer layer (PE asymmetrical ratio = 4-6/96-94) Differences in the fatty acid composition of this phospholipid can also be analysed by this method. This method is a first step towards a further knowledge of the membrane hypothesis in schizophrenia.

ROSTROCAUDAL DIFFERENCES AND CORRELATIONS BETWEEN BDNF AND NMDA RECEPTOR MRNA IN THE HIPPOCAMPUS IN SCHIZOPHRENIA

S. Ghose,* X. M. Gao, K. Lewis-Amezcua, D. Frost, C. A. Tamminga
Psychiatry, UT Southwestern Med Ctr, Dallas, TX, USA

We have previously identified elevated rCBF in the anterior hippocampus (AH) but not the posterior hippocampus (PH) in subjects with schizophrenia using in vivo imaging. We are studying candidate molecular markers in the AH and PH in post mortem tissue to find markers that parallel this distribution. The neurotrophic factor, brain-derived neurotrophic factor (BDNF), is expressed in relationship to the glutamatergic neurotransmitter system, which is implicated in the pathophysiology of schizophrenia. We have examined BDNF, NR1, NR2A, NR2B and GAD67 mRNA expression in the AH and PH in serial tissue samples. In situ hybridization experiments were performed on tissue from matched post mortem brain samples of 14 individuals with schizophrenia (SCH) and 14 normal controls (NC) using radiolabelled oligonucleotide probes. Subregions of the hippocampus analyzed included CA1 - 4, dentate gyrus (DG), subiculum (SC) and entorhinal cortex (ERC). Additionally, we are analyzing expression profiles of these molecular targets in rats chronically treated with antipsychotic medication vs. saline to determine possible effects of drug treatment. In general, an inverse relationship along the rostrocaudal axis was observed in expression profiles of BDNF and NR2B mRNA. BDNF expression in the CA3 pyramidal layer was found to be significantly decreased in the AH and increased in the PH of cases of schizophrenia compared to controls ($p=0.04$). Within the schizophrenia group, BDNF expression is lower in the CA3 molecular layer, pyramidal layer and DG of the AH ($p=0.03$) compared to levels in the PH. Conversely, NR2B mRNA levels in the AH were significantly higher in the CA1, CA2, CA3, DG and ERC (all $p<0.04$) compared to the PH in both groups. Similarly higher levels of GAD67 were seen in the AH ERC ($p = 0.02$). Rostrocaudal differences in NR2A mRNA between groups show a trend in CA1 ($p = 0.07$) and SC ($p = 0.08$). Detailed correlations are underway. So far, these data demonstrate significant differences in the rostrocaudal expression pattern of BDNF and NMDA receptor subunit message in the hippocampus that may be related to rCBF patterns seen in subjects with schizophrenia in vivo.

REGIONAL MYELIN-RELATED GENE EXPRESSION IN ELDERLY PATIENTS WITH SCHIZOPHRENIA

V. Haroutunian,* C. Copland, S. Dracheva, J. D. Buxbaum, J. H. Meador-Woodruff, E. Kreger, J. M. Gorman, K. L. Davis
Psychiatry, Mount Sinai School of Medicine, New York, NY, USA

Neural networks involving prefrontal and association areas, have been implicated as a central abnormalities in schizophrenia (SZ). White matter pathologies indicative of compromised oligodendroglia have been identified in the frontal cortex of schizophrenics; but, oligodendrocyte-related gene expression deficits in other cortical areas have remained unknown. We examined whether the expression of several genes important in myelination and myelin function were altered in different cortical regions of SZ subjects using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). In addition, localization of gene expression changes was probed in

the cingulate cortex by in situ hybridization (ISHH). The expression of 2',3'-Cyclic nucleotide-3'-phosphodiesterase (CNP), proteolipid protein (PLP), gelsolin and both known isoforms of myelin-associated glycoprotein (MAG), S-MAG and L-MAG, were analyzed in post-mortem cortical samples from the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex, inferior parietal lobe, superior temporal gyrus, and occipital cortex by qRT-PCR. Expression of CNP, MAG, Transferrin, Gelsolin, MOGa4 and ERBb2IP was studied in the cingulate cortex by in ISHH. Expression of CNP, gelsolin and both known isoforms of MAG were (ps<0.04) decreased in DLPFC and anterior cingulate cortex of SZ patients relative to normal controls (55-70%). PLP was unaltered. S-MAG was the most affected transcript, and was also expressed at a dramatically higher level in the DLPFC relative to the other regions in controls, an effect that may be amplified in affected patients. In ISHH studies confirmed reduced expression of CNP, MAG and transferrin (ps<0.05) in the anterior cingulate cortex. Gelsolin, MOG and ERBb2IP expression was not significantly altered. Cellular and layer-based analyses are ongoing. Thus, the reduced expression of some myelination-related genes in SZ is cortical region specific and encompasses at least two distinct subregions of the frontal cortex, both with significant relevance to neural networks hypothesized to be impaired in SZ. The normal expression of S-MAG differs between cortical regions, indicating that MAG may have regional functional differences. These findings provide further evidence, using two distinctly different analytic approaches, in support of altered oligodendroglia function in SZ, and underscore the necessity to analyze isoforms independently.

ESSENTIAL FATTY ACID AND B-VITAMIN STATUS IN SCHIZOPHRENIA

R. Kemperman,* M. Veurink, T. van der Wal, H. Knegtering, R. Bruggeman, M. R. Fokkema, I. P. Kema, J. Korf, F. A. Muskiet
Pathology and Laboratory Medicine, University Hospital Groningen, Groningen, Netherlands

The 'membrane phospholipid hypothesis' of schizophrenia postulates a relation between schizophrenia, low status of arachidonic (20:4n-6) and docosahexaenoic (22:6n-3) acids, and impaired S-adenosylmethionine catalyzed methylation of phoshatidylethanolamine to phosphatidylcholine. Metabolic clearance of the homocysteine, formed in the latter process and others, makes use of B-vitamins (i.e. folate, vitamin B12 and vitamin B6) as cofactors. We investigated whether patients with schizophrenia in our hospital have low status of 20:4n-6, 22:6n-3 and B-vitamins. Blood samples were collected from 61 schizophrenics [61% men, median age 30 years (19-53), median duration of psychiatric disease 5 years (1-20)]. We performed the following assays: fatty acids (FAs) in erythrocytes (RBC), folate and vitamin B12 (serum), vitamin B6 (whole blood) and homocysteine (EDTA-plasma). Data were evaluated by comparison with reference values of healthy controls (RBC-FAs, n=69), local reference values (folate, vitamin B12, vitamin B6, homocysteine) or a vitamin-optimized reference value (homocysteine). Patients had significantly lower RBC polyunsaturated FAs, n-6FAs, 20:4n-6, 22:4n-6, n-3FAs and 22:6n-3, and higher saturated and monounsaturated FAs, 20:3n-6 and 22:5n-6/22:6n-3. The percentage patients with above normal 22:5n-6/22:6n-3 (an indicator of low 22:6n-3 status) and 20:3n-9 (an indicator of essential fatty acid deficiency) amounted to 15 and 3%, respectively. Patient percentages with below-reference values for folate, vitamin B12 and vitamin B6 were: 3, 28 and 5%, respectively. Homocysteine was increased in 26% (cut-off 15 micromol/Ll) and 70% (cut-off 10 micromol/L) of patients, with 4 showing extremely high values (range: 57.5-74.8 micromol/L). These four were supplemented with B-vitamins to show that homocysteine values dropped to values close to the cut-off value for vitamin-B optimized reference values in 4 weeks or less. We conclude that subgroups of schizophrenic patients have low status of 20:4n-6, 22:6n-3 and B-vitamins. More attention should be paid to their diet, since at least low 20:4n-6 and 22:6n-3 status may be causally related to their symptoms.

NIACIN SENSITIVITY AND ITS BIOLOGICAL CORRELATES IN EARLY PSYCHOSIS

M. J. Kerr,* T. M. Proffitt, M. A. McConchie, S. Cotton, S. J. Wood, C. Pantelis, W. J. Brewer, S. Smesny, P. D. McGorry, G. E. Berger
Psychiatry, ORYGEN Research Centre, Unversity of Melbourne, Parkville, VIC, Australia

Background & Aim: Bioactive lipids have been implicated in the etiology and pathophysiology of psychosis. Niacin sensitivity is strongly related to prostaglandin D2, a derivate of arachidonic acid (AA), a bioactive lipid. It has been proposed that schizophrenia consists of two diseases, one involving lower levels of AA. It is unclear whether niacin sensitivity, as an indirect measure of AA availability, can differentiate intermediate phenotypes, and if this intermediate phenotype differs in regards to its neurobiology or responsiveness to treatment. Methodology: We administered a topical variant of the niacin skin test (NST) to 100 patients presenting with first episode psychosis (FEP) and 60 controls. We developed a semiquantitative descriptive scale incorporating oedema and erythema at four different concentrations of nicotinic acid) at four time points, with excellent reliability. We performed proton magnetic resonance spectroscopy (1H-MRS) at 3 Tesla in the medial temporal lobe of 20 FEP patients who completed the NST, and cognitive assessment (CANTAB) in 47. Results: Niacin sensitivity was lowest in FEP patients meeting criteria for schizophreniform psychosis (mean score 34), schizophrenia (mean score 42), and schizoaffective psychosis (mean score 48), followed by controls and bipolar disorder (mean score 52). In drug-naïve or early treated FEP patients niacin sensitivity was inversely associated with an increase in energy metabolites (creatine/phosphocreatinine) and glutathione (a major antioxidant & precursor of glutamate) measured in the medial temporal lobe using 1H-MRS. Niacin insensitive patients demonstrated greater improvements in negative symptoms & depression over twelve weeks of standard anti-psychotic treatment, and performed more poorly on recognition & working memory tasks, implicating fronto-temporal systems. Conclusion: Niacin sensitivity is a rapid and reliable way to determine an intermediate phenotype within the psychosis spectrum with an underlying dysfunction in the phospholipid–arachidonic acid–prostaglandin pathway. Its use appears most relevant at onset of psychosis where early detection of a subgroup of patients who have greater metabolic and cognitive impairments at illness onset, due to an increased rate of lipid peroxidation probably reflecting apoptotic activity, may respond better to treatments such as eicosapentaenoic acid.

HIGH EXPLANATORY POWER OF THE ADENOSINE HYPOTHESIS OF SCHIZOPHRENIA

D. R. Lara,* E. S. Ghisolfi, M. G. Brunstein, O. P. Dall'Igna
Physiological Sciences, Pontificia Universidade Catolica do RS, Porto Alegre, RS, Brazil

Our purpose is to outline the evidence suggesting that the neuromodulator adenosine is a key element in the pathophysiology of schizophrenia, possibly accounting for many features of schizophrenia. Adenosine is an inhibitory neuromodulator that inhibits neurotransmitter release through A1 receptors and D2 receptor transmission through A2A receptors. This model integrates the dopamine and glutamate hypotheses, since adenosine exerts key neuromodulatory roles on these systems, and proposes that adenosine rather than GABA mediates the inhibitory deficit found in schizophrenia. Pre and perinatal complications lead to excessive adenosine release from ATP breakdown, inducing neurotoxicity via activation of A1 receptors. These events would lead to an adenosine inhibitory deficit that later emerges as reduced control of dopamine activity and increased vulnerability to excitotoxic glutamate action in the mature brain. The adenosine hypothesis is compatible with symptoms, gray and white matter abnormalities, progressive brain loss, disconnectivity, age of onset, risk factors such as hypoxia, viral infections and urbanicity, response to antipsychotics, glycine and ECT, impaired sensory gating, increased smoking, clinical heterogeneity, shared characteristics with bipolar disorder, human evolutionary aspects and altered brain asymmetry reported in schizophrenia. Adenosine receptor antagonists, such as caffeine and theophylline, are pharmacological models of adenosine hypofunction, and patients with treated adenosine deaminase deficiency may represent a human model of schizophrenia (these patients show an increase in psychiatric symptoms during adolescence). If correct, pharmacological treatments enhancing adenosine activity, especially through A1 receptors, could be effective for symptom control and for alleviating deterioration in the course of the illness. We also outline our recent data, showing that: a) allourinol is effective for almost half of treatment refractory schizophrenic patients (Brunstein et al, *JCPsychiatry*, in press); b) chronic caffeine treatment in mice inhibit the behavioral effects of NMDA receptor antagonists (Dall'Igna et al, *Psychopharmacology*, 2003) and c) theophylline and caffeine impair P50 sensory gating (Ghisolfi et al, *Neuropsychopharmacology*, 2002). Since much of the evidence for the adenosine hypothesis are circumstantial, pivotal experiments, such as determination of A1 receptor density in schizophrenia, are warranted.

EFFECTS OF PRENATAL NMDA RECEPTOR ANTAGONISM ON MYELINATION

J. S. Lindahl,* R. Miskimins
Psychiatry and The Division of Basic Biomedical Sciences, University of South Dakota School of Medicine, Vermillion, SD, USA

Schizophrenia is a debilitating neurodevelopmental disorder that typically presents in young adulthood. Defining the underlying mechanisms leading to the symptoms of schizophrenia is essential to development of improved therapeutics. The broad goal of our research is to understand what molecular changes underlie schizophrenia. Recent data suggesting that decreased function of NMDA receptors leads to unregulated glutamate release and the subsequent excitotoxic death of susceptible cells may provide a mechanism by which early brain development is altered. Both neurons and immature oligodendrocytes, the myelin producing cells of the central nervous system, are susceptible to glutamate-mediated excitotoxic death. Downstream consequences of these vulnerabilities would include neuronal loss, axonopathy and white matter abnormalities. In fact, several white matter anomalies have been documented in schizophrenics including volume reduction, ultrastructural alterations to myelin sheath lamella and loss of myelin sheath compaction. Altered myelin and myelination processes would ultimately contribute to deficits in neurotransmission and cortical connectivity, such as seen in schizophrenia. Using a unique model in which rat pups are exposed to the NMDA receptor antagonist phencyclidine (PCP) in utero, we have produced significant changes in embryonic NMDA receptor subunit levels. By Western blot analysis and immunocytochemistry, we have identified an increase in both the NR1 and NR2B subunits of the NMDA receptor at early postnatal time points. Moreover, our data demonstrate that prenatal NMDA receptor antagonism significantly reduces the number of oligodendrocyte precursor cells present at early postnatal time points and compromises later stage myelination. This early reduction in myelination persists into adulthood and does not appear to be compensated for during brain maturation. These finding significantly extend what is currently known about NMDA receptor function during neurodevelopment and may link developmental NMDA receptor dysfunction to myelination deficits and abnormal white matter neurocircuitry noted in schizophrenia. This research is support by a Mentored Clinical Scientist Award from the National Institute of Mental Health (K08-MH064552).

DIFFERENTIAL-TEMPORAL EFFECTS OF HALOPERIDOL AND OLANZAPINE ON NEUROGENESIS IN THE ADULT RAT HIPPOCAMPUS

S. Mahadik,* A. Pillai, S. Sharma
Psychiatry and Health Behavior, Medical College of Georgia, Augusta, GA, USA

Neurogenesis in hippocampus generates new granular neurons throughout life that become integrated into the dentate gyrus. Recent studies from our lab and others have reported that antipsychotics can stimulate neurogenesis and thus regulate neural plasticity. This study was designed to evaluate the differential-temporal effect of Haloperidol (HAL) and Olanzapine (OLZ) on hippocampal neurogenesis at 14 and 45 days of treatment. Adult male wistar rats (n=3) were administered vehicle, HAL (2 mg/kg body wt) or OLZ (10 mg/kg body wt). At each time point we injected rats with BrdU (50 mg/kg body wt), a marker of DNA synthesis two times daily at 10-12 hr intervals for four days and sacrificed 1 hr after last injection. We euthanized rats by intracardiac perfusion with 4% paraformaldehyde in 0.1 M Phosphate buffer (pH 7.4) and extracted the brains for immunohistochemistry. Our studies demonstrate that HAL treatment for 14 days significantly increases the number of Brdu-labelled cells in the dentate gyrus and hilus of the hippocampus where as at 45 days no change in neurogenesis was observed as compared to the control. OLZ at 14 days caused slight increase in number of Brdu-labelled cells compared to control, but at 45 days a very significant increase in neurogenesis is observed. These preliminary findings indicate that HAL stimulates neurogenesis sooner but that does not sustain for a long period of time where

as OLZ progressively stimulates neurogenesis and that continues over a long period of time. These newly born cells mature and become neurons and glia. These data may have implications to a favorable long-term persistent therapeutic effect of antipsychotics and thus improving and maintaining the functional capacity of hippocampus.

NEUROACTIVE STEROID ALTERATIONS IN SCHIZOPHRENIA AND BIPOLAR DISORDER: NEGATIVE ION CHEMICAL IONIZATION GAS CHROMATOGRAPHY/MASS SPECTROMETRY INVESTIGATIONS IN POSTERIOR CINGULATE AND PARIETAL CORTEX

C. E. Marx,* L. J. Shampine, R. D. Stevens, A. L. Morrow, V. Uzunova, W. T. Trost, R. M. Hamer, J. A. Lieberman
Psychiatry and Behavioral Sciences, Duke University Medical Center and Durham VA, Durham, NC, USA

Neuroactive steroids may be candidate modulators of schizophrenia pathophysiology and contribute to antipsychotic efficacy. We have determined previously that DHEA plasma levels were elevated in first-episode schizophrenia patients compared to control subjects, and that DHEA and pregnenolone levels were negatively correlated with SANS scores. Clozapine and olanzapine elevate allopregnanolone in rodent brain (Marx et al), potentially contributing to the anxiolytic, antidepressant, and antipsychotic actions of these compounds. We therefore investigated neuroactive steroids in postmortem brain tissue from the Stanley Foundation. Posterior cingulate and parietal cortex tissue was analyzed for neuroactive steroids by negative ion chemical ionization gas chromatography/mass spectrometry, preceded by HPLC. DHEA, pregnenolone, and allopregnanolone levels were determined in both brain regions in 60 subjects (15 each with schizophrenia, bipolar disorder, depression, and 15 control subjects). Statistical analyses were performed by ANOVA with post-hoc Dunnett tests on log transformed neuroactive steroid levels. In posterior cingulate, DHEA levels were significantly higher in subjects with schizophrenia and bipolar disorder compared to control subjects (ANOVA $p=0.0015$; post-hoc Dunnett $p<0.01$ for both groups), as were pregnenolone levels (ANOVA $p=0.0017$; post-hoc $p<0.01$ for both groups). In parietal cortex, DHEA (ANOVA $p=0.0087$, post-hoc Dunnett $p<0.01$) and pregnenolone (ANOVA=0.0046, post-hoc $p<0.01$) levels were both significantly higher in bipolar patients. Levels were also higher in schizophrenia patients, but findings were reduced to trends for both DHEA and pregnenolone (post-hoc Dunnett $p=0.059$ and $p=0.061$, respectively). DHEA and pregnenolone levels in posterior cingulate and parietal cortex were higher in both schizophrenia and bipolar subjects compared to control subjects. DHEA is neuroprotective in a number of rodent models, and DHEA augmentation decreases negative, depression, and anxiety symptoms in schizophrenia patients (Strous et al). Pregnenolone and its sulfate enhance learning and memory in preclinical studies (Flood et al, Akwa et al, Vallee et al). DHEA and pregnenolone elevations may therefore represent potential compensatory mechanisms in schizophrenia and bipolar disorder. It is also possible that alterations are related to antipsychotic treatment. Neuroactive steroids may represent novel treatment strategies for future interventions.

GENE EXPRESSION IN PRIMARY VISUAL CORTEX

P. Matthews,* P. J. Harrison, S. L. Eastwood
Psychiatry, University of Oxford, Oxford, United Kingdom

This study examines gene expression in post-mortem schizophrenic brain. Messenger RNA was extracted from primary visual cortex in the Stanley Neuropathology Consortium series of 60 brains, including 15 controls and 15 schizophrenics. Based on RNA integrity, each diagnostic group was stratified into three pools of five subjects. The best two pools were successfully screened for differential gene expression using the Clontech Atlas Human Neurobiology Array, according to the manufacturer's instructions. Array films were analysed using Atlas Image 2.7. Normalisation was carried out using global sum and housekeeping gene methods. A gene was considered to be changed in schizophrenia if it showed a fold change, compared to controls, greater than 1.62 in both RNA pools. Selected genes were followed up using semi-quantitative reverse-transcriptase PCR. Expression of thymosin-β10 and β-actin were thereby confirmed to be reduced in schizophrenia. Other genes are also being examined. These results provide the first expression profiling data in the visual cortex in schizophrenia, and the decrease of thymosin-β10 is potentially of interest because of its known roles in neurodevelopment. However, the reduction of β-actin serves to illustrate that the use of housekeeping genes in this field can be problematic, and the data also highlight several other issues which can affect array studies in the post mortem brain. This work was supported by the Wellcome Trust and the Stanley Medical Research Institute.

THE INTIATING STEP OF THE KYNURENINE PATHWAY IS UPREGULATED IN SCHIZOPHRENIA AND PSYCHOTIC BIPOLAR DISORDER

C. L. Miller,* I. C. Llenos, J. R. Dulay, R. H. Yolken, S. Weis
Stanley Division, Department of Pediatrics, Johns Hopkins University, Baltimore, MD, USA

A growing body of evidence indicates that disruption of the kynurenine pathway occurs in schizophrenia and other disorders that involve psychosis. To further test the relevance of kynurenine pathway function in specific brain regions to different psychiatric manifestations, adjacent sections of postmortem, frozen anterior cingulate from four diagnostic categories (schizophrenia, bipolar disorder, major depression and controls, $7 \leq N \leq 14$ in each group) were extracted for total RNA and the metabolites kynurenine and kynurenic acid analyzed by HPLC. Random-hexamer primed cDNA was generated from the RNA and real-time PCR was used to quantify expression of tryptophan 2,3-dioxygenase (TDO2), an enzyme which initiates the kynurenine pathway. In addition, formaldehyde-fixed sections from the contralateral anterior cingulate were analyzed for TDO2 protein expression by immunohistochemical methods. Relative to controls, we found a significant elevation in: 1) kynurenine in schizophrenia (1.9-fold, $p=0.024$) and bipolar disorder with psychosis (2.1-fold, $p=0.030$); 2) TDO2 mRNA in schizophrenia (1.7-fold;$p= 0.049$; values normalized for GAPDH); and 3) the density of TDO2-immunopositive white matter glial cells in schizophrenia ($p= 0.02$) and in major depression ($p=0.03$) as well as in the density and intensity of glial cells in the gray and white matter stained for TDO2 in bipolar disorder ($p= 0.02$). Thus, the behavioral disorders with psychosis (schizophrenia and psychotic bipolar disorder, but not major depression) were both distinguished from controls by a significant elevation in kynurenine, the primary product of TDO2.

MODIFICATION OF THE ASYMMETRICAL REPARTITION OF THE PHOSPHATIDYLETHANOLAMINE ON THE LIPID BILAYER MEMBRANE OF ERYTHROCYTES FROM SEVERE SCHIZOPHRENIC PATIENTS: A PUTATIVE VULNERABILITY MARKER FOR SUBJECTS AT RISK WITH SCHIZOPHRENIA?

P. Nuss,* C. Tessier, F. Ferreri, M. Ferreri, J. Masliah
Service de psychiatrie, CHU St-Antoine, Paris, France

The aim of our study is to determine the repartition of phosphatidylethanolamine (PE) between inner and outer leaflet of erythrocytes membranes from schizophrenic patients and controls. Numerous data are suggesting abnormalities on the expression of phospholipids (PL) at the erythrocyte membrane level in schizophrenic patients. Among them, one the most constant findings is a decreased rate of phosphatidylethanolamine (PE) at the erythrocytes membranes (identified by GC MS) and brain level (identified by 31P MRS studies). These alterations may be due to modifications in processes involved in the maintenance of the membrane asymmetrical repartition of PL. We labelled erythrocytes from schizophrenic and control subjects with TNBS (trinitrobenzensulfonic acid) a colorimetric probe able to specifically label the externally located PE of the erythrocytes membrane. We could then separate the labelled PE from de non labelled PE by thin layer chromatography (TLC). After recuperation of the 2 distinct PE spots on the TLC plate, and isolation of PE, the measure of the total PE amount and the nature and the amount of their constitutive fatty acids was assessed by mass spectrometry. Three independent samples for each group were measured, allowing a good approximation of the results despite to the unavoidable technical and manipulations errors. Erythrocytes from schizophrenic patients (n=70) and normal controls (n=68) have been punctured. Patients and controls have been carefully selected and matched by sex and age. Inclusion criteria was: DSM-IV criteria for schizophrenia, stabilised patients with high positive and negative subscores, duration of the disease more than 3 years after first diagnostic and less than 15 years of evolution, no change of the antipsychotic medication within the previous 3 months. Exclusion criteria in both groups were the existence of any metabolic disorders, anti-inflammatory treatment and/or medications interacting with the lipid metabolism. Patients with poor diet intake were also excluded. A significant diminution of the asymmetrical PE gradient (the usual ratio between external/internal PE is 4/96) is seen significantly more often in the erythrocyte membrane of patients with schizophrenia compared with erythrocytes membranes from controls.

HOMOCYSTEINE AND SCHIZOPHRENIA—IS THERE AN ASSOCIATION? A CRITICAL ANALYSIS OF THE LITERATURE AND A CROSS-SECTIONAL ANALYSIS IN FIRST EPISODE PSYCHOSIS OF HOMOCYSTEINE LEVELS AND CONFOUNDING FACTORS

C. O'Donnell,* T. Stephens, M. O'Regan, M. Boasman, M. Dell'Olio, G. Berger, P. D. McGorry
Unit for Neuroprotection in Young People, ORYGEN Research Centre, Melbourne, VIC, Australia

An elevated plasma homocysteine level is a risk factor for cardiovascular disease and is often observed in other common disorders, including neural tube defects, pregnancy complications, and Alzheimer's disease.Several conflicting reports on an association between homocysteine and schizophrenia have been published. We sought to examine the evidence to date and critically analyse these reports. Medline, OVID and Psychinfo databases were searched. Results on a current cross-sectional analysis of homocysteine levels in a geographically determined catchment area of people with first episode psychosis aged 15 to 25 will also be presented. A number of studies were identified and critically analysed. Five studies identified a positive association between elevated homocysteine levels and schizophrenia/psychosis. 4 studies reported a negative association. Factors that affect homocysteine levels were not assessed in all studies. Re-analysis of the data in one negative study indicated a possible postive result taking into account confounding factors.Homocysteine levels were particularly raised in young males with schizophrenia. There is evidence to support an association between elevated levels of homocysteine and schizophrenia but design of future studies need to incorporate measurement of confounding factors. Intervention studies using homocysteine lowering agents such as Folic Acid may be effective particularly in people with first episode psychosis.

ALCOHOL ABUSE OR DEPENDENCE IS ASSOCIATED WITH DECREASED ACTIVITY OF CEREBELLAR GRANULE CELLS IN PATIENTS WITH SCHIZOPHRENIA BUT NOT IN CONTROL SUBJECTS

R. D. Paz,* R. C. Roberts, S. Daoub, R. R. Conley, N. C. Andreasen, N. I. Perrone-Bizzozero
Department of Neurosciences, University of New Mexico School of Medicine, Albuquerque, NM, USA

Background: The prevalence of alcohol abuse and dependence is four fold higher in patients with schizophrenia than in normal population. The causes of this association remain unknown. Gene expression studies performed in our laboratory suggest cerebellar granule cells are hyperactive in schizophrenia. Normally, cerebellar granule cells are kept inhibited by a tonic GABAergic current mediated by the δ subunit of the GABA-A receptor (GABA-A δ) in a manner such that only strong pre-synaptic activity can overcome this inhibition. Electrophysiological studies indicate that ethanol is a potent enhancer of tonic currents specifically mediated by receptors containing GABA-A δ. To explore the interaction between high levels of ethanol consumption and cerebellar granule cell activity in schizophrenia, the pattern of gene expression in matched sets of patients and control subjects with or without a history of alcohol abuse or dependence (AA/AD), was compared. Methods: Tissue from 28 patients with schizophrenia (12 with and 16 without AA/AD) and from 26 matched control subjects (11 with and 15 without AA/AD) were obtained from the Maryland Brain Collection. The levels of expression of GAP-43, BDNF, SNAP-25 and GABA-A δ, four genes selectively expressed by cerebellar granule cells in an activity-dependent manner, were measured in the cerebellar cortices of four groups of subjects by real time polymerase chain reaction. Results: Two-way ANOVAs revealed a specific interaction between alcohol abuse/dependence and schizophrenia ($p<0.05$). Patients with schizophrenia with a history of AA/AD had significantly lower levels of GAP-43, BDNF, SNAP-25 and GABA-A δ mRNAs than patients with schizophrenia who did not exhibit a pathological pattern of ethanol consumption ($p<0.05$). No differences in the expression of these genes were found in control subjects with or without AA/AD.

Conclusions: Only in patients with schizophrenia did ethanol abuse or dependence result in reduced expression of activity-dependent, granule cell specific genes. These findings are consistent with the hypothesis that pathologically hyperactive granule cells in schizophrenia are more sensitive to the GABA enhancing properties of ethanol than normally inhibited granule cells in control subjects. Our findings may help to understand the causes of the increased prevalence of alcoholism in patients with schizophrenia.

INCREASED EXPRESSION OF GRANULE CELL-SPECIFIC, ACTIVITY-DEPENDENT GENES IN POST-MORTEM CEREBELLAR TISSUE SUGGESTS THAT THESE NEURONS ARE HYPERACTIVE IN SCHIZOPHRENIA

N. I. Perrone-Bizzozero,* R. D. Paz, R. C. Roberts, S. Daoub, R. R. Conley, N. C. Andreasen
Department of Neurosciences, University of New Mexico School of Medicine, Albuquerque, NM, USA

Background: Two independent groups have found increased basal regional cerebral blood flow and glucose uptake in the cerebellum of patients with schizophrenia. To evaluate if the hyperactivity observed by neuroimaging studies corresponds to increased glutamatergic activity in this brain region, the levels of mRNAs for GAP-43, BDNF and SNAP-25, three genes selectively expressed by glutamatergic neurons in an activity-dependent manner, were measured in human post-mortem tissues. Methods: Specimens from 16 patients with schizophrenia and 15 age-, sex-, and post-mortem interval (PMI)-matched controls were obtained from the Maryland Brain Collection. Since the cerebellar cortex inhibits deep nuclei, the source of hyperactivity could be localized in either region but not in both. Real time polymerase chain reactions (PCR) were used to measure gene expression in cortical and deep nuclei regions of cerebellar hemispheres (Crus I, VIIa). To further localize the source of hyperactivity at a cellular level, we compared the levels of the mRNAs for the GABA-A receptor δ subunit (GABAA δ) and the α6 subunit (GABA-A α6). Both subunits are exclusively expressed by granule cells, however only the expression of GABA-A δ is regulated in an activity-dependent manner. Results: The levels of GAP-43, BDNF and SNAP-25 mRNAs were significantly increased in cortical but not in deep nuclei regions of patients with schizophrenia relative to controls ($p<0.05$). The levels of GABA-A δ subunit mRNA but not those of the α6 subunit were also increased in these patients ($p<0.05$). Conclusions: The hyperactivity revealed by neuroimaging studies in patients with schizophrenia seems to be localized to cortical but not deep nuclei regions of the cerebellum. Our findings also suggest that granule cells, the only glutamatergic neurons in the cerebellar cortex, are hyperactive in schizophrenia. Considering the key role played by these neurons in filtering sensory information within the input layer of the cerebellar cortex, granule cell hyperactivity may have profound physiological consequences for the processing of sensory information in schizophrenia.

ROLE OF VEGF, ANGIOGENIC FACTOR IN DIFFERENTIAL-TEMPORAL EFFECTS OF ANTIPSYCHOTICS ON NEUROGENESIS

A. Pillai,* S. Sharma, S. Mahadik
Psychiatry, Medical College of Georgia, Augusta, GA, USA

There is a substantial literature suggesting that antipsychotic medications can differentially change blood flow in individuals with schizophrenia and these effects are region specific. Recent studies from our lab and others have reported that antipsychotics can stimulate neurogenesis and thus regulate neural plasticity. Blood flow has been shown to regulate angiogenesis. Since angiogenesis and neurogenesis are strictly interconnected through out the life the present study was designed to explore the role of VEGF, a prototypical angiogenic molecule which mediates neurogenesis and thereby cognition, in antipsychotic-stimulated neurogenesis in hippocampus. We studied the differential temporal effect of HAL and OLZ treatment on the expression of VEGF and its receptor (VEGFR-2; also called Flk-1) and neurogenesis in hippocampus. Adult male wistar rats (n=5-6) were administered vehicle, HAL (2 mg/kg body wt) or OLZ (10 mg/kg body wt). VEGF levels were measured by ELISA. For immunohistochemistry at each time point we injected rats with BrdU (50 mg/kg body wt), a marker of DNA synthesis two times daily at 10-12 hr intervals for four days and sacrificed 1 hr after last injection. We euthanized rats by intracardiac perfusion with 4% paraformaldehyde in 0.1 M Phosphate buffer (pH 7.4) and extracted the brains for immunohistochemistry. Our studies demonstrate that HAL treatment for 14 days significantly increases VEGF levels in hippocampus and expression of VEGF and Flk-1 in dentate gyrus and hilus of the hippocampus where as at 45 days no change in their expression was observed as compared to the control. OLZ at 14 days caused slight increase in VEGF levels in hippocampus and expression of VEGF and Flk-1 compared to control, but at 45 days a very significant increase in their expression is observed. The changes were parallel to the changes observed in neurogenesis. These data indicate that increase in hippocampal VEGF and Flk-1 results in increased neurogenesis. These findings for the first time report that VEGF, a known angiogenic as well as neurotrophic factor, mediates the effect of antipsychotics on hippocampal neurogenesis.

EFFECTS OF TYPICAL AND ATYPICAL ANTIPSYCHOTICS ON PHENOTYPIC CHARACTERIZATION AND DIFFERENTIATION OF NEURAL STEM CELLS IN THE ADULT RAT SUBVENTRICULAR ZONE

S. Sharma,* A. K. Sharma, A. Pillai, A. V. Terry, S. P. Mahadik
Department of Psychiatry and Health Behavior, Medical College of Georgia, Augusta, GA, USA

The antipsychotics are the primary treatment drugs for schizophrenia, which have different therapeutic clinical and side effects profiles. However, mechanisms of their long-term action are unclear. Their role in neuroprotection and neuroplasticity has been implicated. Recently, antipsychotics have been indicated to affect the neurogenesis in adult brain. This study is designed to investigate their differential temporal effects on neurogenesis. The subventricular zone of lateral ventricle (SVZ-LV) of adult brain is one of the primary sites of neurogenic activity, generating neural stem cells (NSC). The objective of this study is to characterize the time dependent generation of various cell types (cell lineage) of the newly dividing cells in the SVZ-LV following 14 and 45 days of treatment with a typical antipsychotic- Haloperidol (HAL) and an atypical antipsychotic-Olanzapine (OLZ) in the adult rat. Adult male Wistar rats (N =3/grp) were administered vehicle, HAL (2 mg/day/kg) or OLZ (10 mg/day/kg) in drinking water. At each time point, animals were injected with bromodeoxyuridine (BrdU, 450 mg/kg) in 3 equal doses at 8-10 hr intervals and sacrificed next day. A group of 45 day treated animals were also injected with BrdU on day 14 to determine

migration and survival of the NSC to olfactory bulb (OB). BrdU+ cells in SVZ for HAL showed a two-fold increase in number of BrdU labeled cells at 14 days but there was a complete inhibition of neurogenesis at 45 days treatment time. Similarly, in OB too, HAL showed a two-fold increase in BrdU+ cells (labeled at 14 days) indicating that this atypical has no effect on the survival. Whereas, OLZ showed a slow but continuous increase in neurogenesis in the SVZ reaching a significant level ($p< 0.05$) by 45 days. In the OB, for the OLZ group (labeled at 14 days), BrdU positive cells were also 150% of the control suggesting that newly born cells from SVZ migrated to OB and survived for next 28 days. Similar phenotypic (neuronal and glial) differentiation profiles were seen for HAL and OLZ groups and they reflected the same quantitative differences as seen in the cell number. These results indicate that atypical and typical antipsychotics have significant differential effect on SVZ neurogenesis that may be relevant to differences in their therapeutic clinical profiles.

DIFFERENTIAL EXPRESSION OF GLIAL FIBRILLARY ACIDIC PROTEIN IN SUBREGIONS OF PREFRONTAL CORTEX IN SCHIZOPHRENIA

C. T. Toro,* J. W. Deakin
Neuroscience and Psychiatry Unit, University of Manchester, Manchester, United Kingdom

Introduction: Most studies using glial fibrillary acidic protein (GFAP) immunocytochemistry to detect astrogliosis and astrocyte numbers have reported no change in schizophrenia. This has added weight to the evidence that schizophrenia does not involve neurodegeneration. Counting GFAP-positive cells does not inform about protein expression. The present study reports GFAP protein expression using immunoautoradiography in frozen sections of dorsolateral (DLPFC) and orbitofrontal (OFC) cortex in Stanley Consortium brains from controls and patients with schizophrenia (SCZ), bipolar disorder (BPD) and depression (MDD). Method: Tissue sections were incubated with a monoclonal mouse antibody to GFAP (Sigma, 1:400). Immunoautoradiography with [35S]-labelled secondary antibody (Amersham) was used to quantify GFAP. Autoradiographic film optical density measurements were taken from Brodmann area 9 of DLPFC and BA11/47 from OFC using Bioquant software. Optical density profiles for individual laminae of BA9 were calculated using thick line horizontal histograms. Correlation analysis was used to reveal potential confounding variables. They were included as covariates in univariate or repeated measures ANOVAs. Cell counts of immunopositive cells for GFAP were calculated for individual laminae of BA9 from sections treated for immunocytochemistry. Results: Repeated measures using individual laminae of BA9 as a factor revealed a significant between-subjects effect of diagnosis ($p = 0.02$). An increase was found in schizophrenia relative to controls ($p = 0.003$); MDD ($p = 0.002$) and BPD ($p = 0.03$). No changes in GFAP immunopositive cell counts were found in any laminae of BA9. In BA11 of OFC there was a significant main effect of diagnosis ($p = 0.003$) with a significant decrease in both SCZ and BPD relative to controls and MDD. In both regions cumulative antipsychotic exposure (chlorpromazine equivalents) correlated with GFAP expression. Discussion: This is the first study to use the method of immunoautoradiography for analysis of GFAP protein expression. In schizophrenia, GFAP immunoreactivity was increased in BA9, while there was no change in GFAP cell density. This suggests an increase in GFAP in processes surrounding neurons. This could be due to greater exposure to antipsychotics in the schizophrenia group but this cannot explain reduced GFAP levels in OFC in the psychotic groups. The latter could contribute to pathogenesis through effects on glutamate function.

6. Neuropathology, Histology

REDUCED MYELIN BASIC PROTEIN (MBP) EXPRESSION IS CORRELATED TO MIGRATIONAL DISTURBANCES IN THE ENTORHINAL CORTEX IS SCHIZOPHRENIA

A. Bergmann,* B. Breunig, T. Kamer, T. Schneider-Axmann, I. Ovary, K. Majtenyi, L. Havas, G. Kovacs, W. Honer, P. Falkai
Psychiatry and Psychotherapy, Saarland University Hospital, Homburg/Saar, Germany

Introduction: Searching for potential mechanisms underlying migrational disturbances in the entorhinal region in schizophrenia we found significantly reduced expression of Myelin Basic Protein (MBP), a suitable axonal marker. This global deficit was however not correlated with migrational abnormalities. As the migrational disturbances are confined to the pre-alpha-cell clusters situated superficially, we decided to perform layer specific measurements of MBP expression. Sample description and Methods: Paraffin embedded sections of the entorhinal cortex of 18 schizophrenic patients and 10 control subjects were stained for MBP using routine immunohistochemical methodology. On each section representative regions of interest were scanned to attain optimal quality images of the grey matter. In the center of each image six boxes were placed so that each of them represented a separate cytoarchitectonic layer. A relative value for staining intensity was determined for each box resp. layer. When normal distribution was not rejected, ANOVA was calculated, otherwise the Mann-Whitney U-test was performed. Results: The mean values of all six layers demonstrated a significantly reduced relative staining intensity of MBP in schizophrenic patients compared to controls (-25%, $F = 4.7$, $p = .039$). This effect was most pronounced in the layers 2,3 and 4 (between -39 and -55%), but for reasons of large variances within each layer it did not reach the level of significance in any of them. On the other hand there was a significant correlation between the parameter (c-b)/c (left side), which characterized best the misplaced pre-alpha-cell clusters in schizophrenia and the mean value of reduced MBP staining ($rho = .37$, $p = .05$). Discussion: The data presented show a layer specific reduction of MBP, which in general is correlated with pre-alpha-cell migrational abnormalities in schizophrenia. Data on experimental lesions in the cortex of animals seem to support this finding, that subtle developmental abnormalities are accompanied by significant abnormalities in connectivity. Supported by a generous grant of the Medical Research Institute of the Vada and Theodore Stanley Foundation (P.F.).

MAMILLARY BODIES AND SCHIZOPHRENIA: REDUCED NEURONAL DENSITY BUT NORMAL VOLUME

H. Bernstein,* S. Krause, D. Krell, H. Dobrowolny, B. Bogerts
Psychiatry, University of Magdeburg, Magdeburg, Germany

Limbic brain structures have been implicated in the pathophysiology of schizophrenia. Being part of the limbic system mamillary bodies contain important relais nuclei linking the hippocampus and thalamic areas to hypothalamic and brain stem nuclei. Amazingly little is known about possible roles of mamillary bodies in schizophrenia, however. We determined the volume and neuronal density of this brain region in 15 cases with schizophrenia and 15 matched controls. While the volume was unchanged in schizophrenia, a significant reduction (by one third) of cell number and density was found in schizophrenic brains in comparison to controls. Additional investigations revealed that calretinin-immunoreactive neurons were not affected. Our data show that mammillary bodies belong to the brain areas which show structural alterations in schizophrenia. Supported by Stanley-Foundation, NBL-2 and NBL-3 of BMBF of Germany.

NUMERICAL DENSITIES OF ENTORHINAL CORTEX NEURONS EXPRESSING PARVALBUMIN ARE DECREASED IN BIPOLAR DISORDER

S. Berretta,* H. Pantazopoulos, N. Lange
Translational Neuroscience Laboratory, McLean Hospital, Belmont, MA, USA

Substantial evidence supports the involvement of the entorhinal cortex (ERC) in schizophrenia (SZ) (e.g. Longson et al., 1996; Arnold, 2000; Hemby et al., 2002; Kovalenko et al., 2003). Consistent with reports from other cortical regions, ERC GABAergic intrinsic neurons have been found to be affected in SZ (Bachus et al., 1997; Mizukami et al., 2002). Recently, a role for the ERC in bipolar disease (BD) has also been suggested (e.g. Webster et al., 2002). As a first step toward testing the hypothesis that specific subpopulations of interneurons within ERC may be affected in these diseases, we measured densities of neurons expressing the calcium binding protein parvalbumin (PVB) in a cohort composed of 16 normal controls, 10 SZ and 10 BD patients. Interneurons expressing PVB have been found to be altered in several cortical regions such as the hippocampus and prefrontal cortex (Lewis et al., 2001; Zhang and Reynolds, 2002). Subjects were matched by age, postmortem time interval (PMI) and gender (controls: 5 female / 11 male, age 64.0 ± 3.4 SEM, PMI 21.4 ± 1.4 SEM; SZ: 7 female / 3 male, age 62.4 ± 5.6 SEM, PMI 20.3 ± 2.1 SEM; BD: 4 female / 6 males, age 66.4 ± 5.8 SEM, PMI 19.04 ± 2.6 SEM). For each subject, 8-10 serial sections (40 μm thick) containing the rostral ERC were immunostained using antisera raised against PVB. Numerical densities of PVB-immunoreactive (IR) neurons were measured throughout each ERC section using computer-assisted light microscopy. A linear regression model was used to estimate the relationship between numerical densities of PVB-IR neurons and diagnosis, controlling for age, PMI and gender. Numerical densities of PVB-IR neurons are significantly reduced in the ERC of BDs ($p = 0.007$). SZ effects are only marginally significant without controlling for the effects of these covariates. There were no significant correlations of densities of PVB-IR neurons with doses of chlorpromazine-equivalent antipsychotics or lithium. These results indicate that a decrease of neurons expressing PVB may occur in the ERC of BDs. These neurons are located in layers II and III as well as V of ERC and their terminals synapse around the cell bodies and proximal axons of projection neurons reaching the hippocampus as well as other cortical and subcortical regions. Abnormalities of PVB-IR neurons in BD could thus profoundly alter the outgoing flow of information from the ERC to these regions.

EVIDENCE SHOWING A DECREASE IN NEUROGRANIN IMMUNOHISTOCHEMISTRY IN LAMINA III IN AREA 32 IN SCHIZOPHRENIC PREFRONTAL CORTEX

K. G. Broadbelt
Biology, Lehman College CUNY, Bronx, NY, USA

Studies have shown that the prefrontal cortex is greatly involved in schizophrenia. Many of the studies have focused on cellular and subcellular alterations in the prefrontal cortex while others have concentrated on the circuitry of this part of the brain. We recently demonstrated a schizophrenia-associated decrease in MAP2 immunostaining in laminae III and V of prefrontal cortex and a decrease in primary and secondary basilar dendrites on pyramidal cells in areas 32 and area 9. This finding suggests a loss of dendritic material. Currently we are looking at the protein Neurogranin, which belongs to the Calpacitin family. Neurogranin is an upstream regulator of calcium through the binding of calmodulin. Neurogranin is an important protein involved in signal transduction and is located in cell bodies, dendrites and dendritic spines. A loss of neurogranin or a change in the localization of the protein is suggestive of a dendritic lesion and could alter the calcium-calmodulin signal transduction pathway, which in turn could affect the cell's ability to process incoming information. Postmortem tissues from the medial aspect of the prefrontal cortex, specifically area 32, 5 schizophrenic and 5 non-psychiatric controls were examined. Area fraction analysis was used to quantify neurogranin immunohistochemistry. Results revealed a 40% decrease in neurogranin immunostaining in layer III in this region of the prefrontal cortex. The findings combined with the morphological studies suggest a decrease in synaptic surface area which may then manifest itself through a loss of neurogranin into aberrant information processing.

GLUTATHIONE DEFICIT DURING DEVELOPMENT INDUCES ANOMALIES IN ANTERIOR CINGULATE GABA INTERNEURONES: RELEVANCE TO SCHIZOPHRENIA

J. Cabungcal,* D. Nicolas, M. Cuenod, K. Q. Do, J. Hornung
Center for Psychiatric Neuroscience, Dept. of Adult Psychiatry, University of Lausanne, Lausanne, VD, Switzerland

Increasing evidence suggests that a deficit in glutathione (GSH) could be a critical vulnerability factor towards schizophrenia. GSH is decreased in prefrontal cortex and cerebrospinal fluid of patients (Do et al., 2000). A decreased in mRNA levels were also observed in fibroblasts for two GSH synthesizing enzymes, decrease which correlates negatively with the severity of symptoms (Tosic et al., 2004). GSH is an important endogenous redox regulator, protecting cells from damage by reactive oxygen species generated, among others, by dopamine. GSH deficit induced oxidative stress would lead to lipid peroxidation and micro-lesions in the surrounding of catecholamine terminals, possibly related to a structural disconnectivity. In order to test this hypothesis, we developed a rat model with GSH deficit: treatment with L-buthionine-(S,-R)-sulfoximine, an inhibitor of GSH synthesis, and GBR12909, an inhibitor of the dopamine re-uptake system, from post-natal day 5 to 16, leading to a transitory brain GSH decrease of about 50%. Since post-mortem studies in patients suggest a selective deficit in parvalbumin expression in a subclass of GABA neurons in prefrontal cortex (Hashimoto et al., 2003), immunohistochemistry of rat brain tissue was investigated at P16 using calcium binding protein markers. Rats treated with GSH deficit and GBR12909 showed a dramatic and specific reduction in immunostaining for parvalbumin, but not for calbindin and calretinin. Quantitative analysis of parvalbumin-immunoreactivity was performed on semi-thin sections of anterior cingulate cortex and somatosensory cortex. GSH deficit and GBR12909-treated rat showed significant loss of small size parvalbumin-immunoreactive particles (surface area of less than 1.5 μm^2), which account for a large part of the axonal arborisation of these interneurones. This observation was evident only in the anterior cingulate cortex. The finding of reduced parvalbumin-immunoreactivity observed in the anterior cingulate cortex in our animal model is analogous to the report of selective deficit in the prefrontal cortical GABAergic neurons in schizophrenia. Supported by Swiss National Foundation 31-62113 and 31-559224.98.

HISTOLOGICAL EVALUATION OF PREFRONTAL WHITE MATTER IN SCHIZOPHRENIA

A. J. Dwork,* B. Ilevski, B. Mancevski, M. Kurzon, T. Serafimova, I. Trencevska, G. Rosoklija, J. Keilp
Neuroscience, New York State Psychiatric Instiute, New York, NY, USA

Abnormalities of cerebral white matter have been observed in schizophrenia with in vivo imaging and post mortem biochemistry. White matter abnormalities are also consistently associated with vascular dementia. We undertook the current study to determine whether histologic evidence of myelin loss in white matter is associated with the cognitive impairment that is commonly present in elderly individuals with schizophrenia, or whether such evidence was associated with schizophrenia in general. Detailed chart reviews and neuropathological examinations were performed on 95 subjects with schizophrenia or schizoaffective disorder and 28 subjects without psychiatric disease. A set of histological sections, comprising the dorsal half of the frontal lobe at the level of the rostral tip of the lateral ventricle, was stained with Verhoeff's stain. Using systematic random sampling of the white matter, at least 100 microscopic fields from each case were examined at high magnification by a trained neuropathologist from whom all clinical and demographic data were masked. Integrity of myelin in each field was assigned an ordinal rating, and the average of the ratings for all fields was determined for each case. Cases with prefrontal lobotomy had the lowest myelin ratings and were excluded from further analysis. Among the remaining schizophrenia cases, there were no significant differences in myelin ratings between those with (N=65) and without (N=27) definite cognitive impairment. Compared with the nonpsychiatric group, the schizophrenia group had lower myelin ratings, but these were readily explained by older age and more frequent vasculopathy. In a purified subpopulation without identified infarcts, vasculopathy, or neuritic senile plaque counts meeting Khachaturian criteria for Alzheimer's disease, there was no significant difference in myelin ratings between schizophrenia (N=20) and nonpsychiatric cases (N=12). Neither cognitive impairment in schizophrenia nor schizophrenia per se is associated with diffuse histological changes in myelin of the dorsal prefrontal white matter. Support contributed by: MH60877, NARSAD, Lieber Center for Schizophrenia Research.

DECREASED HIPPOCAMPAL EXPRESSION OF THE SUSCEPTIBILITY GENE PPP3CC AND OTHER CALCINEURIN SUBUNITS IN SCHIZOPHRENIA

S. L. Eastwood,* T. Salih, P. W. Burnet, P. J. Harrison
Psychiatry, University of Oxford, Oxford, United Kingdom

Calcineurin (CaN) is a protein phosphatase centrally involved in synaptic plasticity. The gene encoding the gamma isoform of the catalytic subunit (CaN A), PPP3CC, has been associated with schizophrenia. However, before the pathophysiological implications of a susceptibility gene, such as CaN, can be established, determining the expression pattern of such susceptibility genes, and establishing whether they are altered in schizophrenia, are two essential steps. The aim of this study was to use such an approach to CaN A gamma. CaN A expression was analyzed in the hippocampal formation of 13 patients with schizophrenia and 12 control subjects matched for age, gender, post mortem interval and brain pH. All three isoforms were examined, using in situ hybridization histochemistry and RT-PCR coupled with laser-assisted microdissection. CaN A protein was assessed using ELISA and immunocytochemistry. CaN A mRNAs were also measured in the hippocampus in rats, both during brain development (from a late embryonic stage through to adulthood), and in adult rats treated with haloperidol or chlorpromazine. The major findings of this study are: (1) All three isoforms of the CaN A catalytic subunit are expressed in the human hippocampal formation, though the gamma isoform is not detectable in CA1. (2) CaN A expression occurs predominantly in excitatory neurons. (3) In rats, CaN A gamma was most abundant during early hippocampal development, after which it progressively decreased, in contrast to the opposite pattern of expression observed for the other isoforms (4) CaN A protein, and all three mRNA isoforms, were significantly decreased in the hippocampus in schizophrenia. (5) CaN A expression was unaltered in the antipsychotic-treated rats. Decreased hippocampal CaN expression, and its localization to excitatory neurons, extends the evidence suggesting aberrant synaptic plasticity occurs in schizophrenia, and that it may particularly affect glutamatergic transmission. In addition, the pattern of CaN A subunit expression during rat hippocampal development highlights the potential importance of CaN A gamma in the formation of this structure. The reduced expression of CaN A gamma may relate to its genetic involvement in schizophrenia, and could be part of the mechanism by which variation in the PPP3CC gene, which encodes the gamma subunit, is associated with the disease.

TISSUE MICROARRAY (TMA) PROFILING IN WHITE MATTER REVEALS MYELIN BASIC PROTEIN DECREMENTS IN SCHIZOPHRENIA

J. English,* L. Hudson, A. Jamal, S. Chu, D. Cotter
Psychiatry, Royal College of Surgeons in Ireland, Dublin, Ireland

White matter abnormalities in the dorsolateral prefrontal cortex (DLPFC) are implicated in the pathophysiology of schizophrenia (Scz). Investigations have shown reductions in myelin and oligodendroglial-associated proteins and genes and these findings are in keeping with cytoarchitectural studies that suggest the presence of a glial cell defect in Scz and bipolar disorder (BPD). These studies provide a strong argument for the examination of white matter tissue at the protein level in Scz and BPD. The Stanley Foundation Brain Consortium provided sixty-two fixed blocks of DLPFC BA9 from each of Scz, BPD and normal control groups (n = 20-22 per group) matched for age, sex, and race. These "donor blocks"were processed to paraffin before tissue microarray (TMA) construction with a Beecher Instruments Arrayer. Two tissue microarray (TMA) blocks were constructed containing four (1mm) cores per case of DLPFC sub-cortical white matter. Three sections per TMA were taken at 7μm and immunohistochemistry for glial fibrillary acidic protein (GFAP), myelin basic protein (MBP), and proteolipid protein (PLP) was undertaken. The Image-Pro Plus software package (Version 4.1) was used to measure the intensity of immunopositive staining (i.e. optical density) for each core. Significant reductions in MBP immunoreactivity were observed between Scz and control groups ($P\langle 0.01$), while no major differences were observed between BPD and control subjects ($P\rangle 0.1$). Moreover, when known concomitants (post-mortem interval, brain PH, and refrigerator interval) of protein integrity were considered as covariates, reductions in MBP immunoreactivity remained significant ($P\langle 0.01$) for Scz and control groups. Comparisons of PLP and GFAP immunohistochemistry between groups did not yield any significant findings. This study has used TMAs to confirm that a decrement of MBP protein expression is a component of the pathology of schizophrenia. TMA-based immunohistochemistry analysis permits the simultaneous analysis of hundreds of tissue samples with several antibodies, and could prove to be important tools in validating high-throughput proteomic findings. This study provides important complementary data to that already implicating presynaptic, myelin and oligodendroglial-associated genes in Scz and supports the argument for disturbed neuronal connectivity in as a central abnormality in the disease. Acknowledgement: Research supported by the Stanley Institute and NARSAD.

ALTERATIONS IN CALCIUM SIGNALING IN SCHIZOPHRENIC PREFRONTAL CORTEX

L. B. Jones
Biology, Lehman College, Bronx, NY, USA

Schizophrenia is one of the most disabling neuropsychiatric disorders. Much evidence implicates the prefrontal cortex in schizophrenia. Morphological studies in the PFC have shown a loss of MAP2, basilar dendrites, and spines in pyramidal cells. Recently, a new theory has been proposed that suggests that alterations in calcium signaling may account for many of the observed changes in schizophrenia. Recently we have begun to examine proteins important in calcium signaling. Calcium is an important second messenger with in the cell. My lab is focusing on proteins involved in the activation of CAM K II which is important for dendritic formation through the phosphorylation of MAP2 and the activation of CREB. Currently we have shown a decrease in Neurogranin in area 9 and area 32 in schizophrenic prefrontal cortex. Functionally, neurogranin acts as an upstream regulator of calcium, by binding calmodulin. In area 9 we are seeing a 50% decrease in staining in layer V and a 72% decrease in staining in layer III. In area 32 we are seeing a 40% decrease in immunostaining in layer III. A second protein involved in this pathway is calmodulin. The binding of calcium to calmodulin activates CAM Kinase II as well as CAM Kinase Kinase and CAM Kinase I. We have examined the density of pyramidal cells and non-pyramidal cells in area 9 of schizophrenic prefrontal cortex immunopositive for calmodulin. Preliminary data suggests a 32% decrease in the density of non-pyramidal cells and a 21% decrease in pyramidal cells immunopositive for calmodulin. Taken together these data suggest a disruption of the calcium signaling pathway in schizophrenic prefrontal cortex which may account for the observed morphological alterations.

INTEGRIN BETA 5 SUBUNIT EXPRESSION IN THE PREFRONTAL CORTEX IN SCHIZOPHRENIA

B. Kirkpatrick,* M. Ragheb, H. Mousta, T. Ahmad, R. C. Roberts
Psychiatry, University of Maryland, Baltimore, MD, USA

Several lines of clinical evidence suggest early developmental abnormalities increase the risk of schizophrenia in adult life. In this context, the replicated decrease in the mRNA and protein concentrations of reelin, a glycoprotein that plays an important role in early neuronal migration, is intriguing. In rodents, reelin interacts with an integrin dimer in order to exert its influence on neuronal migration, and also interacts with an integrin molecule in adult synaptosomes. Our evidence suggests that alpha 3/beta 5 integrin dimer serves as a reelin receptor. Using tissue from the Maryland Brain Collection, we tested the hypothesis that the beta 5 subunit is upregulated in schizophrenia. The density of beta 5-immunoreactive neurons and glial cells was measured in postmortem tissue from Brodmann area 46 in 14 schizophrenia and 14 control subjects, using systematic, random sampling. We found a significant shift in the expression of beta 5 integrin from neuronal to glial cells in schizophrenia compared to control subjects. This shift appeared to be due to a decrease in the percentage of immunoreactive cells among both pyramidal and non-pyramidal neurons, as well as an increase in the percentage of immunolabeled astrocytes, but not oligodendrocytes. Postmortem interval, demographics, and antipsychotic treatment did not appear to account for this change, but further study of the effects of antipsychotic medications on the integrins would be desirable. An alteration in integrin expression may be associated with schizophrenia; and may be due to the decrease in reelin. As reelin receptors become identified and alterations in their expression become clarified, the reelin signaling pathway may prove to be a useful target for the development of therapeutics. Supported in part by a grant from the Stanley Medical Research Institute, and PHS grant MH60744 (Dr. Roberts).

ALTERATIONS OF NEUREGULIN1 AND ERBB4 EXPRESSION IN THE CEREBELLUM IN SCHIZOPHRENIA

A. J. Law,* C. Shannon Weickert, T. M. Hyde, J. E. Kleinman, P. J. Harrison
Dept Psychiatry, University of Oxford, Oxford, United Kingdom

Neuregulin 1 (NRG1) has been convincingly identified as a schizophrenia susceptibility gene. NRG1 and its receptor ErbB4, play major roles in the development of the cerebellum, an area implicated in the pathophysiology of the disorder. In this region, NRG1-ErbB4 signalling is critically involved in synapse formation and the regulation of NMDA and GABA receptor expression. We hypothesized that altered expression of NRG1 in the brain may explain the genetic association. We also proposed that altered expression of NRG1 may impact on expression of the ErbB4 receptor. Utilising in-situ hybridization and immunoautoradiography we measured gene and protein expression levels for NRG-1 and ErbB4 in the post-mortem cerebellum from 32 control subjects and 32 schizophrenic patients, matched for age, pH, PMI and RNA quality. Preliminary data suggested low level expression of NRG1 in granule cells, with high levels in presumed Purkinje and Golgi cells. Therefore, quantitative measurements were obtained from autoradiographic film for the granule cell and molecular layer and single-cell analyses (100-200 cells per cell type/person) were performed for Purkinje and Golgi cells. NRG1 mRNA was decreased in Purkinje cells (-30% p=0.0001) and Golgi cells (-16%; p=0.001) in schizophrenia, with a trend reduction in the granule cell layer (p=0.06). ErbB4 mRNA was decreased in the granule cell layer of patients with schizophrenia (p=0.04). NRG1 protein was increased in the molecular layer of the cerebellum in schizophrenia (p=0.03). No changes were seen in the expression levels for the housekeeping genes cyclophilin and B-actin. Altered expression of NRG1 in schizophrenia may compromise NRG1 mediated neuronal signalling and cerebellar development. These findings compliment our recent observations of altered NRG1 gene expression in the hippocampus in schizophrenia and extend the evidence that NRG1 is involved in the disorder. A model linking NRG1 expression in the cerebellum in schizophrenia with aberrant cerebellar development and function will be offered.

THE SYNAPTIC ORGANIZATION OF THE PATCH AND MATRIX COMPARTMENTS IN THE STRIATUM OF SUBJECTS WITH DIFFERENT SUBGROUPS OF SCHIZOPHRENIA: A POSTMORTEM ULTRASTRUCTURAL STUDY

R. C. Roberts,* J. K. Roche, R. R. Conley
Psychiatry, Maryland Psychiatric Research Center, Baltimore, MD, USA

The patch and matrix compartments of the striatum process different types of information and are differentially affected in subjects with schizophrenia (SZ). The purpose of this study was to determine if the synaptic organization in different DSM-IV subgroups of schizophrenia (SZ) was differentially affected. Postmortem striatal tissue was obtained from the Maryland Brain Collection from 8 normal controls (NC), 5 SZ cases that were paranoid (SZp), and 8 SZ cases that were undifferentiated (SZu). The mean ages and postmortem intervals (PMIs) for the three groups were: NC, 43±13 yrs,5.2± 1.8 hrs; SZp, 47±8 yrs, 6.0±2.1 hrs; and SZu, 53±13yrs, 4.8±1.8 hrs. Tissue was prepared for calbindin immunohistochemistry to identify patch matrix compartments, prepared for electron microscopy and analyzed using stereological methods. Data is presented as mean ±SD per 100μm^3. Overall synaptic density and synapses characteristic of corticostriatal inputs (asymmetric axospinous, AS) were higher ($p<0.05$) in striatal matrix compartments in the SZu (3.13±0.80, 2.50±0.80) than the NC (2.46±0.46, 1.92±0.32) and SZp (2.41±0.56, 1.98±0.60). The pattern was present in both caudate and putamen, but only significant in the caudate. Overall synaptic density and AS synapses were equivalent in striatal patch compartments in the SZu (2.91±0.63, 2.30±0.53) vs. SZp (2.90±0.73, 2.25±0.80) groups and tended to be higher than the NC (2.33±0.42, 1.88±0.39). There was a pattern of higher synaptic density in the caudate patch in the SZp vs NC and SZu). In the putamen patch, overall and AS synaptic densities were highest ($p<0.05$) in the SZu group (2.97±0.76, 2.40±0.66) as compared to SZp (2.68±0.79, 2.06±0.78) and NC (2.09±0.53, 1.62±0.49). The data indicate that synaptic organization in SZu and SZp are differentially affected in striatal patch and matrix compartments. Increased cortical inputs to striatal spiny neurons would have different functional implications depending on which downstream striatal circuits are affected. Supported by MH60744 (to RCR).

SPINE LOSS ON SUBICULAR APICAL DENDRITES IN SCHIZOPHRENIA AND MOOD DISORDERS IS UNRELATED TO TREATMENT OR DURATION OF ILLNESS

G. Rosoklija,* B. Mancevski, S. Rauski, A. Duma, T. Serafimova, A. Filipovska, M. Kurzon, R. Berman, J. J. Mann, A. J. Dwork
Neuroscience, New York State Psychiatric Institute, New York, NY, USA

We reported (*Arch. Gen. Psychiatry* 57(2000)349) that the density of spines on the apical dendrites of left subicular pyramidal cells, impregnated by the rapid Golgi method, was 79% lower in a group of chronically institutionalized schizophrenia subjects (mean age 66) than in a comparison group without history of psychiatric disease. We now present confirmatory data from a younger sample of subjects. Golgi-Kopsch impregnations were performed on the left hippocampi of subjects autopsied at the Institute for Forensic Medicine in Skopje, Macedonia. Psychiatric diagnoses (or their absence) were determined by standardized interviews with relatives and by review of psychiatric records with the modified Diagnostic Evaluation After Death. This preliminary report includes 8 schizophrenia cases (mean age 46), 13 mood disorder cases (mean age 56), and 6 nonpsychiatric cases (mean age 43). Mean post mortem interval for each group was 12 hours. Duration of illness ranged from 9 to 32 years in the schizophrenia cases, and from several months to 34 years in the mood disorder cases. At least 5 well-impregnated pyramidal neurons were analyzed from each subiculum by raters masked to clinical information. Spines along the main shaft of the apical dendrite were counted manually in successive 60-micron segments. As in our older cohorts, there was a profound (>75%) loss of spines on subicular apical dendrites in schizophrenia and mood disorders ($F=169$, $df=26,2$, $P<0.00001$), including 4 treatment-naive mood disorder subjects. Combining these results with our earlier study, it is apparent that neither neuroleptic nor antidepressant drugs are necessary or sufficient to produce the observed loss of dendritic spines. A profound loss of spines on the apical dendrites of subicular pyramidal neurons is common to several psychiatric conditions, is present early in the course of disease, and is not the result of treatment or institutionalization.

NO ALTERATIONS IN CAPILLARY LENGTH DENSITY IN THE PREFRONTAL CORTEX OF SCHIZOPHRENICS

C. Schmitz,* P. Kreczmanski, R. Schmidt-Kastner, H. Heinsen, P. R. Hof
Dept. Psychiat. Neuropsychol., Div. Cell. Neurosci., Maastricht University, Maastricht, Netherlands

The presence of microvasculature abnormalities in the prefrontal cortex of schizophrenics was proposed in a recent study of molecular signatures of schizophrenia (Prabakaran et al [2004]: Mol Psychiat 9:684-697). To assess this possibility further we investigated capillary length densities within prefrontal cortex (area 9) and anterior cingulate cortex (area 24) in postmortem brains from 13 schizophrenics and 13 age- and sex-matched controls. To control that our sample of brains shared cardinal neuropathologic features of schizophrenia with previously reported case studies, we also measured cortical gray matter volumes and cortical thickness in area 9 and area 24. The mean cortical gray matter volume was significantly reduced in brains from schizophrenics compared to controls. Mean cortical thickness was significantly reduced in area 24 in schizophrenics but not in area 9. There were no differences in mean capillary length densities within area 9 and area 24 between the two groups. Thus, alterations in capillary length density in the prefrontal cortex cannot be considered a general feature of schizophrenia. Compromised brain metabolism and occurrence of oxidative stress in the brain of schizophrenics are likely caused by other mechanisms. In this context, mitochondrial programming may represent an attractive hypothesis.

NEURON NUMBER, DENSITY, AND SIZE IN THE PRIMARY AUDITORY CORTEX IN SCHIZOPHRENIA

J. F. Smiley,* A. J. Dwork, B. Mancevski, G. Rosoklija, A. Duma, D. C. Javitt
Cognitive Neuroscience and Schizophrenia, Nathan Kline Institute, Orangeburg, NY, USA

Postmortem cerebral cortex was used to measure cytoarchitectonic features of the primary auditory cortex in schizophrenia. Both left and right hemispheres were used, in order assess hemispheric asymmetries. Methods: Heschls gyri were dissected from 10 subjects with schizophrenia and 10 nonpsychiatric controls that were matched for age, postmortem interval and time in formalin. All subjects were male, and nearly all were confirmed right handers. Tissue was embedded in plastic, and Nissl-stained sections, spaced at 1mm intervals, were used for quantitative measurements. The boundaries of primary auditory cortex were identified in Nissl-stained and parvalbumin-immunolabeled sections. Stereological measurements were made in 3 laminar compartments from each hemisphere (layers III, IV, and V/VI). Results: The volume of primary auditory cortex was similar in both diagnostic groups, and in both hemispheres. Comparison of laminar volumes showed a subtle hemispheric asymmetry, such that layers IV and V/VI were about 5% larger in the left than right. In schizophrenia, this asymmetry was less pronounced but not significantly different from controls. Neuron densities were not significantly different between diagnostic groups. There was a slight right greater than left asymmetry in layers IV and V/VI that was more prominent in controls. Estimates of neuron numbers per laminar compartment also did not show a difference between diagnostic groups. Neuron sizes were not significantly different between diagnostic groups. There was some evidence for a larger neuron size on the right than on the left in layers IV and V/VI that was more pronounced in schizophrenia. Conclusions: We did not find clear cytoarchitectonic changes in the primary auditory cortex in this sample of brains from subjects with schizophrenia. Slight differences is neuron density and size in layers IV and V/VI might reflect subtle changes that could not be established with our methods. Future measurements will extend this analysis to auditory association areas, where some structural MRI studies found decreased gray matter volumes in schizophrenia. Supported by the Stanley Medical Foundation, MH067138, MH64168 and MH60877.

ULTRASTRUCTURAL STUDY OF MITOCHONDRIA IN POSTMORTEM STRIATAL PATCH AND MATRIX COMPARTMENTS IN SCHIZOPHRENIA

S. M. Somerville,* J. K. Roche, R. R. Conley, R. C. Roberts
Neuroscience, MPRC, Baltimore, MD, USA

Regional cerbral blood flow studies have shown a decrease in the striatal metabolism of patients with schizophrenia (SZs), which is

normalized by antipsychotic drugs (APDs) but only when symptoms improve. This research expanded our previous study that hypothesized that this decreased metabolism is the result of abnormalities in mitochondria, the energy producing organelles. The striatum is composed of striosomal (patch) and extrastriosomal matrix (matrix) compartments that differ in several aspects including neurochemical content and connectivity. Mitochondrial number in the patch and matrix were analyzed separately to test the hypothesis that there are more profound differences in the patches (linked with limbic function which is perturbed in Schizophrenia) of SZs versus normal controls (NCs). Postmortem tissue obtained from the Maryland Brain Collection: SZ, n=15, mean age=50, mean PMI=5; NCs, n=8, mean age=43, mean PMI=5. Electron micrographs were taken from the caudate and putamen and mitochondrial and synapse number were tallied in serial sections using stereology. Calbindin immunocytochemistry, which selectively stains the matrix, was used to differentiate patch from matrix compartments. Significant differences ($p<0.05$, ANOVA or t-test) are reported. Mitochondria (mito) per synapse in the entire cohort of SZs compared to NCs was reduced by 23% in the whole caudate and 30% in the whole putamen. In the putamen matrix, there was a 24% decrease in mito/synapse and 24% fewer mito in axon terminals in SZs compared to NCs. When dividing the SZ cohort by DSM IV subtype there were fewer mito in the neuropil of paranoid SZs compared to NCs (21%) and chronic undifferentiated (CUT) (24%) in the caudate matrix. In the whole putamen there were 41% fewer mito/synapse in paranoid SZs compared to NCs. There was also a 43% decrease in the number of mito/synapse in SZs that were treatment responsive compared to NCs in the whole putamen. In the putamen matrix there were fewer mito in axon terminals (30%) and mito/synapse (44%) in SZs that are treatment responsive compared to NCs and compared to treatment resistant (36%) cases. Based on this data there are mitochondrial number is differentially affected in SZs according to diagnostic criteria, treatment response and compartmental organization. Fewer mitochondria could mean there are less energy demands in the striatum of SZs or the energy demands are not being met.

LOCATION AND VOLUMES OF THE AUDITORY CORE, LATERAL BELT, AND PARABELT CORTICES IN THE HUMAN SUPERIOR TEMPORAL GYRUS

R. A. Sweet,* K. A. Dorph-Petersen, H. J. Gundersen, D. A. Lewis
Department of Psychiatry, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Subjects with schizophrenia demonstrate deficits in auditory sensory processing, with associated loss of gray matter volume of the auditory cortex of the superior temporal gyrus (STG). Recent postmortem studies have begun to delineate alterations in the underlying auditory corticocortical circuits. In non-human primates, auditory sensory information is processed in the STG in the hierarchically related auditory core (primary), lateral belt (secondary), and parabelt (tertiary) cortices. Interpretation of the abnormalities detected in subjects with schizophrenia would clearly be enhanced by identifying the human analogues of core, lateral belt, and parabelt. The auditory core has been mapped in humans, where it corresponds to BA41. Criteria for the lateral belt and parabelt have not been previously described in humans, nor have they been mapped on the human STG. To map the auditory lateral belt and parabelt in humans, and to confirm prior observations of the localization of the auditory core, we undertook to delineate these regions in human auditory cortex of the STG, developing and applying combined cytoarchitectonic and chemoarchitectonic criteria established in macaque. We further applied an unbiased stereologic approach to processing and sampling the human tissue in order to estimate the volumes of these regions in 8 right handed male normal control subjects. The lateral belt and parabelt appeared in humans as subdivisions of BA42, distinguishable by cytoarchitectonic features, immunoreactivity for parvalbumin, and staining for acetylcholinesterase. The lateral belt was localized predominantly in Heschl's sulcus, at times appearing on Heschl's gyrus and/or the planum temporale. The parabelt was predominantly localized to the planum temporale, but also extended onto the lateral STG at the rostral end of Heschl's gyrus. A subdivision of the parabelt into internal and external components was identified. Detailed description of the cytoarchitectonic and chemoarchitectonic features used to identify these regions will be presented, as will detailed maps and unbiased estimates of the regional volumes for the normal control subjects. Supported in part by: MH66231, MH71533, and MH45156.

ATYPICAL BUT NOT TYPICAL ANTIPSYCHOTIC DRUGS REVERSE DOPAMINE DEPLETION-INDUCED LOSS OF DENDRITIC SPINES IN THE PREFRONTAL CORTEX

H. Wang,* A. Deutch
Psychiatry and Pharmacology, Vanderbilt University Medical Center, Nashville, TN, USA

Postmortem studies have revealed a decreased volume but not a corresponding decrease in the number of neurons in the prefrontal cortex (PFC) in schizophrenia. Decreases in PFC pyramidal cell dendritic length and spine density have been reported in the PFC in schizophrenia and may contribute to the loss of cortical volume. A decreased dopamine (DA) innervation of the PFC has also been reported in schizophrenia. Because lesions of the striatal DA innervation decrease dendritic spine density and length on striatal medium spiny neurons, we posited that a similar process is operative in the PFC in schizophrenia: the loss of the cortical dopamine innervation is the proximate cause of dendritic changes in PFC pyramidal cells. Rats were injected with 6-OHDA into the VTA to lesion the DA innervation of the PFC, and three weeks later were sacrificed. Golgi-impregnated neurons in layer V of the prelimbic (area 32) part of the PFC were randomly selected and reconstructed using Neurolucida. We found a decrease in basilar dendritic spine density of layer V pyramidal neurons. To determine if the spine loss could be reversed by treatment with antipsychotic drugs (APDs), three weeks after lesioning the PFC DA innervation animals were started on treatment with either haloperidol, olanzapine, or vehicle, which continued for three weeks. Olanzapine reversed the effects of DA depletion on dendritic spine density in the PFC; haloperidol had no such effect. These data suggest that treatment with an atypical APD may reverse the changes in cortical structure present in schizophrenia, and may thereby improve certain cognitive deficits. Supported in part by MH-45124 and NS-44282 and Eli Lilly and Co.

ALTERED EXPRESSION OF NEUTRAL AMINO ACID TRANSPORTER 1 (ASCT1) IN THE CINGULATE CORTEX IN SCHIZOPHRENIA, BIPOLAR DISORDER, AND MAJOR DEPRESSION

S. Weis,* J. R. Dulay, I. C. Llenos, S. Sabunciyan, E. F. Torrey, R. H. Yolken
Neuropathology, The Stanley Medical Research Institute, Bethesda, MD, USA

Schizophrenia, bipolar disorder, and major depression are complex multigenetic, multifactorial diseases, leading to disruptive psychopathologies involving thought, perception, emotion, movement, behavior, cognition, and mood. The possible pathogenetic mechanisms at work are still not clearly understood. Various neurotransmitter systems are reported to have altered expression patterns of their receptor and transporter proteins. Changes in the expression of the neutral amino acid transporter 1 in the cingulate gyrus of the brains from individuals with schizophrenia, bipolar disorder and depression were investigated using immunohistochemistry. The results of the present study show that the protein expression of the neutral amino acid transporter ASCT1 showed different patterns of changes between schizophrenia, bipolar disorder, and depression when compared to controls. A significant decrease in immunoreactive neurons in the cortex as well as astrocytes of the white matter was seen in the brains of patients with schizophrenia. In the brains of patients with bipolar disorder and major depression, similar results were seen for the neurons. However, there were no changes in immunoreactive astrocytes of the white matter. No changes were seen for the astrocytes of the gray matter. The functions of ASCT1 in glutamate transmission are two-fold: (1) it mediates the efflux of glutamate from the neuron into the synaptic junction via Calcium-independent release, (2) it mediates both the release of alanine from glial cells and its uptake by neurons. Thus, the loss of ASCT1 on neurons might have a profound effect on glutamatergic neurotransmission in the brains of individuals with schizophrenia, bipolar disorder and major depression.

7. Genetics, Clinical

WHICH SCHIZOTYPAL SYMPTOMS DIFFERENTIATE RELATIVES OF PSYCHOTIC PATIENTS FROM GENERAL POPULATION SUBJECTS?

A. Albeniz,* I. Mata, M. Beperet, J. M. Lopez-Ilundain, F. Perez-Nievas
Fundacion Argibide, Pamplona, Navarra, Spain

Originally, the concept of schizotypal personality disorder (SPD) was developed following the observation of a higher rate of "latent, borderline, or uncertain schizophrenia" among the biological rather than adoptive relatives of schizophrenia adoptees. This was later confirmed by family studies that found a higher rate of SPD among the relatives of schizophrenics compared to controls. However, questionnaire-based studies have reported inconsistent results, some finding higher schizotypy scores in relatives of psychosis patients than controls, and some others failing to differentiate these two groups. It has been suggested that defensive response and lack of insight might account for this lack of differences. In the present study, scores on the Schizotypal Personality Questionnaire (SPQ) were compared between a sample of 280 first-degree relatives of psychosis patients and a comparison group of 391 general population controls. General population controls scored significantly higher than relatives of psychosis patients on the SPQ total scale and on the cognitive-perceptual and disorganized factors. In a second step, scores of "high schizotypy relatives" were compared with those of "high schizotypy controls". In these analyses, "high schizotypy relatives" scored than "high schizotypy controls" on the interpersonal factor. It is suggested that defensive response among relatives of psychosis patients might account for the lower scores of relatives compared to controls, especially on those symptoms that show a greater similarity with psychotic symptoms. Results among "high schizotypals", which probably do not show this defensiveness in response, might suggest that interpersonal deficits define the real psychosis-related schizotypy.

METHODS FOR DISCOVERY OF GENETIC MARKERS ASSOCIATED WITH CLOZAPINE-INDUCED AGRANULOCYTOSIS

M. Athanasiou,* C. Reed, B. Dain, J. Carr, H. Whalen, M. Lachowicz, K. Foye, A. Malhotra, S. Gerson, J. Kane
Genaissance Pharmaceuticals, New Haven, CT, USA

Clozapine is a highly efficacious drug for the treatment of schizophrenia, but its use is limited, in part due to the side effect of agranulocytosis. In order to reduce the incidence of clozapine-induced agranulocytosis (CIA), patients are required to submit to a monitoring program that requires frequent blood draws. If a genetic test to identify patients less likely to develop CIA existed, clozapine would be a safer drug, and more patients could benefit from its superior efficacy, possibly without the blood-monitoring program. To that end, we have identified a cohort of 33 cases and 54 controls and obtained clinical history and blood samples from them. Cell lines have been transformed from all patients, DNA isolated, and, when possible, the exons, intron-exon boundaries, 5-prime un-translated region and promoter region sequenced for each of 9 candidate genes. An additional 65 candidate genes will also be sequenced. Using polymorphisms and haplotypes from these candidate genes, we will perform statistical analyses to discover genetic markers associated with case status, using novel high-throughput methods that include adjustments for multiple comparisons. Here, we report the characteristics of the cohort and present the methods that will be used for the analysis.

NEUROLOGICAL SOFT SIGNS: A FOLLOW-UP STUDY OF FIRST-EPISODE SCHIZOPHRENIC PATIENTS AND HEALTHY CONTROL

S. Bachmann,* C. Bottmer, J. Schroeder
Psychiatry, University of Heidelberg, Heidelberg, Germany

Objective: Neurological soft signs (NSS) are frequently found in schizophrenia. They are indicators of both genetic liability and psychopathological symptoms. To further differentiate trait- and state-relations we compared the one-year-course of NSS in patients and controls. Method: Thirty-nine first-episode patients with schizophrenic disorders were examined after remission of acute symptoms and 14 months later using established instruments to assess diagnoses, psychopathological symptoms, predictors of outcome, handedness, and NSS. Twenty-two age- and gender-matched controls were also examined twice. Results: NSS scores in patients were significantly elevated compared to controls at both measurement points. Whereas NSS remained stable in controls (4.8 ± 3.3 at t1; 4.6 ± 3.9 at t2), they significantly ($p<0.001$) decreased in patients (15.7 ± 7.1 at t1; 10.1 ± 7.9 at t2). This effect was more pronounced ($p<0.05$) in patients with a favorable than with a chronic course and mainly accounted for by motor signs. Predictors of follow-up NSS scores were NSS at remission and compliance with treatment. Conclusions: Although NSS are intrinsic to schizophrenia, their level varies with the clinical course. Thus, NSS may correspond to both genetic liability and the activity of the disease process and be considered as potential predictors of outcome.

NEUROCOGNITION IN FAMILIES LINKED TO 1Q22

A. S. Bassett,* M. Watson, D. A. Young, L. M. Brzustowicz, E. Chow
Clinical Genetics Research Program, Centre for Addiction and Mental Health, Toronto, ON, Canada

We have previously ascertained a relatively homogeneous sample of 25 families found to have highly significant linkage of narrowly defined schizophrenia/schizoaffective disorder (SZ) to chromosome 1q22 (*Science*, 2000). We have recently reported evidence of linkage disequilibrium to a gene in this region, carboxyl-terminal PDZ ligand of neuronal nitric oxide synthase (CAPON), with important functions involving the glutamate and nitric oxide neurotransmitter systems and synaptogenesis. We have now embarked on further phenotyping of affected (SZ) and unaffected (UA) family members and present initial neurocognitive findings. We used a comprehensive battery of neurocognitive tests and compared our initial results of individuals affected with schizophrenia or schizoaffective disorder (n=26) to those UA family members (n=28). The two groups did not differ in sex and mean age. The Wechsler Test of Adult Reading (WTAR), a measure of premorbid intelligence, indicated that the premorbid IQ of the SZ group was similar to that of the UA group. As expected, on most other neurocognitive tests the SZ group performed significantly worse than the UA group. Most notably, the SZ group had significantly lower current WAIS-III Full-Scale IQ than the UA group (78 vs 108, $p<0.001$), and had worse performance on measures

of verbal learning, visual memory and motor skills (all p<0.0001). However, the results on the Stroop (word, colour), and symbol search tests were not significantly (p>0.05) different between the two groups. The results are in line with the previous literature comparing heterogeneous groups of patients and family members. Schizophrenia linked to a susceptibility gene on 1q22 therefore appears to have a similar neurocognitive phenotype to schizophrenia in the general population. The results further suggest that there may be certain tests of neurocognition that reflect minor expression of vulnerability to a 1q22 schizophrenia susceptibility gene.

AN INVESTIGATION OF DNA COPY NUMBER CHANGES IN NORMAL HUMAN BRAIN AND IN SCHIZOPHRENIA USING ARRAY COMPARATIVE GENOME HYBRIDISATION

C. Beasley,* G. Wilson, W. G. Honer, R. Holt
Psychiatry, University of British Columbia, Vancouver, BC, Canada

Recent studies have indicated that during embryonic neurogenesis many neural progenitor cells are aneuploid and that some of these cells survive into adulthood as mature neurons. In the hippocampus neurogenesis continues throughout adulthood. In this study we investigated changes in DNA copy number between the hippocampus and prefrontal cortex both in normal adult brain and in schizophrenia to identify non-inherited DNA abnormalities within the adult brain. Recent advances in microarray based comparative genome hybridization (array-CGH) now make it possible to rapidly scan the entire genome for DNA copy number alterations. Using array-CGH, we evaluated DNA copy number profiles in five individuals with schizophrenia and five unaffected controls. Arrays were spotted with DNA from large insert (~200 kb) genomic BAC clones, approximately evenly spaced across the genome. Each array comprised 2464 clones, spotted in triplicate, giving direct coverage of approximately 15% of the genome. For each individual case DNA obtained from prefrontal cortex was hybridized against DNA obtained from hippocampus. Each array was performed in duplicate. Analysis using stringent thresholds revealed putative copy number differences between hippocampus and prefrontal cortex at a number of sites throughout the genome in both individuals with schizophrenia and in control subjects. However, further examination showed these potential changes in DNA copy number to be replicable at only 1 site. This clone, situated at 6p21, was affected in one individual with schizophrenia. This aberration will be further explored by quantitative real time PCR. This preliminary study provides some evidence for the presence of DNA copy number variation between brain regions in the adult human brain, which may be consistent with localized aneuploidy. Non-inherited DNA copy number variation could be relevant to schizophrenia.

DYSBINDIN (DTNBP1): AN INFLUENCE ON NEUROCOGNITION?

K. E. Burdick,* J. M. Ekholm, B. Funke, C. T. Finn, R. J. Kucherlapati, A. K. Malhotra
Psychiatry Research, Zucker Hillside Hospital-NSLIJHS, Glen Oaks, NY, USA

Dysbindin is an evolutionarily conserved protein, which binds alpha and beta dystrobrevin, components of the dystrophin complex (DPC) in muscle and brain. Converging evidence supports its role in schizophrenia (SZ), with data derived from molecular genetic studies of the disorder demonstrating a significant association of several variants in the gene that encodes for dysbindin (DTNBP1) located on chromosome 6p22.3. Our group has recently replicated previous reports of association and identified a risk haplotype (CTCTAC) in a US population, further implicating the gene for dysbindin in the etiology of SZ. Dystrophin is known to be defective in a group of patients with Duchenne muscular dystrophy (DMD), a common, lethal, chromosome X-linked disease. Patients with DMD have demonstrated specific cognitive impairment, raising the possibility that the cognitive abnormalities are attributable to synaptic dysfunction associated with deficits in brain dystrophin molecules. Significant neurocognitive impairment is also a consistent finding in patients with SZ, with established generalized decline and accompanying deficits in specific domains. The overlapping cognitive phenotypes in DMD and SZ suggest that the DPC might be involved in the etiology of both DMD and SZ. Despite evidence indicating a possible role for dysbindin genotype in neurocognitive functioning, there have been no systematic investigations of this relationship in healthy volunteers. Thus, we tested for association between a 6-locus dysbindin risk haplotype, recently identified by our group, and neurocognition in 154 healthy Caucasian volunteers. Subjects were genotyped across a cassette of single nucleotide polymorphisms (SNPs) within the DTNBP1 gene, and haplotype analyses were conducted. Each subject underwent neurocognitive assessment of multiple domains of cognition. We detected significant associations between the presence of the risk haplotype and poorer performance on measures of auditory attention (Digit Span) and estimated verbal intellectual functioning (WRAT-III Reading). Moreover, the minor allele at DNTBP1 marker 1578 was associated with poorer performance on the same measures and an additional measure of executive functioning (Trails B). These data suggest that the effect of DTNBP1 genetic variation may be associated with neurocognition in healthy subjects. Studies are underway to assess the relationship of DTNBP1 to cognitive function in patients with SZ.

MOTOR ABNORMALITIES IN FAMILY MEMBERS OF PATIENTS WITH SCHIZOPHRENIA

M. Caligiuri,* J. Lohr, C. Dean, S. Sponheim, B. Hegeman
Psychiatry, UCSD, La Jolla, CA, USA

Diseases of complexity, such as schizophrenia, are likely influenced by a number of interacting genetic and non-genetic factors. The identification of each of these factors is complicated because the effect of any one of them may be obscured by the effects of others. One approach to resolving this complication is to identify endophenotypes that are correlated with and mediate disease susceptibility. Endophenotypes can help resolve the genetic basis of a complex disorder by allowing genetic studies to focus on more specific phenotypes likely to be under direct and unique genetic control and by potentially helping to identify subgroups of diseased individuals with a common, and more homogenous, genetic profile for disease susceptibility. Numerous studies have revealed increased neurological signs, especially motor signs, in non-psychotic parents, children and siblings of patients with schizophrenia. Two particular motor abnormalities, motor disinhibition and failure to scale movement velocity, may be ideal candidate endophenotypes for schizophrenia because of their underlying basal ganglia pathophysiology and because these motor signs parallel the positive and negative symptoms of schizophrenia, respectively. Their heritability, however, is unknown at this

time. In the present study, we investigated the heritability and co-heritability of motor disinhibition and velocity scaling impairment using nuclear families ascertained through a schizophrenic proband. Schizophrenia probands and their first-degree family members underwent quantitative motor assessments of hand force steadiness (FS, to measure motor disinhibition) and speed and accuracy of ballistic wrist flexion movements to fixed targets (VS, to measure velocity scaling). Results indicated that substantially more siblings of patients who had FS abnormalities also showed FS abnormalities (44%) compared to siblings of patients who did not show FS abnormalities (18%). The results for VS were similar, with 72% of the siblings of schizophrenia patients with VS abnormalities demonstrating VS abnormalities themselves; whereas only 42% of the siblings of schizophrenia patients with normal VS had similar motor abnormalities. While these data are insufficient at this time to address heritability of the motor traits, they do support the hypothesis that motor disturbances may have a higher genetic load in families of schizophrenia patients with motor abnormalities than without.

INCREASED MORTALITY IN SCHIZOPHRENIA ASSOCIATED WITH DEVELOPMENTAL ANOMALIES

O. Caluseriu,* E. W. Chow, V. Wong, K. Tam, A. S. Bassett
Clinical Genetics Research Program, Centre for Addiction and Mental Health, Toronto, ON, Canada

The presence of congenital anomalies in schizophrenia (SZ) patients supports a neurodevelopmental theory of SZ pathogenesis. Patterns of these anomalies may identify homogeneous subgroups of SZ. One such pattern, found in ~ 2% of all patients with SZ, is represented by a recognized genetic syndrome: 22q11 Deletion Syndrome (22qDS). It is known that patients with SZ have a high level of natural mortality, in part due to unrecognized illnesses, but mortality in SZ associated with developmental syndromes is unknown. We compared the natural mortality rate in adults with 22qDS and SZ (22qDS-SZ) and in another subgroup of dysmorphic patients with SZ. We screened patients with SZ for birth defects (eg congenital heart defects), hypernasal speech, endocrine features (eg hypoparathyroidism/hypocalcemia), dysmorphic facial features and learning difficulties in order to identify individuals who might have 22qDS. Patients who fulfilled our clinical screening criteria for 22qDS were offered a standardized karyotype and molecular cytogenetic test (FISH, fluorescence in situ hybridization), which detects >95% of 22q11.2 deletions. There were 43 22qDS-SZ patients (21 males; 22 females; mean age 35.6, SD 9.6 y); one female (2.3%), with no major congenital heart defects (CHD), died at age 18 y of shock as a possible result of autonomic system dysfunction reported previously in patients with 22qDS. We also identified 39 SZ patients with high scores on our screening criteria (4-5/5) consistent with 22qDS but with no detectable 22q11.2 deletion or karyotypic anomalies. In recontacting these subjects for further genetic studies, we found that 4 (10.3%), two men and two women with no CHD, had died at a mean age of 31.6 y (range: 23.3-43.3 y). They were younger than the remaining 35 subjects (18 males; 17 females; mean age 42.6, SD 10.9 y; p=0.06). Cause of death was considered to be of cardiovascular origin in all cases. All patients were on neuroleptics. The syndromal features in this homogeneous subgroup of subjects warrant further genetic investigations to detect molecular anomalies such as atypical deletions or duplications. 22qDS, which is characterized by known multisystemic problems, latent or manifest, can provide guidelines to investigate and treat patients with only clinical features of 22qDS. This study underlies the importance of having an index of suspicion for minor physical anomalies and birth defects when diagnosing patients with schizophrenia.

DISC1/TRAX HAPLOTYPES ASSOCIATE WITH SCHIZOPHRENIA, REDUCED PREFRONTAL GRAY MATTER, AND IMPAIRED SHORT- AND LONG-TERM MEMORY

T. D. Cannon,* W. Hennah, T. van Erp, P. Thompson, J. Lonnqvist, M. Huttunen, T. Gasperoni, A. Tuulio-Henriksson, T. Pirkola, A. Toga, J. Kaprio, J. Mazziotta, L. Peltonen
Psychology and Psychiatry & Biobehavioral Sciences, UCLA, Los Angeles, CA, USA

Chromosome 1q42 is among several genomic regions showing replicated evidence of linkage with schizophrenia, but the specific susceptibility mechanisms underlying this relationship remain to be identified. In complexly inherited illnesses, association with endophenotypic traits involved in disease pathogenesis provides convergent validation of putative disease-related polymorphisms. Here we examined a series of haplotype blocks of single nucleotide polymorphic (SNP) markers from a segment of 1q42 spanning the Disrupted-In-Schizophrenia-1 (DISC1) and Translin-Associated Factor-X (TRAX) genes using samples of Finnish twin pairs concordant and discordant for schizophrenia and healthy control twins. Recessive transmission of a common 3-SNP haplotype incorporating markers near a translocation breakpoint of DISC1 and dominant transmission of a rare 4-SNP haplotype incorporating markers from both the DISC1 and TRAX genes were significantly more common among individuals with schizophrenia (OR=2.6, p=.015; OR=13.0, p=.001, respectively). These haplotypes were also associated with several quantitative endophenotypic traits previously observed to co-vary with schizophrenia and genetic liability to schizophrenia, including impairments in short- and long-term memory functioning and reduced gray matter density in the prefrontal cortex, as demonstrated using a population-based brain atlas methodology, with a trend toward association with reduced hippocampal volume. Thus, specific alleles of the DISC1 and TRAX genes on 1q42 appear to contribute to genetic risk for schizophrenia through disruptive effects on the structure and function of the prefrontal cortex, medial temporal lobe, and other brain regions, effects that are consistent with their production of proteins that play roles in neurite outgrowth, neuronal migration, synaptogenesis, and glutamatergic neurotransmission.

SINGLE NUCLEOTIDE POLYMORPHISM IN THE α_{1A}-ADRENOCEPTOR PROMOTER IS ASSOCIATED WITH RESPONSE OUTCOME TO RISPERIDONE

D. Clark,* M. Arranz, I. Mata, R. W. Kerwin
Clinical Neuropharmacology (PO51), Institute of Psychiatry, London, United Kingdom

In comparison to other atypical antipsychotics, risperidone demonstrates high affinity to the α_1-adrenergic receptor subtypes. The importance of this in the treatment of psychotic disorders has been demonstrated by combining prazosin (an α_1-antagonist) with haloperidol (typical antipsychotic) to produce a limbic selective dopaminergic effect similar to that seen with atypical antipsychotics. We chose to investigate the influence of polymorphisms in the gene coding for the α_{1A} subtype of the α_1-adrenergic receptor family in response outcome to risperidone. We hypothesised that polymor-

phisms in the promoter region of this gene may contribute to the inter-individual variations observed in response to risperidone by altering the process of receptor expression. This was explored by assessing the distribution of 8 known single nucleotide polymorphisms (-9625-G/A, -7255-A/G, -6274-C/T, -4884-A/G, -4155-C/G, -2760-A/C, -1873-G/A and -563-C/T) between responders and non-responders using Chi-squared tests and linear regression. 75 subjects of Basque origin were examined. All received risperidone treatment that was assessed prospectively using the Positive and Negative Symptoms Scale and the Global Assessment Scale. An association between the -1873-G/A polymorphism and risperidone response was discovered (p=0.03) which appears to relate to change in positive symptoms (p=0.04).

ASSOCIATION STUDY BETWEEN THE SER-9-GLY POLYMORPHISM OF THE D3 DOPAMINERGIC RECEPTOR GENE AND RESPONSE TO CONVENTIONAL ANTIPSYCHOTICS IN PATIENTS WITH SCHIZOPHRENIA

Q. Cordeiro,* K. Miguita, E. Miracca, H. Elkis, H. Vallada
Department of Psychiatry, School of Medicine, Sao Paulo, Sao Paulo, Brazil

Conventional antipsychotics have a high affinity for dopamine receptors, which are therefore interesting loci to be investigated in pharmacogenetic studies of psychosis. We have previously found an association between the Ser-9-Gly polymorphism of the D3 dopaminergic receptor (DRD3) gene and response to conventional antipsychotics in patients with schizophrenia. In the present study, we investigated the hypothesis that the Ser-9-Gly polymorphism of the DRD3 gene may play a role in the inter-individual difference on the response to typical antipsychotic drugs, using a bigger sample of schizophrenic patients who have undergone long term treatment with these drugs. Patients who failed to respond clinically to at least three different conventional antipsychotics of two different classes in the last five years were considered poor responders (n=59). The remainder (n=53) were good responders. No significant differences were found in allelic (OR=0.88, 0.49<OR<1.56; X2=0.23, 1 d.f., p=0.63) and genotypic (X2=0.25, 2d.f., p=0.88) distributions between the groups of poor and good responders. The results do not support our preliminary finding that the Ser-9-Gly polymorphism of the DRD3 gene may influence the response to conventional antipsychotics in our Brazilian sample of patients with schizophrenia.

NEW CANDIDATE GENES IN TARDIVE DYSKINESIA: INTERACTION BETWEEN DRUG TRANSPORTER AND TRANSDUCTION PATHWAY

V. De Luca,* G. Remington, H. Y. Meltzer,
J. A. Lieberman, S. G. Potkin, J. L. Kennedy
Neurogenetics, Centre for Addiction and Mental Health, Toronto, ON, Canada

Pharmacogenetics, using a candidate gene association approach, investigates pharmacodynamic and pharmacokinetic gene factors that may influence drug response and side effects. For example, about 20% of patients with schizophrenia receiving antipsychotic treatment develop tardive dyskinesia (TD), an involuntary movement disorder associated with long-term conventional antipsychotic administration. To date though, there are no published reports correlating certain candidate genes (e.g. drug transporters and transduction signaling pathways) with the pathogenesis of TD. This study, carried out at 4 sites and focusing on the Multi Drug Resistance 1 and G-protein Beta3 subunits, recruited 160 patients with schizophrenia who were assessed for TD using the Abnormal Involuntary Movement Scale (AIMS). DNA samples were subsequently genotyped for the MDR1 C3435T polymorphism and GNB3 C825T polymorphisms, while Gene-Gene interactions analysis was applied to calculate the Observed and Expected Odds Ratio for all 9 MDR1-GNB3 genotypes combinations. The highest effect size (OR=1.9) occurred in the interaction between GNB3 CT and MDR1 CC genotypes conferring risk for TD; however, the overall model was not significant (p=.98). Further investigations of these genes are required to confirm our findings.

EVIDENCE FROM A PRELIMINARY STUDY THAT DYSBINDIN-1 IS IMPLICATED IN PREFRONTALLY MEDIATED COGNITIVE PERFORMANCE IN SCHIZOPHRENIA

G. J. Donohoe,* A. Corvin, D. Morris, H. Garavan,
I. H. Robertson, S. Clarke, K. McGee, S. Schwaiger,
J. M. Nangle, M. Gill
Department of Psychiatry, Trinity College Dublin, Dublin, Ireland

Introduction: Dysbindin-1 has been identified as a likely susceptibility gene in schizophrenia in independent association samples. Although the function of this gene is uncertain, studies of post mortem tissue have found evidence for expression of the gene throughout the brain, including prefrontal and hippocampal regions. The aim of the present study was to compare cognitive functioning in patients with and without the dysbindin risk allele in a sample previously reported to show an association with the gene (NM Williams et al, *Arch Gen Psychiatry*. 2004 Apr;61(4):336-44). Method: 10 patients identified as risk haplotype carriers were compared with 20 patients identified as non risk haplotype carriers on neurocognitive measures of a) premorbid and current general cognitive functioning (WTAR and WAIS subtests), b) working memory (CANTAB SWM, Weschler LN sequencing), c) episodic memory (CANTAB PAL, Weschler logical memory), and d) attention (CANTAB IED, XY task). Results: No differences were observed between risk haplotype carriers and non-carriers on either pre-morbid or current cognitive functioning, or verbal or spatial episodic memory. By contrast, risk haplotype carriers showed significantly better strategic performance scores than non-carriers on our spatial working memory task (t=2.33; p=.029) and significantly better performance scores on the XY task, a go/no-go measure of attentional inhibition (t=2.62; p=.022). Discussion: This study suggests that the Dysbindin-1 risk haplotype may mediate aspects of cognition that involve prefrontal lobe functioning. We will discuss these findings in light of recent speculation in the literature concerning the possible neurobiological function of Dysbindin-1.

HYPOCHOLESTEROLEMIA AND VIOLENT SUICIDE: A PEDIGREE ANALYSIS

P. F. Edgar,* K. Ungerer, J. Burnett, N. R. Poa
Molecular Psychiatry Group, University of Otago, Christchurch, New Zealand

A number of studies have demonstrated an association between low plasma cholesterol levels and antisocial personality disorder, violence and suicide. In addition, a recent meta-analysis indicated low plasma cholesterol and, specifically, violent suicide was associated.

In a young man that presented with schizophrenia, paranoid subtype, we found hypocholesterolemia (1.2 mmol/L), low plasma vitamin E (8 μmol/L) acanthocytosis and hypobetalipoproteinemia (< 0.23 g/L). We found he was heterozygous for apolipoprotein B truncated at 1366Tyr (TAC → TAA). He had no history of violence towards self or others, but his father, two paternal uncles, his paternal grandfather and a paternal great uncle died by suicide using firearms. In addition, one of these uncles perpetrated a double-murder suicide. A surviving uncle was tested and exhibited hypocholesterolaemia (2.2 mmol/L) and low vitamin E(12 μmol/L). He had a distinctly hyperthymic temperament. This pedigree includes six paternal uncles and one paternal aunt. Further pedigree analysis is underway. Demonstration of an inheritable phenotypic association between impulsive violent behaviour and a biochemical marker could lead to insights into the molecular basis for a predisposition to impulsive violent behaviour.

AVOIDANT PERSONALITY DISORDER IN RELATIVES OF PATIENTS WITH SCHIZOPHRENIA: A SEPARABLE SCHIZOPHRENIA SPECTRUM DISORDER

D. L. Fogelson,* K. H. Nuechterlein, R. A. Asarnow, K. L. Subotnik, D. L. Payne, K. C. Jacobson, M. C. Neale, K. S. Kendler

Department of Psychiatry and Biobehavioral Sciences, University of California Los Angeles, Los Angeles, CA, USA

Previously we reported that avoidant personality disorder (APD) aggregates in first degree relatives of schizophrenia probands (Sz Rels) and appears to be another Sz spectrum disorder (SzSpD). However, is it merely a forme fruste of other SzSpDs? Does detection of APD in Sz Rels without other SzSpDs mainly reflect a near miss for a diagnosis (Dx) of another SzSpD? Are some symptoms (Sxs) of APD distinctively more characteristic of Sz Rels than community controls (CCs) as measured by the base rates of avoidant Sxs in Sz Rels compared to CCs? 378 Rels 18 years & older of probands with adult or childhood onset Sz and 246 Rels of CCs were blindly interviewed with the DIS, PSE, & SCID. Dxs were made using direct interview, family history, & med records. The number of schizotypal (SPD) & paranoid personality disorder (PPD) Sxs was examined in the Sz Rels with APD and no other SzSpD (only APD), n=25, & compared to CC Rels with no Sz spectrum Dx or only APD, n=245, to address if APD is a forme fruste of other SzSpDs. Only 8% of the Sz Rels with only APD were 1 criterion short of a DSM-III-R Dx of SPD (compared to 0% of the CCs); only 4% were 1 criterion short of a Dx of PPD (compared to 1% of CCs). Dimensional scores were also examined & showed a median score of 14 for SPD in Sz Rels with only APD and 10 in CCs. The median scores for PPD were 11 and 7. The mean frequency of individual avoidant Sxs in Sz Rels with only APD, n=25, was compared to CCs with only APD, n=4, to examine whether certain APD symptoms are more characteristic of Sz Rels. Three Sxs were 1.65 times more likely to occur in Sz Rels: avoids people unless certain of being liked, avoids interpersonal contact at job/socially, & reticent in social situations. The base rates of avoidant Sxs were also examined in Sz Rels, n=368, & in CCs, n=245. The first five DSM-III-R APD criteria were more frequent in the Sz Rels than CCs, P=.001 where p<.007 is significant. These data indicate that APD is a separate SzSpD, not merely a forme fruste of sub-clinical SPD/PPD. Most APD cases were not near misses for SPD/PPD, although as expected Sz Rels with only APD have slightly more SPD/PPD Sxs than CCs. APD in the Sz Rels is more likely to include certain APD symptoms. The base rates of 5 APD Sxs were more frequent in Sz Rels than in CCs. These data suggest that avoidant Sxs & APD represent an extended phenotype that may be helpful in the delineation of the familial transmission of Sz.

NEUROCOGNITIVE MEASURES IN GENETIC STUDIES OF SCHIZOPHRENIA

R. E. Gur,* M. Calkins, J. D. Ragland, J. Richard, R. C. Gur

Psychiatry, Penn, Philadelphia, PA, USA

Cognitive deficits in schizophrenia are well established and are increasingly recognized as important targets for intervention and as providing potential quantitative endophenotypic markers of vulnerability. We developed a computerized neurocognitive battery that was validated in healthy people (1) and patients with schizophrenia (2). We documented deficits in executive and memory functions in patients, and have observed that unaffected family members, as a group, have an intermediate level of performance between that of probands and that of healthy controls. This battery is currently being administered in three collaborative genetic studies of schizophrenia that apply alternative models and ascertainment strategies in diverse populations. Data accumulated to date includes 301 participants from a multiplex multigenerational Caucasian sample (MGI), 720 participants from an African-American sample (PAARTNERS: sibling pairs, trios and multiplex) and 344 participants from a consortium sample (COGS: parents and sibling). Across samples, the profile of probands shows deficits in executive and memory functions. Unaffected family members are intermediate between patients and controls and have a similar profile to that of patients. In the multiplex multigenerational sample we tested the hypothesis that neurocognitive deficits reflect the degree of genetic predisposition for schizophrenia. Supporting this hypothesis, individuals with schizophrenia (n=55) were more impaired than their non-psychotic first-degree relatives (n=130), who in turn were more impaired than second-fourth degree non-psychotic relatives (n=116) on measures of attention and memory. The groups did not differ in gender distribution, age and parental education. The results support the utility of neurocognitive measures as endophenotypes that can help establish genetic mechanisms for schizophrenia. Work was supported by NIMH grants MH42191 (MGI is a 3-site collaboration: PENN, PITT, SFBR); MH66121 (PAARTNERS is a 8-site collaboration: UA, Duke, UM, MSM, PENN, PITT, SCSM, UT); MH65578 (COGS is a 7-site consortium: Harvard, Mt. Sinai, PENN, UCHSC, UCLA, UCSD, U WA) 1. Gur RC, et al. (2001). Computerized Neurocognitive Scanning: I. Methodology and validation in healthy people. *Neuropsychopharmacology*, 25:766-776. 2. Gur RC, et al. (2001). Computerized Neurocognitive Scanning II: The profile of schizophrenia. *Neuropsychopharmacology*, 25:777-788.

EVIDENCE OF NOVEL NEURONAL FUNCTIONS OF DYSBINDIN, A SUSCEPTIBILITY GENE FOR SCHIZOPHRENIA

R. Hashimoto,* T. Numakawa, Y. Yagasaki, T. Ishimoto, T. Okada, T. Suzuki, N. Iwata, N. Ozaki, T. Taguchi, M. Tatsumi, K. Kamijima, R. Straub, D. Weinberger, H. Kunugi

Mental Disorder Research, National Institute of Neuroscience, NCNP, Kodaira, Tokyo, Japan

Genetic variation in dysbindin (DTNBP1: dystrobrevin binding protein 1) has recently been shown to be associated with schizophrenia. The dysbindin gene is located at chromosome 6p22.3, one of the

most promising susceptibility loci in schizophrenia linkage studies. We attempted to replicate this association in a Japanese sample of 670 patients with schizophrenia and 588 controls. We found a nominally significant association with schizophrenia for four single nucleotide polymorphisms and stronger evidence for association in a multi-marker haplotype analysis (p=0.00028). We then explored functions of dysbindin protein in primary cortical neuronal culture. Overexpression of dysbindin induced the expression of two presynaptic proteins, SNAP25 and synapsin I, and increased extracellular basal glutamate levels and release of glutamate evoked by high potassium. Conversely, knockdown of endogenous dysbindin protein by small interfering RNA (siRNA) resulted in the reduction of pre-synaptic protein expression and glutamate release, suggesting that dysbindin might influence exocytotic glutamate release via upregulation of the molecules in pre-synaptic machinery. The overexpression of dysbindin increased phosphorylation of Akt protein and protected cortical neurons against neuronal death due to serum deprivation and these effects were blocked by LY294002, a phosphatidylinositol 3-kinase (PI3-kinase) inhibitor. SiRNA-mediated silencing of dysbindin protein diminished Akt phosphorylation and facilitated neuronal death induced by serum deprivation, suggesting that dysbindin promotes neuronal viability through PI3-kinase-Akt signaling. Genetic variants associated with impairments of these functions of dysbindin could play an important role in the pathogenesis of schizophrenia.

BRAIN-DERIVED NEUROTROPHIC FACTOR VAL66MET POLYMORPHISM: ITS EFFECTS ON COGNITIVE FUNCTIONS AND MRI GRAY MATTER BRAIN VOLUMES IN HEALTHY VOLUNTEERS AND SUBJECTS WITH SCHIZOPHRENIA

B. Ho,* T. H. Wassink, P. Milev, N. C. Andreasen
Psychiatry, University of Iowa, Iowa City, IA, USA

Background: Activity-dependent release of brain-derived neurotrophic factor (BDNF) modulates synaptic plasticity, and plays a key role in hippocampus-mediated memory functions. Recent studies suggest that the $BDNF_{Met}$ variant of the Val66Met polymorphism is associated with reduced intracellular BDNF trafficking and release, and with poorer declarative memory performance. Since activity-dependent BDNF release also occurs in neocortical neurons, this functional SNP may mediate other cognitive functions as well, though its role in cognitive impairment among schizophrenia patients has not been systematically studied. Methods: A comprehensive battery of standardized neuropsychological tests was administered to 157 healthy volunteers and 340 patients with DSM-IV schizophrenia. Approximately two-thirds of the sample also received multispectral MRI brain scans. We examined the effects of genotype (Met/Met or Met/Val versus Val/Val) on five cognitive domain scores, and on measures of gray matter (GM) volumes. Results: There was a significant genotype effect on verbal memory. Both patients and healthy volunteers with at least one Met allele had poorer verbal memory performance when compared to their Val/Val counterparts. For visuospatial abilities, there was a significant genotype-by-diagnosis effect such that impairment in visuospatial abilities associated with the Met allele was found in schizophrenia subjects, but not observed in healthy volunteers. There were significant genotype effects on GM volumes within brain regions known to subserve these two domains of cognition, with Met allele subjects having smaller temporal and occipital GM. No statistically significant genotype effects were seen with the three remaining cognitive domain scores, or with frontal or parietal GM volumes. Conclusions: Our findings provide further support that the $BDNF_{Met}$ variant is associated with poorer memory performance mediated by medial temporal lobe structures. The Met allele may also have a specific role in conferring visuospatial dysfunction in schizophrenia.

ASSOCIATION BETWEEN POLYMORPHISMS IN THE BDNF AND THE G72 GENE AND LATERAL VENTRICLE VOLUME IN SCHIZOPHRENIA

M. Hoogendoorn,* N. van Haren, S. Bakker, J. P. Selten, R. Sinke, P. Pearson, R. Kahn
Psychiatry, UMC Utrecht, Utrecht, Netherlands

The most prominent structural brain abnormalities in schizophrenia are enlarged ventricle size and reduced cerebral volume. To date, little is known about the relationship between these abnormalities and genes that may be involved in the pathogenesis of schizophrenia. Recently, several putative candidate genes were identified by positional genetic approaches. We hypothesized that genes underlying schizophrenia might also modulate variation in gray and white matter and ventricular volume in schizophrenia patients. Therefore, we investigated the influence of polymorphic markers in six positional candidate genes (NRG1, Dysbindin, G72, RGS4, BDNF and a gene of which the identity will be revealed) on volumetric measures in a sample of Dutch patients. The sample consisted of 91 unrelated patients (71/20 M/F) with a primary diagnosis of schizophrenia (DSM-IV). All patients were physically healthy, and had no history of head injury or a diagnosis of alcohol/drug abuse or dependence. Magnetic Resonance Imaging (MRI) brain scans were acquired from all patients. Volumes of intracranium, cerebral gray matter and white matter and lateral ventricles were measured. Volumes of gray and white matter and lateral ventricles were adjusted for intracranial volume, age and gender using linear regression analyses. Genotypes of thirteen previously associated SNPs within the six candidate genes and 2 BDNF microsatellite markers were obtained. Tests of association to quantitative traits were performed to study the influence of alleles on adjusted volume measures of cerebral gray and white matter and lateral ventricles. We found no association between gray and white matter volume and any of the tested polymorphisms. However, we observed significant associations between lateral ventricle volume and one of the BDNF microsatellite markers, and also between lateral ventricle volume and a two marker haplotype of this microsatellite marker and BDNF SNP rs6265 (Val66Met polymorphism) (p=0.025 and p=0.022 respectively). Additionally, a significant association between lateral ventricle volume and a three marker haplotype of the G72 SNPs was observed (p=0.049). The results show that MRI-derived intermediate phenotypes could be useful for genetic association analyses in complex psychiatric disorders, and deserve further exploration as quantitative traits in association studies. We are currently investigating the influence of these genes on volumetric measures in healthy controls.

"KRAEPELINIAN" AND "BLEULERIAN" SCHIZOPHRENIA: A GENETIC DISSECTION OF A COGNITIVE ENDOPHENOTYPE

A. Jablensky,* M. Dragovic, J. Badcock, L. Kalaydjieva
Psychiatry and Clinical Neurosciences, University of Western Australia, Perth, WA, Australia

Cognitive deficit was conceived by Emil Kraepelin (1919) to be a core feature of a single disease, dementia praecox. In contrast, Eugen

Bleuler (1923) hypothesised that schizophrenia was the "common final pathway" for an aetiologically mixed group of disorders. The controversy engendered by these two great clinicians survives unscathed into the present diagnostic concepts of schizophrenia. Since schizophrenia is clinically heterogeneous and genetically complex, ICD-10 and DSM-IV diagnoses may not provide the optimal phenotypes for genetic analysis. We explored a novel, endophenotype-based approach in the search for susceptibility genes by generating a composite quantitative phenotype which integrates multiple measurements of neurocognitive performance in the domains of attention, working memory, verbal learning, speed of information processing and personality dimensions, using a variant of latent class analysis known as Grade of Membership (GoM). The Western Australian family sample (N=97; 386 individuals) used in this analysis yielded two distinct neurocognitive and clinical phenotypes, each correlated with schizophrenia: one indexing severe neurocognitive deficit and predominantly 'negative' symptoms; and one neurocognitively unimpaired, with florid 'positive' psychotic symptoms. The composite neurocognitive trait was used in linkage analysis as a liability covariate, on which each individual in the sample (affected and unaffected) was assigned a score. A 10 cM genome scan, followed by ordered sets analysis (OSA) resulted in consistent, significant or suggestive linkage signals for the neurocognitive deficit subtype in several genome regions (6p, 8p and 10q); no comparably consistent findings have yet been obtained for the neurocognitively unimpaired subtype, suggesting a greater genetic heterogeneity. These results support "splitting" schizophrenia into aetiologically distinct subtypes and demonstrate an increase in power resulting from use of composite quantitative endophenotype.

POLYMORPHISM IN THE COMT GENE IS ASSOCIATED WITH SCHIZOTYPY

S. John,* E. Barkus, J. Stirling, F. Jury, S. Lewis, B. Deakin
CIGMR, Manchester University, Manchester, United Kingdom

Background: Recent research has identified several promising susceptibility genes for schizophrenia. Family studies suggest, vulnerability to schizophrenia is continuously distributed in the population and influenced by multiple genes of small effect, therefore, susceptibility genes may associate with a trait of psychosis-proneness. Much evidence suggests that schizotypy is a quantifiable trait of psychosis-proneness, which is stable, heritable and normally distributed in the general population. We investigated whether recently described schizophrenia polymorphisms also associate with schizoptypy. Aim: To determine if genes DRD2, COMT and CNR1 influence variation in schizotypy score. Methods: 109 Student volunteers filled in the O-Life questionnaire on the university intranet and 92 (84% return rate) returned buccal swabs through the post. DNA was eluted directly from the IsoCode paper for use in genotyping assays. Seven polymorphisms in CNR1, DRD2 and COMT were genotyped by capillary electrophoresis or Taqman assays. Linear regression analysis was used to test for associations between genotypes and schizotypy scores. Results: There was no significant association with a trinucleotide repeat or SNP in the CNR1 gene or a 3 SNP haplotype in the DRD2 gene. An intronic SNP (rs165599) in the COMT gene was significantly associated with schizotypy score ($p = 0.025$). Discussion: This preliminary data provides evidence that polymorphism in the COMT gene may influence susceptibility to schizophrenia via its effects on schizotypy. The method of recruitment used in this study will allow rapid and cost-effective collection of endo-phenotype data in a healthy population in which to further explore the role of genes in psychosis-proneness.

USING THE FINDINGS OF THE EDINBURGH HIGH RISK STUDY TO PREDICT SCHIZOPHRENIA

E. C. Johnstone,* S. M. Lawrie, P. Miller, D. G. Owens
Psychiatry, University of Edinburgh, Edinburgh, United Kingdom

This study identifies the pre-morbid characteristics of the subjects of the Edinburgh High Risk Study which distinguish those who will go on to develop schizophrenia from those who will not. It concerns 163 subjects of mean age 21 years with a high familial risk of schizophrenia together with matched controls, who were examined every 18 months in terms of clinical features, neurodevelopmental variables, structural brain imaging and neuropsychology for seven years or until they developed schizophrenia. Twenty high risk subjects developed schizophrenia and more than 50 showed isolated or partial psychotic symptoms. Pre-morbid features of personality and behaviour distinguished those who would develop schizophrenia from those who would not. In this prospective study, the five best predictors were neuropsychological assessment of memory (RAVLT1) and observer (SIS2) and self assessments of personality and behaviour (RISC3). Positive predictive power of 50% was obtained for the best of these and negative predictive power of over 90% in four of them. Neuropsychological and neurodevelopmental measures in general were more successful in distinguishing high risk subjects from well controls than they were in distinguishing high risk subjects who will develop schizophrenia from those who will not. It is concluded that the mode of inheritance of schizophrenia affects many more individuals than will develop the illness and partial involvement may be found in them. Highly significant predictors of the development of schizophrenia are detectable years before onset. References 1. Rey A. *L'examen clinique en psychologie*. Paris: Presses Universitaires de France, 1964. 2. Kendler KS, et al. *Schizophr. Bull*. 1989;15(4):559-71. 3. Rust J. *Schizophr. Bull*. 1988;14(2):317-22.

CANNABIS AND SCHIZOPHRENIA: ARE WE ALL EQUAL?

M. Krebs,* C. Goldberger, S. Leroy, M. C. Bourdel
E0117-SHU, Centre Hospitalier Sainte Anne, Paris, France

There is now strong evidence that cannabis has a causal influence on the onset of schizophrenia. Nevertheless, since obviously no all subjects exposed to cannabis will not trigger schizophrenia, there is still much to be understood regarding the existence of a specific vulnerability to cannabis and its biological or genetic substrates. In French Caucasian patients with schizophrenia, we characterized «cannabis sensitive» patients (CSS) because the onset of psychosis occurred in a context of a recent consumption onset or increase or because they displayed prominent delusions or hallucinations when using cannabis. CSS patients were younger at first psychotic episode than the remaining patients (20.4 ± 3.1 vs. 22.5 ± 4.9, $P = 0.04$). The positive schizophrenic symptomatology, evaluated with Positive and Negative Syndrome Scale (PANSS) (3), adjusted on the duration of disease, was significantly more marked in CSS patients (20.8 ± 5.3 vs. 15.9 ± 5.2; P =10-4) even in men only or when the recent users (within the year, n = 7) were withdrawn. Interestingly, when comparing users vs non users, the difference in age at first episode was not significant (20.9 ± 4.9 vs. 22.6 ± 5; P=0.07). We suggest that the individual "sensitivity" to cannabis could reflect a specific vulnerability to cannabis. We genotyped the (ATT)n polymorphism of the cannabinoid receptor 1 (CNR1) and found a positive association with "cannabis sensitivity" in patients with schizophrenia (213 patients).

Confirming our earlier observations, the allele 8 was significantly less frequent in CSS patients compared to patients not sensitive to cannabis (CLUMP T3 : p =0.002) or to controls (CLUMP T3 p=0.025). . This result suggest that CNR1 gene variants could confer a specific vulnerability to cannabis regarding the risk of schizophrenia. An intriguing question still remains: is "vulnerability to trigger schizophrenia when taking cannabis" the same as "vulnerability to psychosis" and/ or are they distinct and interacting?

THE POWER OF ASYMMETRIC ASCERTAINMENT IN LINKAGE ANALYSIS

D. Levy,* F. Ji, O. Krastoshevsky, C. B. Harte, P. S. Holzman, N. R. Mendell, S. Matthysse
Psychology Research Laboratory, McLean Hospital, Belmont, MA, USA

In family studies of psychiatric endophenotypes (e.g., eye tracking, P50, attentional impairment, thought disorder), the ascertainment design is usually asymmetrical. That is, probands are ascertained for having a disease but relatives are examined for recurrence on a schizophrenia-related trait (SRT). We have developed methods for estimating power to detect linkage that take into account the asymmetry of the ascertainment design. Here, we illustrate these methods using data on thought disorder. Our methods are complementary to those of Risch, who developed methods for calculating power when a symmetrical ascertainment design is used. Using parameter-free methods, we show that power to detect linkage to a thought disorder phenotype is much higher than power to detect linkage for schizophrenia. The primary reason is that the thought disorder phenotype has such a high recurrence risk in relatives of schizophrenics that using it to identify gene carriers dramatically reduces the false negative rate. It is also possible to evaluate the power of specific single gene models with pleiotropic effects whose predictions are consistent with key epidemiology parameters about schizophrenia (rate of schizophrenia in the general population and in siblings of schizophrenics, rate of the SRT in the general population, in siblings of schizophrenics, and in schizophrenics). These analyses are based on genetic models that were generated by an unbiased search through model space and show that power is excellent for detecting linkage to a bivariate phenotype (schizophrenia and/or thought disorder) even in relative modest sample sizes. The methods we have developed are relevant to a wide variety of applications in genetic studies of complex disorders.

SCHIZOPHRENIA SUSCEPTIBILITY GENES: EFFECTS OF RISK ALLELES AND RISK HAPLOTYPES ON BRAIN STRUCTURE AND FUNCTION

A. K. Malhotra,* B. Funke, K. Burdick, P. Szeszko, C. Hodgkinson, R. Lipsky, J. Kane, C. Finn, D. Goldman, R. Kucherlapati
Psychiatry Research, The Zucker Hillside Hospital, Glen Oaks, NY, USA

Despite the difficulties in standardizing phenotypic information, genome wide scans have now reliably implicated several loci in the etiology of schizophrenia. Moreover, linkage disequilibrium mapping efforts and candidate gene association studies are now beginning to identify the first convincing susceptibility genes under these linkage peaks including dystrobrevin binding protein 1 (DNTBP1, 6p22, {Straub et al. 2002}), neuregulin 1 (NRG1, 8p12, {Stefansson et al. 2002}), G72 (13q33, {Chumakov et al. 2002}) regulator of G-protein signaling 4 (RGS4, 1q23; {Chowdari et al. 2002}) and catechol-O-methyltransferase (COMT 22q11-13, {Egan et al. 2001)}. Despite the success of these initial gene-finding efforts, the implications of these results are less clear. The mechanisms by which these genes predispose to illness development is not known, the specific phenotypes associated with risk genotypes remain to be determined, and the relationship of disease genes to treatment response are ongoing lines of investigation. Our group has recently detected significant associations between risk haplotypes in the genes coding for dysbindin (Funke et al. American Journal of Human Genetics, in press), DISC-1 (Hodgkinson et al. AJHG, in press), BDNF (Lipsky et al. 2004) and COMT (Funke et al. 2004), utilizing a large (n >1000) cohort of schizophrenia patients and healthy controls collected at the Zucker Hillside Hospital. We are now testing the identified risk haplotypes versus neurocognitive indices and brain imaging measures to help establish the specific phenotypes associated with these risk genotypes. To date, we have observed a significant association between our 6-locus dsybindin risk haplotype and decrements in attention and verbal IQ, consistent with the pattern observed in Duchenne muscular dystrophy, another disorder in which dysbindin is implicated; as well as a relationship between BDNF Val66Met genotype and hippocampal morphology, in which BDNF genotype predicted greater than 20% of the variance in overall hippocampal volume. These data, as well as new data on the influence of these genotypes on treatment response, provide additional evidence that these schizophrenia susceptibility genes may have complex effects on brain structure and function.

NMDAR AND D1 RECEPTOR GENES IN THE RESPONSE TO CLOZAPINE TREATMENT AND NEGATIVE SYMPTOMS

L. Martucci,* M. Masellis, T. Klempan, R. Hwang, H. Y. Meltzer, J. Lieberman, J. Volavka, J. L. Kennedy
Neurogenetics, Centre for Addiction and Mental Health, Toronto, ON, Canada

A growing body of evidence has implicated glutamatergic and dopaminergic abnormalities in major psychiatric conditions. Several lines of research have shown extensive interactions between NMDA receptor and D1 receptor, including a direct protein-protein interaction (Lee, 2002). Thus, NMDAR subunit genes and DRD1 may play a role in the response to treatment. We genotyped Two markers located on GRIN1: C–100G, located on the 5'UTR, and A1970G, located on exon 6; four markers located on GRIN2B: G–200T marker, located in the 5'UTR, and the T5072G, the A5806C and the T5988C markers, located in the 3'UTR; two markers located on DRD1, at positions T–800C, and A–94G of the promoter region. HYM, JL and JV collected the sample of 240 DSM-IIIR schizophrenic subjects, and response to clozapine over six months was assessed using the BPRS and SADS. Specific assessments on negative symptoms changes were available in the sample of 90 DSM-IIIR schizophrenics collected by HYM. We tested our markers for association with response to overall clozapine treatment, and studied more specific subphenotypes such as the improvement of negative symptoms. No association was found between overall response to clozapine treatment and the GRIN1 or the DRD1 markers. Among the GRIN2B markers, C5988G shows an overtransmission of the G allele in association with response to treatment (Chi-Sq=6.220; p=0.045). The same marker was more strongly associated with significant improvement of negative symptoms measured with SADSneg

(F=3.668; p=0.031). The other markers on GRIN1 and those on DRD1 did not show preferential transmission with the negative symptoms improvement. Our results suggest an association between GRIN2B and change in negative symptoms in response to clozapine treatment, but a larger sample is needed in order to increase the power of the analyses.

ASSOCIATION BETWEEN COMT GENE AND COGNITIVE DETERIORATION IN PSYCHOTIC PATIENTS

I. Mata,* M. J. Arranz, M. Beperet, S. Staddon, J. M. Lopez-Ilundain, R. W. Kerwin
Fundacion Argibide, Pamplona, Navarra, Spain

COMT is regarded as a candidate gene for functional psychoses. Although case-control and family-based association studies have reported conflicting results, several lines of evidence support its involvement in the cognitive deficits often seen in psychosis patients. The purpose of this study was to investigate the association between COMT Val158Met polymorphism genotype and cognitive deterioration in a sample of psychosis patients from a human isolate in Navarra (North Spain). Human isolates are characterised by low genetic heterogeneity and facilitate the identification of genes involved in complex diseases. Patients were assessed with the Information, Vocabulary, and Digit Symbol-Coding subtests of the WAIS battery. Using these three WAIS subtests, a cognitive deterioration index was calculated for each patient. COMT Val158Met genotypes were analysed through conventional laboratory procedures. Linear regression analyses were carried out to examine the association between cognitive deterioration index and the number of Met alleles. Results on 83 patients showed that patients with the Val/Val genotype had a significantly higher score on the cognitive deterioration index than patients with the Met/Met genotype. The number of Met alleles was related to the cognitive deterioration index (p=0.01), with evidence of monotonic linear decrease in the cognitive deterioration index with higher number of Met alleles. Our results support the involvement of COMT gene in the cognitive impairments often seen among psychosis patients, in the same direction of those reported in previous studies using other neuropsychological measures.

RP-C4-CYP21-TNX MODULAR VARIATION OF COMPLEMENT C4 GENES IN SCHIZOPHRENIA

K. Mayilyan,* P. M. Schneider, D. Rujescu, B. Stradmann-Bellinghausen, A. Hartmann, A. Soghoyan
Institute of Molecular Biology, Armenian National Academy of Sciences, Yerevan, Armenia

The general objective of this study was to investigate possible association of the genetic C4 polymorphism with schizophrenia. The modular variation of C4 genes together with the serine/threonine nuclear kinase gene RP, the steroid 21-hydroxylase CYP21, and extracellural matrix protein TNX (RCCX module) have been studied to determine the C4 gene dosage, the number of C4 long and short genes, the occurrence of C4 gene deletion, and C4 converions (both A to B and B to A). For this purpose a C4 genotyping approach based on long PCR has recently been established (P.M. Schneider et al., unpublished data). Schizophrenic patients (SP: n=56) vs. healthy volunteers (HV: n=46) from Armenian population have been investigated. Common haplotypes were identified in investigated subjects groups that carry either long or short C4B genes, as well as C4A/CYP21A or CYP21A/C4B gene deletions, respectively. A number of rare haplotypes were identified with unusual combinations: e.g. two haplotypes with CYP21A/C4B-long / CYP21A/C4B-short duplications, and one haplotype with C4B to C4A gene conversion. One haplotype with C4B-long and C4B-short genes duplication was accompanied by a very rare haplotype with C4 type III deletion (C4B/CYP21B). This type of C4 deletion in investigated SP was higher in comparison not only with HV, but the frequency was 4.5 times higher in the SP than in a control group studied by Schneider at al. (1992, HLA -1991, Proceedings of the 11th International Histocompetability Workshop and Conference Held in Yokohama, Japan, 6-13 November. P525-7). Regarding C4 gene deletions, there was not any difference between the groups in C4A deletion, and also in C4B homozygous deletion. From this viewpoint our data contradict the data suggesting an increase in homozygous C4B deficiency among SP [Rudduck et al., 1985, Hum Hered. 35(4): 223-6]. Nevertheless, a significant difference has been found for C4B heterozygous deficiency between SP vs. HV (Fisher's exact test: genotypes p<0.025; haplotypes p<0.015). Thus, the C4B heterozygous deficiency in SP could appear not only due to C4B gene deletion, but also due to its conversion to C4A. Our data support a possible association of C4B gene haploinsufficiency with schizophrenia. K.M. was supported by DAAD fellowship A/04/32935.

LINKAGE ANALYSIS OF SCHIZOPHRENIA-RELATED TRAITS UNDER A PLEIOTROPIC MAJOR GENE MODEL

N. R. Mendell,* F. Ji, D. L. Levy
Applied Mathematics & Statistics, Stony Brook University, Stony Brook, NY, USA

The genetic analysis of complex diseases, such as schizophrenia, frequently focuses on endophenotypes, or disease-related traits (DRTs), in addition to the disease itself. The objective is to locate a major gene that is pleiotropic for the disease and the DRT. We develop an extension to classical gene-model based linkage analysis that allows for simultaneous analysis of both the disease and DRT phenotype. We assume that both schizophrenia(S) and a schizophrenia-related trait (SRT) are determined by a single pleiotropic S/SRT allele for which the penetrance of the SRT is substantially larger than that of the disease and that the phenocopy rate of the SRT is substantially less than that of the disease. Any linkage study of an SRT is therefore presumably more powerful than a linkage analysis of schizophrenia itself, especially in the case where families are ascertained through a schizophrenic proband (which we refer to as asymmetric ascertainment). To understand the power of analyzing an SRT using asymmetric ascertainment, we designed a simulation program that takes into account this ascertainment scheme. Through simulation we compare the ELOD and power of linkage analysis of: (1)schizophrenia, (2)the SRT, and (3)both schizophrenia and the SRT simultaneously (bivariate analysis) under a pleiotropic major gene model. We report the findings considering a range of values for the generating model parameters (i.e., mode of inheritance, penetrances, phenocopy rate, allele frequency, recombination fraction). Bivariate linkage analysis results in a substantial increase in ELOD and power over linkage analysis of schizophrenia alone or the SRT alone. Analysis of the SRT alone results in an increase of ELOD and power over analysis of schizophrenia under most conditions. This simulation program and linkage analysis method can be applied to the analysis of any complex disease and its DRTs, and it is tailored to take into account the asymmetrical ascertainment strategy.

POSTMORTEM HIPPOCAMPAL EXPRESSION PROFILING IN SCHIZOPHRENIA: CONSIDERING THE EFFECTS OF PSYCHOPATHOLOGY AND CHRONIC CIGARETTE SMOKING

S. Mexal,* R. Berger, M. Frank, R. Ross, R. Freedman, S. Leonard
Psychiatry, University of Colorado Health Sciences Center, Denver, CO, USA

High throughput expression analysis is emerging as a valuable tool in elucidating the complex pathophysiology of schizophrenia at the molecular level. Expression profiling using microarrays and two-dimensional gel electrophoresis have been applied to examine expression differences in lymphocytes, as well as prefrontal, entorhinal, and temporal cortices in patients compared to non-mentally ill controls. However, the comorbidity of nicotine dependence and schizophrenia, which is approximately 80%, has yet to be considered in such an analysis. The various expression changes identified in schizophrenic brains could therefore be due to cigarette smoking rather than to disease pathophysiology. To address this issue, we have used microarray analysis to evaluate hippocampal gene expression in control nonsmokers (n=6), control smokers (n=6), schizophrenic nonsmokers(n=6), and schizophrenic smokers (n=6). The hippocampus was selected for analysis as this region is involved in nicotine-related cognitive and sensory processing measures that are aberrant in the disorder. Schizophrenia and smoking were evaluated as main effects and interactive effects utilizing a 2-Way ANOVA. Various pre- and postmortem variables were also considered in the analysis. Utilizing a gene grouping analysis program, several functional categories, including ribosomal, glutamatergic, and immune response genes, were identified as overrepresented among the transcripts differentially expressed in schizophrenics. The latter two groups were also overrepresented among the genes differentially expressed in smokers, suggesting that cigarette smoking and schizophrenia may affect similar biological processes. Several genes with altered expression in the hippocampus of patients were also differentially expressed in skin fibroblasts. To evaluate whether any of the transcripts differentially expressed in schizophrenics could be utilized to predict schizophrenia, the dataset of 24 subjects was used as a training set to generate a schizophrenia gene expression profile. An additional set of five schizophrenics and five non-mentally ill controls was then examined to test the diagnostic accuracy of this profile. Our results show that smoking history is an important consideration for microarray data analysis in postmortem brain.

5HT2C RECEPTOR POLYMORPHISMS, WEIGHT GAIN, AND CLINICAL RESPONSE TO CLOZAPINE TREATMENT

D. D. Miller,* V. L. Ellingrod, T. Holman, P. F. Buckley
Psychiatry, University of Iowa, Iowa City, IA, USA

BACKGROUND: The -759C/T polymorphism of the gene that codes for the 5HT2C receptor has been associated with weight gain related to clozapine and other atypical antipsychotics. Several investigators have also reported that clinical response to clozapine is related to clozapine-induced weight gain. AIM: To determine the relationship between changes in body weight and clinical response, and the -759C/T and Cys23Ser polymorphisms of the genes that code for the 5HT2C receptor during clozapine treatment. METHODS: This study included 58 subjects with treatment-refractory schizophrenia (DSM-IV) who were prospectively followed for 6-months during treatment with clozapine. Ratings of psychopathology (BPRS & SANS), weight, and height measurements were obtained prior to starting clozapine and scheduled intervals throughout the 6-month trial. Clozapine doses were determined based on plasma concentration measurements and clinical response. Genomic DNA was isolated from a whole blood sample and analyzed for the -759C/T and Cys23sSer polymorphisms of the genes that code for the 5HT2C receptor. RESULTS: The end point body mass index (BMI) was significantly predicted by the presence or absence of a T allele at -759 and the baseline BMI. Changes in BMI were not related to the Cys23Ser polymorphism. There was no relationship between changes in BMI and clinical improvement, or between clinical improvement and the -759C/T or Cys23sSer polymorphisms of the genes that code for the 5HT2C receptor. CONCLUSIONS: The presence of the T allele from the -759C/T polymorphism of the 5HT2C receptor appears to reduce the likelihood of significant clozapine-induced weight gain. We did not find a relationship between clozapine-induced weight gain and improvement in psychopathology, or between improvement in psychopathology and two polymorphisms of the genes that code for the 5HT2C receptor.

CATECHOL-O-METHYLTRANSFERASE VAL158MET GENOTYPE VARIATION IS ASSOCIATED WITH VERBAL SHORT-TERM MEMORY PERFORMANCE IN SCHIZOTYPAL AND OTHER PERSONALITY DISORDER PATIENTS

M. Minzenberg,* V. Mitropoulou, K. Xe, P. D. Harvey, J. D. Flory, A. S. New, D. Goldman, L. Siever
Psychiatry, Mount Sinai School of Medicine/Bronx VA Medical Center, Bronx, NY, USA

A single-nucleotide polymorphism of the gene coding for Catechol-O-methyltransferase (COMT) is associated with variation in performance on cognitive tasks including working memory and executive functions in schizophrenia. We sought to evaluate the effect of COMT genotype variation on short-term memory and executive function in schizotypal and other personality disorder patients. 143 unmedicated outpatients with either Schizotypal Personality Disorder (SPD, n=52) or Other Personality Disorders (OPD, n=91) by DSM-III-R, and 42 normal control (NC) subjects performed the following tests: Paced Auditory Serial Addition Test (PASAT), California Verbal Learning Test (CVLT), visuospatial working memory (DOT Test), visual delayed recall (Wechsler Memory Scale Visual Reproduction, WMS-VR), Wisconsin Card Sorting Test (WCST); and WAIS Vocabulary to assess general verbal ability. Genotyping was performed for COMT at the Val158Met locus. COMT genotype distribution did not vary between any of the three diagnostic groups. Significant effects of diagnostic group (SPD vs. other [NC and OPD]) were observed on PASAT, CVLT, DOT, and WMS-VR. COMT genotype (the presence of at least one Val allele) made a significant independent contribution to the variance in performance on PASAT, CVLT and WAIS Vocabulary. In addition, the SPD group performed significantly worse than NC on PASAT, CVLT, DOT and WMS-VR; regression of SPD subjects' scores on COMT genotype showed a trend effect of genotype (presence of at least one Val allele) on PASAT and CVLT. We conclude that: 1) Schizotypal personality disorder patients exhibit consistent deficits in short-term memory;

2) Allelic variation in COMT activity is unrelated to diagnostic status in SPD, yet is related to performance on verbal short-term memory tasks and may specifically contribute to the deficit in prefrontal-dependent short-term memory in SPD as it does in schizophrenia.

ECOGENETIC STUDIES OF SCHIZOPHRENIA IN HIGH-RISK ADOLESCENTS FROM A PACIFIC ISLAND ISOLATE

M. Myles-Worsley,* L. Ord, H. Ngiralmau, J. Tiobech, I. Asang, F. Blailes
Dept. of Psychiatry, University of Utah School of Medicine, Salt Lake City, UT, USA

Our family-genetic study of schizophrenia in Palau, Micronesia provides a valuable resource for a new generation of ecogenetic studies designed to investigate gene-environment interactions that could explain why schizophrenia develops in some high-risk offspring but not others. Palau is an isolated island nation with a 2.7% lifetime morbid risk for broadly defined schizophrenia and strong aggregation of cases in 20 extended pedigrees with large sibships. We are conducting a prospective study of 500 Palauan adolescents with varying degrees of genetic risk for schizophrenia. These adolescent subjects include 300 genetic high-risk (HR) offspring whose parents belong to the 20 high-density pedigrees with multiply affected sibships. In these families, recurrence risk is estimated to be 27% in the offspring of schizophrenic patients and 16% in the nieces/nephews of affected sib-pairs/trios, approximately double the rates found in smaller Western European families (Gottesman et al., 1982). The 300 genetic HR adolescents are being compared to a population-based sample of 100 clinically but not genetically HR adolescents and 100 normal control subjects. Our assessments to date have found that psychopathology and neurocognitive abnormalities, including P50 sensory gating deficits, occur at the same high rate in both the offspring of schizophrenia patients and the nieces/nephews of affected sib-pairs/trios. Over 15% of the HR adolescents have already transitioned to schizophrenia and another 25% have severe prodromal symptoms. We will present the findings of our initial examination of quantitative measures of non-genetic familial risk factors with particular emphasis on adverse family-rearing conditions as predictors of schizophrenia in genetic HR adolescents. Our long-term goal is to accelerate progress toward preventive intervention strategies for young people with a genetic susceptibility for schizophrenia by identifying the potentially modifiable environmental exposures that increase risk for illness onset.

RETROPOSON-INSERTION SITES OF MONOZYGOTIC TWINS DISCORDANT FOR SCHIZOPHRENIA

S. Nanko,* M. Ueno
Psychiatry, Teikyo University, Tokyo, Japan

A possible role of repetitive elements (LINE, SINE, MER, MITE, mariner and endogeneuos retroviruses) termed transposons and retroposon has been increasingly implicated in the etiopathogenesis of human brain diseases such as epilepsy (Xie et al. 1998). The transcripts containing retroposon Alu are present in the fetal brain and the brain of mental disorder. Furthermore, several fragile sites including repetitive elements are located on the gene-map locus associated with schizophrenia. On the hypothesis that the retroposition of repetitive elements may make some contribution to susceptibility to schizophrenia, we attempted to detect the insertion sites of repetitive elements using genomic DNA from the monozygotic twins discordant for schizophrenia (patient with schizophrenia and her sister). By the method of Alu locus specific- PCR screening, we detected several fragments in a patient with schizophrenia which were not recognized in her sister. These fragments may contain the susceptibility genes for schizophrenia. This approach will allow us to use repetitive elements as tools to detect the risk genes associated with schizophrenia. This research was done under the approval of the Ethical Committee for Genetic Research, Teikyo University School of Medicine.

ASSOCIATION BETWEEN 2592C>TINS POLYMORPHISM OF ADENOSINE A2A RECEPTOR GENE AND SCHIZOPHRENIA

G. Ottoni,* I. Lucchese, F. Martins, R. Grillo, M. Bogo, D. Lara
Department of Biochemistry, UFRGS, Porto Alegre, Brazil

Schizophrenia is a severe psychiatric disorder that affects approximately 1% of the worlds population in which genetic factors exert an important role in the etiopathogeny. Our group suggested the participation of adenosinergic system in the pathophisiology of this illness. In this genetic study of association, a sample of 88 patients with schizophrenia was compared to a group of 100 controls without personal and familiar history of psychiatric disorders, in relation to 2592C>Tins and 263C>T polymorphisms of the adenosine A2A receptor gene. The whole group of patients was divided in the following sub-groups: patients with predominantly positive symptoms, patients with negative symptoms, patients with disorganized symptoms, patients with negative and disorganized symptoms. Patients were compared among themselves according to the above characteristics and to the controls in relation to the studied polymorphisms. Our results indicate an association of the 2592C/C genotype with the disorder, in which genetically determined variations of the level of adenosine A2A receptors expression would play a role in its development. Particularly the negative and the disorganized symptoms, related with the proposal of schizotaxia, were associated with the 2592C/C genotype. Our study strengthens the evidence for adenosinergic system participation in the pathophysiology of schizophrenia, with more distinction in schizotaxia, supplying preliminary genetic support to this theory.

ASSOCIATION OF GENETIC VARIATIONS WITHIN 5′ END OF NEUREGULIN 1 WITH SCHIZOPHRENIA IN KOREAN POPULATION

D. Park,* E. Cho, H. Jeun, Y. Lee, S. Cho, S. Jang, Y. Jang, J. Kim, K. Hong
Psychiatry, Sungkyunkwan University of Medicine, Samsung Seoul Hospital, Seoul, South Korea

Chromosome 8p21-12 has been reported to be a susceptiblilty locus of schizophrenia from genomewide linkage scans with American and European families. After Neuregulin 1 was identified as a positional and functional candidate gene of schizophrenia in this locus, several independent association studies have reported positive results with various markers and their haplotypes within this gene. We recently found a suggestive evidence of linkage of this locus to schizophrenia in Korean multiplex families. The purpose of this study is to determine if neuregulin 1(NRG1) is associated with schizophrneia

in Korean population. Three SNPs (SNP8NRG221533, SNP8NRG241930, SNP8NRG243177) and two microsatellites markers (478B14-848, 420M9-1395) were genotyped for 242 unrelated schizophrenia patients and the same number of normal controls. These markers are located at the 5′ end of NRG1 and composing the at-risk haplotype of schizophrenia identified from the Icelandic schizophrenia families. Genetic association was tested by x2-test (df=1) for single markers and markers haplotypes. Haplotype frequency was estimated by PHASE v2.1. We performed these analysis not only for the total schizophrenia patients but also for a subgroup of patients with auditory hallucination. This subtype showed stronger linkage signals in the prior study of the authors with Korean multiplex families. Although we could not find significant association with schizophrenia for the original at-risk haplotypes of the Icelandic population, G allele of SNP8NRG241930 was significantly in excess in the subgroup of patients with auditory hallucination (92.9% in patients with auditory hallucination vs 88.2% in controls;p=0.030, odds ratio(or)=1.76). We also found that 3 SNPs haplotype TTC(p=0.038, or=0.58) and five markers haplotype TTC53(p=0.012, or=0.49) were associated with schziophrenia with a protective effect. This study provides another suggestive evidence of association of genetic variations on 8p12, a locus of NRG 1 with schizophrenia. NRG1 might either play a role in the predisposition to schizophrenia or be in linkage disequilibrium with a causal locus of this illness.

GENETIC LIABILITY TO SCHIZOPHRENIA AND EXECUTIVE FUNCTIONING: INITIAL RESULTS FROM A LARGE-PEDIGREE, MULTIPLEX SAMPLE

M. F. Pogue-Geile,* R. E. Gur, R. C. Gur, L. Almasy, J. Wood, J. Thompson, S. Tarbox, V. Nimgaonkar
Psychology, University of Pittsburgh, Pittsburgh, PA, USA

The overall importance of genetic variation in the etiology of schizophrenia is well established. However, reliably identifying specific genetic polymorphisms that contribute to this overall risk has been very difficult, presumably because there are many contributing loci, each with small effect. One strategy that may aid in such situations is to develop phenotypes that are more sensitive to genetic liabilities than is the clinical diagnosis itself (i.e., endophenotypes, Gottesman & Shields, 1972). The current study employs this approach using neuropsychological phenotypes within the context of an ongoing linkage study of large multiplex schizophrenia pedigrees. Here we report preliminary results on the familial association between the Trails Making Test (TMT), a neuropsychological test of executive function, and schizophrenia in an interim sample from this ongoing study. If the TMT is sensitive to genetic liability to schizophrenia, then performance should decrease as relatives genetic relatedness to schizophrenia probands increases. Large families were ascertained that had at least two relatives diagnosed with schizophrenia or schizoaffective disorder. One hundred twelve members from nine families were assessed with the TMT and diagnosed using the Diagnostic Interview for Genetic Studies (DIGS). Eighteen probands were diagnosed with schizophrenia, leaving 94 of their non-schizophrenia relatives for analysis. Each relative was assigned a kinship coefficient based on their degree of genetic relatedness to a schizophrenia proband (e.g., .50 for a sibling, .25 for a nephew, etc.). Using multiple regression with age as a covariate, there were significant linear associations between the time to complete TMT-A and TMT-B and genetic relatedness to schizophrenia probands (b=.34, p=.001 and b=.27, p=.005). As the genetic relationship to a schizophrenia proband increased, the time to complete TMT-A and B also increased, in a linear fashion. Such results suggest that the TMT may be sensitive to genetic liability to schizophrenia and thus may be of value in genetic linkage studies.

IS THERE A RELATIONSHIP BETWEEN THE PSYCHOTIC SYMPTOMS OF PSYCHOTIC PATIENTS AND THE SCHIZOTYPAL SYMPTOMS OF THEIR UNAFFECTED RELATIVES?

C. Prado,* I. Mata, J. M. Lopez-Ilundain, A. Albeniz, M. Beperet, F. Perez-Nievas
Fundacion Argibide, Pamplona, Spain

Originally, the concept of schizotypal personality disorder (SPD) was developed following the observation of a higher rate of "latent, borderline, or uncertain schizophrenia" among the biological rather than adoptive relatives of schizophrenia adoptees. This was later confirmed by family studies that found a higher rate of SPD among the relatives of schizophrenics compared to controls. However, most studies comparing schizotypy questionnaire scores between relatives of schizophrenic and affective patients have failed to find any difference. Several studies have investigated the familial resemblance between symptoms shown by psychotic patients and their unaffected relatives, reporting correlations for negative symptoms, anhedonia, and perceptual aberration. Furthermore, positive symptoms in psychotic patients have been found to be correlated with total schizotypy among their relatives. In this study we wished to examine if is there a symptomatological homotypy within the well and ill members of the families of psychotic patients. 280 nonpsychotic first-degree relatives of 107 unrelated psychotic patients completed the Schizotypal Personality Questionnaire (SPQ). Correlation coefficients were then calculated between their scores on this scale and the factor analysis-derived OPCRIT symptom dimensions in their affected relatives. We did not found any degree of homotypy between schizotypal symptoms in relatives and symptom dimensions in patients. The only significant correlations were found between total schizotypy in relatives and higher manic and lower negative symptoms in patients, positive schizotypy in relatives and higher manic symptoms in patients, and negative schizotypy and lower negative and disorganized symptoms in patients. We conclude that, in this sample, the symptom patterns in psychotic patients and the schizotypy patterns in their relatives are independent, with no evidence of homotypy.

COMT POLYMORPHISMS AND CEREBRAL MORPHOMETRY IN FIRST EPISODE SCHIZOPHRENIA AND HEALTHY SUBJECTS

K. M. Prasad,* M. E. Talkowski, K. V. Chowdari, M. K. Keshavan, V. L. Nimgaonkar, M. S. Keshavan
Department of Psychiatry, Western Psychiatric Institute and Clinic, Pittsburgh, PA, USA

COMT (catechol-O-methyl transferase) has been proposed as a risk gene for schizophrenia. A large study reported significant association of a *COMT* haplotype consisting of G-alleles of rs4680 (Val/Met), rs737865 (Intron 1) and rs165599 (3′UTR) with schizophrenia. Examining in vivo biological correlates of these genetic variations

may provide clues about the relative biological impact of such variations. Therefore, we evaluated the gray matter density using voxel-based morphometry (VBM) in first episode schizophrenia patients and controls genotyped for Val/Met, rs737865 and rs165599 SNPs. We genotyped 63 age-matched Caucasian subjects (schizophrenia/schizoaffective disorder=33 and controls=30) for *COMT* Val/Met, rs737865 and rs165599 polymorphisms using single-base extension reaction (SNAPSHOT) assay. We performed VBM (threshold $p<0.001$; cluster size>30 voxels) on structural MRI scans obtained on all these subjects to compare across the genotypes and examine the allele dose effect on gray matter density within each group controlling for age and gender, blind to genetic and clinical data. Val/Val patients showed decreased gray matter concentration in the DLPFC compared to Met/Met individuals and the former showed increased gray matter density in the substantia nigra pars compacta (SNPC) and dorsal thalamus. Patients showed a positive correlation of gray matter density in the DLPFC with Met allele dose. SNPC and dorsal thalamus gray matter positively correlated with Val allele dose. No such correlations were observed for rs737865 and rs165599. Decreased gray matter density in the DLPFC in individuals homozygous for Val allele supports previous reports of decreased efficiency of prefrontal perfusion and working memory performance in such individuals. Increased SNPC gray matter density in Val/Val subjects may suggest overactive dopaminergic neurons, probably compensating for deficits in prefrontal DA transmission. A post-mortem report of increased tyrosine hydroxylase expression in Val/Val individuals suggesting a possible increase in biosynthesis supports this finding. Such observations in patients but not in controls may suggest an interaction of the *COMT* polymorphisms with other illness-related variables. This finding is in contrast to earlier studies that found altered working memory and perfusion in both patients and controls with *COMT* Val/Met polymorphism. This may be because structural changes may represent pathology at more severe end of the spectrum.

NONVERBAL DELAYED RECOGNITION IN FIRST-DEGREE RELATIVES OF SCHIZOPHRENIA PATIENTS AND THE MEDIATING EFFECT OF SCHIZOPHRENIA SPECTRUM PERSONALITY DISORDERS

O. Robles Aranda,* J. M. Gold, T. A. Blaxton,
H. M. Adami, C. Arango, G. K. Thaker
Dpto. Psiquiatria. Unidad de Adolescentes, Hospital General Universitario Gregorio Maranion, Madrid, Madrid, Spain

This study evaluates the contribution of familiality and symptomatology of schizophrenia spectrum personality disorders (SSPD) in the ability to discriminate previously studied target stimuli from novel distracter stimuli. Both auditory and visuospatial delayed recognition are assessed through the presentation of 20 five-note unfamiliar melodies and 35 non-nameable abstract visuospatial designs, respectively. The four groups assessed include first-degree relatives of schizophrenia patients with (n=22) and without (n=31) SSPD, and individuals from the community without a family history of schizophrenia with (n=22) and without (n=48) SSPD. Family relationship mediates poor performance in both tasks of nonverbal delayed recognition (auditory [$F(1, 108)=12.2$, $p=.001$]; visuospatial [$F(1, 73)=4.3$, $p=.041$]). SSPD symptoms negatively affect performance on the visuospatial recognition task [$F(1, 108)=12.2$, $p=.001$]. The group of SSPD relatives shows the worst discriminability (A prime) performance in both auditory and visuospatial tasks, with effect sizes between moderate (0.6227) and large (1.0139) when compared to nonSSPD community controls. Results suggest that first-degree relatives are impaired in nonverbal delayed recognition as measured with auditory and visuospatial material. Deficits in visuospatial recognition are worsened as a function of the presence of SSPD symptomatology in family members of schizophrenia patients. SSPD symptomatology subtly affects visuospatial delayed recognition in individuals without schizophrenia in their families.

SCHIZOTYPAL SYMPTOMS AND NEUROCOGNITIVE PERFORMANCE IN SIBLINGS OF PATIENTS WITH SCHIZOPHRENIA

Z. Sabuwalla,* D. M. Barch
Department of Psychology, Washington University, St. Louis, MO, USA

Patients with schizophrenia manifest deviant patterns of performance on tests of attention, executive function, verbal and visuospatial working memory, and learning and memory (for a review, see Heinrichs & Zakzanis, 1998). Similar patterns can be observed in individuals with schizotypal personality disorder (Cadenhead et al, 1999; Diforio, Walker & Kestler, 2000; Voglmaier et al, 1997), a disorder thought to be behaviorally and genetically related to schizophrenia. Schizotypal traits are partially heritable and are elevated in relatives of patients with schizophrenia (Kendler et al, 1993) as compared to a normal population. Relatives of patients with schizophrenia also show impairments on various measures of cognitive functioning (Cannon et al, 1994, Keffe et al, 1994). Furthermore, they manifest more neuropsychological deficits than relatives of affective psychotic patients (Gilvarry et al, 2001). Thus, schizotypal personality traits and cognitive dysfunction represent potential indicators of a genetic risk for schizophrenia, as both are elevated in first-degree relatives of patients with schizophrenia. Few studies have investigated the relationship between schizotypy and cognitive function in relatives of patients with schizophrenia, and have produced conflicting results. These inconsistencies can be attributed to various methodological differences, including mixed sampling method (siblings, half-sibling, parents, co-twins), sampling size, variable criteria for assessing schizotypy (interviews, self-report questionnaires, clinical vs. psychometrically derived samples), and limited measures for assessing cognitive deficits. Using an extensive battery of neurocognitive tests and several measures of schizotypy, we will investigate the relationship between the severity of schizotypal symptoms and various measures of cognitive functioning in first-degree relatives of patients with schizophrenia. We hypothesize that performance on neuropsychological tests will be inversely correlated with symptoms of schizotypy, particularly the negative and disorganized symptom clusters. Exploratory analyses will also be conducted to test the effects of age as a moderator between test performance and symptom severity. Such analyses may provide support for the hypothesis that schizotypal symptoms in adolescence may be indicative of a risk factor for developing schizophrenia.

AUDITORY HALLUCINATIONS AND FOXP2 POLYMORPHISMS

J. Sanjuan,* A. Tolosa, C. Najera, M. D. Molto,
J. C. Gonzalez, E. J. Aguilar, R. de Frutos
Medicine, Universidad de Valencia, Valencia, Spain

The aim of this study is to investigate the possible association between the FOXP2 polymorphisms and auditory hallucinations

(AH) in patients with schizophrenic. FOXP2 was the first gene relevant to the human ability to develop language. A point mutation at the forkhead domain of this gene results in a severe speech and language disorder. We have performed a case-control study of ten single nucleotide polymorphisms (SNP) and variations in the polyglutamine tract in 200 psychotic patients (mainly DSM-IV schizophrenic) with history of AH and 200 healthy controls. PSYRATS scale was used to asses the dimensions of AH in all patients. 60 patients were considered with chronic hallucinations since they fulfilled the following criteria: (i) Voices talking about them, at least once a day over a period of no less than two years. (ii) At least three periods (of six months each) in the preceding 2 years of treatment, with conventional and atypical antipsychotics, at a dose equivalent to at least 1000mg chlorpromazine per day, without relief in hallucinations. Most of the SNP are located at the 5' putative regulatory region, meanwhile the polyglutamine tract in the coding region of the gene. Genotype frequencies of the analysed polymorphisms are in Hardy-Weinberg equilibrium. From the ten SNP studied only two of them, SNP1358278, and SNP2396722, are in linkage disequilibrium. It can be suggested that FOXP2 gene is not critically involved in the development of the schizophrenia because no significant differences between schizophrenic patients and controls were found for any of the analysed polymorphism.1 However, we found that SNP 7803667 was significantly associated with chronicity, frequency, and duration of AH. Our findings suggest that FOXP2 could confer vulnerability to an extreme phenotype of the AH in psychotic patients. 1. Sanjuan J., Tolosa A., Gonzalez JC, Aguilar EJ, Molto MD, Najera C, de Frutos R FOXP2 polymorphisms in patients with schizophrenia *Schizophrenia Research* 2004 (in press).

MIXED-HANDEDNESS AND SCHIZOTYPAL DIMENSIONS

F. Schurhoff,* A. Laguerre, I. Roy, M. Leboyer
Departement Hospitalo-Universitaire de Psychiatrie, Hopital Albert Chenevier (AP-HP), Creteil, France

Background: An excess of mixed-handedness has been repeatedly reported in schizophrenia and schizotypy. Handedness is a measure of atypical cerebral lateralization, the mechanism that may be responsible for psychotic symptomatology. Several studies have attempted to identify correlations between handedness and psychosis symptom dimensions, but the results obtained so far remain inconclusive. Objective: To determine whether there was a link between mixed-handedness and the three classical dimensions of psychosis. Speech and language disorders may be associated with cerebral lateralization. Thus, we predicted that there was a correlation between mixed-handedness and the disorganized dimension. Methods: We used the Schizotypal Personality Questionnaire (SPQ) and the Edinburgh Handedness Inventory (EHI) to study whether there was a correlation between positive, negative and disorganized dimensions and mixed-handedness scores in a sample of 62 healthy subjects. Results: We identified a significant negative correlation between EHI scores and the disorganized dimension of schizotypy: individuals with more prominent mixed-handedness also showed more severe disorganization. Conclusion: These results suggest that an excess of mixed-handedness might be associated with speech disturbances. Our identification of a link between mixed-handedness and the disorganized dimension may help to identify genetic vulnerability factors involved in psychosis.

JOINT RISK DUE TO CHROMOSOME 6P VARIATION AND EXPOSURE TO CMV IN SCHIZOPHRENIA SUSCEPTIBILITY?

B. Shirts,* J. J. Kim, M. Dayal, S. Bacanu, J. Wood, W. Xie, K. V. Chowdari, R. Yolken, B. Devlin, V. L. Nimgaonkar
Human Genetics, University of Pittsburgh, Pittsburgh, PA, USA

There is a growing consensus that the etiopathogenesis of schizophrenia involves the interaction of genetic and environmental factors. However, specific gene-environmental interactions resulting in an increased rate of szhizophrenia have not been previously identified. We present data supporting infection with the neurotropic human herpesviruses cytomegalovirus (CMV) as an environmental risk factor, and report associations between CMV infection and several SNPs on chromosome 6p in CMV positive patients. We used a novel combination of familial aggregation and association studies to investigate the connection of CMV with liability to schizophrenia. We first evaluated exposure to CMV, using serum antibodies, among simplex and multiplex families. Exposure to CMV was significantly increased amongst multiplex families, supporting a connection between CMV exposure and schizophrenia. We also evaluated the role of genetic variation in enhancing risk in CMV seropositive patients by investigating 50 SNPs in 11 genes selected because they localize to chromosome 6p21 and encode proteins mediating CMV infectivity. Comparisons of allele and genotype frequencies in CMV+ and CMV- individuals showed highly significant associations at two SNPs at MICB and one at TNF ($p < 0.005$) indicating that associations at these loci are driven by CMV+ cases. Notably, M6S125 is localized only 6kb from MICB and 71kb from TNF. In preliminary analysis from a replicate of these findings in a separate sample we found significant differences in allele frequencies between schizophrenia patients and controls in six markers at MICB, LTA, and TNF ($p < 0.05$) regardless of CMV status. Interaction of CMV exposure in schizophrenic patients and genetic variation at MICB and TNF is biologically plausible. Our analyses suggest an intriguing interaction between exposure to CMV and variation at MICB and TNF or linked loci in the etiology of schizophrenia. If replicated, these findings would open new vistas of research into gene-environment interactions and schizophrenia pathogenesis.

PSYCHIATRIC PROFILE OF CHILDREN WITH VELO-CARDIO-FACIAL SYNDROME (VCFS)

A. F. Stevens,* L. E. Campbell, R. Morris, E. Simonoff, D. G. Murphy, A. Karmiloff-Smith, M. J. Owen, K. C. Murphy
Brain Maturation PO50, Institute of Psychiatry, London, United Kingdom

Background: The genetic disorder, Velo-cardio-facial syndrome, is associated with variably sized deletions in the q11 region of chromosome22. Phenotypic expression is extremely variable and includes congenital heart disease, palatal abnormalities, renal abnormalities, borderline to mild learning disability, behavioural difficulties and mental health problems (eg schizophrenia and mood disorders). In this study, we aimed to characterize the mental health, behaviour and cognitive profile (behavioural phenotype) of children and adolescents with VCFS. Method: We recruited 50 children (age 6-16) with VCFS and 30 age matched sibling controls. The participants then underwent a battery of psychiatric and behavioural questionnaires (including the Vineland Adaptive Behaviour Questionnaire, The Child and Adolescent Psychiatric Assessment and The

Strengths and Difficulties Questionnaire). Results: We found that emotional symptoms were found in 53% of the VCFS cohort (10% of controls), conduct problems in 40% (20% of controls), attentional/hyperactivity problems in 46% (20% of controls) and peer problems in 73% (0% of controls). Conclusions: Individuals with VCFS, when compared to their siblings, have more difficulties in areas of socialization, hyperactivity/attention/concentration, prosocial behaviour, emotional symptoms, peer problems and autistic spectrum disorder traits. We intend to prospectively follow-up these individuals and identify predictors of future mental health problems in later life.

IS THE *RGS4* GENE ASSOCIATED WITH SCHIZOPHRENIA? META-ANALYSES OF INDIVIDUAL GENOTYPES FROM 12,615 SAMPLES ACROSS 12 INTERNATIONAL SITES

M. Talkowski,* A. S. Bassett, L. M. Brzustowicz, X. Chen, K. V. Chowdari, D. A. Collier, Q. Cordeiro, A. Corvin, S. Deshpande, M. F. Egan, M. Gill, K. S. Kendler, G. Kirov, P. Levitt, D. A. Lewis, K. Mirnics, D. W. Morris, M. C. O'Donovan, M. J. Owen, H. Seltman, J. L. Sobell, B. K. Thelma, D. R. Weinberger, N. M. Williams, V. L. Nimgaonkar
University of Pittsburgh, Pittsburgh, PA, USA

Following the discovery of decreased expression of *RGS4* in the prefrontal cortex of schizophrenia (SZ) post-mortem samples, a genetic study found associations with a four single nucleotide polymorphism (SNP) haplotype at the *RGS4* locus in three different samples (Chowdari et al., 2002). Since the initial reports, four independent replications have been published with some positive association to these 4 SNPs and/or haploytpes, rendering *RGS4* as one of the most highly replicated SZ liability genes to date. Yet, the associated alleles and haplotypes have differed. We therefore conducted a meta-anlaysis using individual genotypes from over 12,000 individuals across 12 international sites in a collaborative effort to resolve the putative association. Data collection resulted in genotypes from 12,615 total individuals for the associated SNPs 1,4,7,18 at the *RGS4* locus from 12 different sites. Our case-control sample was comprised of 6,065 cases and unrelated controls from 7 sites, of which 4,420 individuals were Caucasian. Our family sample included 2,158 nuclear and extended families from 10 sites, including 1,714 case-parent trios. The use of individual genotypes allowed for a wide spectrum of analyses, including case-control and family based associations for individual SNPs and haplotypes by site and across all samples. Individual site analysis revealed significant case-control associations in 3 of the 7 samples for individual SNPs and/or haplotypes. However, significant associations were not noted across the entire case-control sample or the Caucasian only samples. The trio and extended pedigree samples revealed associations with multiple individual sites, but again showed no evidence of transmission distortion for individual SNPs or the previously associated haplotypes across the pooled samples. However, global analyses revealed significant transmission distortions amongst all haplotypes ($p<0.001$). The results of our pooled analyses amongst all samples found little evidence for association with either of the putatively associated 4 SNP haplotypes at the *RGS4* locus. Yet, significant global transmission distortions across all haplotypes was obtained. In light of previous associations with multiple alleles and haplotypes, these results suggest multiple risk haplotypes may exist with *RGS4*. Evolutionary based haplotype analyses and multivariate analyses are ongoing and may help further characterize these associations.

INVOLUNTARY MOVEMENTS AND FAMILIAL LIABILITY TO SCHIZOPHRENIA

S. I. Tarbox,* A. Grippo, M. Pogue-Geile
Psychology, University of Pittsburgh, Pittsburgh, PA, USA

Although studies indicate that the diagnosis of schizophrenia is itself highly heritable, the search for specific genetic abnormalities has not yet clearly identified any genes of major effect. This suggests that several genes affect the diagnosis of schizophrenia, but the diagnosis is itself not highly associated with any individual genetic variant. One possible means of making progress in this area is to identify non-diagnosis phenotypes that are more associated with specific genetic liabilities than is the schizophrenia diagnosis itself. Several factors suggest that spontaneous, involuntary movement abnormalities may be useful phenotypes for further elucidating the nature of genetic effects in schizophrenia. For example, there are numerous reports in the literature of observations of involuntary movement abnormalities in both medicated and unmedicated schizophrenia patients, and there is some evidence that movement abnormalities may be present in the non-psychotic relatives of schizophrenia patients. However, inconsistencies and confounds present in the current literature make any conclusions tentative. The current study sought to systematically and blindly assess for the presence of involuntary movement abnormalities in schizophrenia probands, their unaffected siblings, and controls, while minimizing confounds that currently exist in the literature, in order to resolve these methodological problems and clarify the value of spontaneous, involuntary movement abnormalities as potential endophenotypes. Videotaped interviews of 51 schizophrenia probands, 33 unaffected siblings, and 55 controls, were rated for the presence of a range of involuntary movement abnormalities. Analyses indicated that increased duration and severity of akathesia-like movements and tremor significantly differentiated stabilized, schizophrenia outpatients from controls. However, involuntary movement abnormalities did not significantly distinguish the unaffected siblings of schizophrenia probands from controls. These results suggest that although involuntary movement abnormalities are present in individuals with schizophrenia, they are not associated with the familial liability to schizophrenia. Thus, involuntary movement abnormalities may not be useful adjuncts in genetic studies of schizophrenia.

DOES PPI, P50, AND EYE TRACKING MARK THE SAME OR DIFFERENT ASPECTS OF SCHIZOPHRENIA RISK?

G. K. Thaker,* L. E. Hong, A. Summerfelt, I. W. Wonodi, R. W. Buchanan, H. A. Adami, M. T. Avila
Psychiatry, Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD, USA

Background: We have initiated a large-scale study that is based on the premise that a schizophrenia diagnosis reflects a heterogeneous combination of several causal paths from specific genetic variants to changes in neuronal functioning to behavioral and functional impairments to ultimately the clinical symptoms. In this family case-control study, we will collect information on several neurophysiological and cognitive measures and examine the relationships among them to determine which deficits reflect a common underlying phenotype and which represent independent aspects of disease risk. In the second phase of the study we plan to examine the associations of candidate genes with independent phenotypes and phenotype clusters. Method: In preliminary studies we administered P50, pre-pulse inhibition (PPI), and smooth

pursuit eye movement tests in 93 patients with schizophrenia. We are in the process of scoring the electrophysiological data, and information is available for 38 patients from all three tests. Results: There was a significant inverse correlation between the predictive gain and P50 ratio ($r = -0.50$, $p<0.01$). Patients with poor predictive gain showed poor sensory gating on P50. The two measures of sensory gating did not significantly correlate ($r = -0.09$, $p>0.1$); PPI suppression also did not correlate with predictive gain ($r = 0.01$). In the second phase of the analyses, we examined the effects of SNAP 29 and COMT genotype on these measures. These genes were selected because of our earlier findings of associations of Val allele of COMT gene and *-849A/G single nucleotide polymorphism (SNP) of the SNAP29 gene promoter region with schizophrenia diagnosis. Examination of variants of these two genes with PPI, P50 and predictive pursuit in a small number of subjects showed significant effects of SNAP 29 on PPI ($p<0.05$; G allele associated with worse performance), and COMT on predictive pursuit (Met allele associated with poor predictive pursuit in patients). Additional results from the complete analysis will be presented.

NEUROCOGNITIVE DEVIATIONS IN TWINS WITH SCHIZOPHRENIA AND IN THEIR UNAFFECTED CO-TWINS

T. Toulopoulou,* M. M. Picchioni, T. Ribchester, M. Hua Hall, R. M. Murray
Division of Psychological Medicine, Section of General Psychiatry, Institute of Psychiatry, De Crespigny Park, London, United Kingdom

The idea that deficits in cognition may represent a genetic vulnerability for schizophrenia is much discussed in the literature. 45 twin pairs varying in their zygosity and concordance for schizophrenia and 45 unaffected control twin pairs, also varying in zygosity, were assessed in a comprehensive battery of neuropsychological assessments examining Full IQ (IQ), Verbal Comprehension (VC), Perceptual Organisation (PO), Working Memory (WM), Processing Speed (PS), Flexibility and Verbal fluency for words (wVF) or categories (cVF). Irrespective of their zygosity, patients performed worse than controls on all measures. Interestingly, the non-psychotic co-twins of the MZ sample scored significantly lower than controls on all assessments and did not differ significantly from their affected co-twins. The scores of well members of the DZ discordant pairs were comparable to those of controls on all measures except on Flexibility and Perceptual Organization. The latter is a collective term used to describe functions such as the ability to perceive relationships within spatial or visual components as well as social settings. Among the DZ sample, the well co-twins performed significantly better than the affected twins, and their MZ counterparts, on IQ, VC, WM and PS. There were no significant differences in Intraclass Correlation Coefficients (ICC) between the MZ discordant group and MZ controls arguing against the notion that the illness had a significant impact on cognitive dysfunction. Nonetheless, some ICCs between the DZ discordant group and DZ controls were statistically different, in that the intra-pair differences in the DZ discordant group were larger compared to the DZ controls, which indicates a greater within-pair discrepancy among the DZ discordant sample. Overall, these results suggest that the closer the genetic proximity (MZ vs DZ) to the proband, the greater the cognitive dysfunction.

NCAM1 GENETIC POLYMORPHISMS AND ASSOCIATION WITH BIPOLAR DISORDER

M. P. Vawter,* M. E. Atz, B. Galke-Rollins, K. C. Cooper, K. Overman, H. Tomita, W. Byerley
Psychiatry, University of California, Irvine, CA, USA

NCAM1 is involved in multiple neural functions such as synaptic plasticity, neurodevelopment processes, memory, long-term potentiation, and neurogenesis. The brain expression of certain NCAM1 isoforms is altered in bipolar disorder while different NCAM1 isoforms are altered in schizophrenia [reviewed in Vawter, M., *Eur J Pharmacol*. 2000 Sep 29;405(1-3):385-95]. Recently, several single nucleotide polymorphisms were strongly associated with bipolar disorder in the Japanese population [Arai, M. et al., *Biol Psychiatry*. 2004 Apr 15;55(8):804-10.]. We are conducting a case-control study of bipolar disorder in a Caucasian sample using the same SNPs found to be strongly associated in the Japanese population with bipolar disorder. If we can replicate the Japanese finding, the next question to be pursued is what mechanisms might be responsible for conferring risk for bipolar disorder within the NCAM1 gene. We will report the results of the SNP association study in bipolar disorder.

LACK OF ASSOCIATION BETWEEN COMT GENE AND DEFICIT AND NONDEFICIT SCHIZOPHRENIA

I. Wonodi,* B. D. Mitchell, O. C. Stine, J. M. Gold, G. K. Thaker, R. W. Buchanan
Psychiatry, Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD, USA

The dopamine dysregulation hypothesis of schizophrenia posits that positive, negative and cognitive symptoms correlate with cortical/subcortical imbalances in dopaminergic transmission. A functional polymorphism (Val158Met) in the catechol-O-methyltransferase (COMT) gene is implicated in the pathophysiology of schizophrenia by its effect on prefrontal dopamine transmission (4-fold variation in enzyme activity), and its unique impact on prefrontal cognitive and behavioral phenotypes. Cognitive impairments and negative symptoms in schizophrenia have been hypothesized to be associated with hypodopaminergic states. Schizophrenia patients with the deficit syndrome are characterized by primary enduring negative symptoms, impairment on neurocognitive tasks sensitive to frontal and parietal cortical functioning, and poorer functional outcome compared to nondeficit schizophrenia patients. One hundred and thirty seven schizophrenia cases that met DSM-IV criteria for schizophrenia were recruited. Additional categorization into deficit and nondeficit syndrome was performed using the Schedule for the Deficit Syndrome (SDS). Allele and genotype frequencies of the Val158Met polymorphism were compared in schizophrenia cases with the deficit ($n = 36$), and nondeficit syndrome ($n = 101$). There was no significant difference in allele frequencies between deficit and nondeficit cases ($p = 0.27$). Comparison of genotype frequencies showed a trend that did not approximate significance levels ($p = 0.15$). Our preliminary results in a small sample of schizophrenia cases with the deficit, and nondeficit syndrome failed to show a significant allele or genotype by subtype interaction. This work is supported in part by the NIMH Grants MH45074, MH49826, and MH68580.

EXAMINATION OF LYMPHOCYTE DNA DAMAGE IN SCHIZOPHRENIC SUBJECTS

J. Young,* S. McKinney, B. Ross, K. W. Wahle, S. P. Boyle
School of Pharmacy, The Robert Gordon University, Aberdeen, United Kingdom

Purpose: To examine the effects of oxidative stress in a British population of schizophrenic subjects on the level of DNA damage in freshly isolated and cryopreserved lymphocytes with the effect of patient gender being investigated. Method: The comet assay was used to evaluate DNA damage in endogenous and hydrogen peroxide (H202)-induced DNA damage in freshly isolated and cryopreserved lymphocytes from male and female schizophrenic and control subjects. Results: Significantly greater endogenous (54%, $p<0.05$) and H202-induced DNA damage (57%, $p<0.05$) was seen in lymphocytes from male schizophrenic patients compared to female patients. A similar gender difference was observed in the cryopreserved lymphocytes although data only reached statistical significance at 5 weeks. Conclusion: Increased levels of DNA damage were observed in freshly isolated and in short-term cryopreserved lymphocytes from male schizophrenic patients relative to their female counterparts.

HARNESSING THE POWER OF GENE EXPRESSION PROFILING IN SCHIZOPHRENIA: A PUTATIVE CANDIDATE OBTAINED FROM SUPPRESSION SUBTRACTIVE HYBRIDISATION

J. S. de Belleroche,* S. Ftouh, M. T. Akbar, S. R. Hirsch
Division of Neuroscience and Mental Health, Imperial College London, London, United Kingdom

In order to obtain insight into functional abnormalities occurring in schizophrenia we have focussed on the analysis of gene expression at the mRNA level using rapid autopsy brain tissue obtained as part of a long-term prospective study, We are currently using a range of expression profiling techniques to identify differentially expressed genes in defined brain regions including differential display, gene chip microarrays and suppression subtractive hybridisation (SSH). Transcriptome and expression analysis has already yielded a number of potential candidate genes involved in synaptic transmission, myelin function, and neurodevelopment and the current challenge is to authenticate these changes in large patient cohorts and to determine their contribution to the development of schizophrenia. We report here results obtained using SSH to isolate differentially expressed genes in superior temporal cortex (BA22) of schizophrenics compared to controls. One major sequence found to be under expressed in schizophrenics was selected for further analysis. This was a 190bp transcript showing identity to the sequence of a regulator of the wnt signalling pathway. Differential expression of this gene was validated by mRNA quantitation using slot blot hybridisation and by real-time PCR of a panel of control and schizophrenia cases. Using real-time PCR with two primer sets specific to this gene, we found a significant decrease in mRNA levels of 41% ($p < 0.03$) in patients compared to normal controls using a panel of 12 control and 12 schizophrenia cases. Regional and cellular distribution was carried out using in situ hybridisation and showed abundant expression in cortical neurones. This gene is known to be a potent inhibitor of the neurodevelopmental wnt signalling pathway and may therefore be a relevant candidate in the pathogenesis of schizophrenia.

KLINEFELTER SYNDROME (47,XXY): BIOLOGICAL-GENETIC VULNERABILITY TO SCHIZOPHRENIA AND IMPAIRMENTS IN SOCIAL-EMOTIONAL PROCESSING

S. van Rijn,* H. Swaab, A. Aleman, R. S. Kahn
Psychiatry, University Medical Center Utrecht, Utrecht, Netherlands

Klinefelter syndrome is the most common sex chromosome disorder affecting approximately 1 in 400 to 800 males. Patients are characterized by an additional X chromosome, leading to the 47,XXY karyotype. This sex chromosomal aneuploidy results in a variety of physicial phenotypes. Regarding psychiatric disturbances, some studies have shown that the prevalence of Klinefelter Syndrome in a schizophrenia population is higher when compared to the prevalence of Klinefelter syndrome in the general population. The aim of our study was to examine the relationship between the 47,XXY karyotype and liability to schizophrenia. In addition, we investigated social-emotional processing in this group at increased risk for schizophrenia. The Schizotypal Personality Questionnaire (SPQ), the Positive and Negative Syndromes Scale (PANSS) and a diagnostic psychiatric interview (MINI-Plus) were used to assess schizophrenia spectrum pathology. Social-emotional measures included facial affect recognition, perception of social cues and an affect regulation (Alexithymia) questionnaire. 26 Males with Klinefelter Syndrome and 26 males from the general population, matched for age, education and I.Q., participated in the study. 7 of the 26 Klinefelter patients (27%) met diagnostic criteria for a psychotic disorder. High levels of schizophrenia spectrum pathology were observed in the Klinefelter group with effect sizes that parallel those reported in schizophrenia. In addition, Klinefelter patients showed impairments on all social-emotional measures. Performance profiles were comparable to those found in schizophrenia. In sum, Klinefelter syndrome can be associated with high levels of schizophrenia spectrum pathology and disturbances in social-emotional processing. These findings might have important implications for treatment. Moreover, the X chromosome may be critically involved in the etiology of schizophrenia. The social-emotional impairments reported in both schizophrenia and Klinefelter syndrome may be an X chromosome-linked endophenotype. Studying the genetics of schizophrenia may help localizing genes that are involved in the development of schizophrenia.

8. Genetics, Basic

AN INTERACTION OF THREE GENES INCREASES SUSCEPTIBILITY TO NON-DEFICIT SCHIZOPHRENIA

S. C. Bakker,* M. L. Hoogendoorn, J. P. Selten, P. L. Pearson, R. J. Sinke, R. S. Kahn
Psychiatry, University Medical Center Utrecht, Utrecht, Netherlands

Several genes have repeatedly been reported to be associated with schizophrenia in different populations. We have recently confirmed the involvement of Neuregulin 1 (NRG1), Regulator of G-protein Signalling 4 (RGS4) and a third gene in a less studied region of reported linkage (details will be presented). Interestingly, both NRG1 and RGS4 were associated with non-deficit schizophrenia, but not with the deficit syndrome, which is characterized by idiopathic, enduring negative symptoms. The third gene was equally associated with both disease subtypes. We hypothesized that susceptibility to clinical schizophrenia subtypes is increased by an interaction of at-risk variations in multiple genes, rather than by multiple genes acting alone. Therefore, we investigated if combinations of variations of the associated Single Nucleotide Polymorphisms (SNPs) in the three genes were more frequent in non-deficit schizophrenia, than would be expected by chance, i.e. if the three genes were independent risk factors. The sample consisted of 273 Dutch schizophrenia patients, mainly collected from psychiatric hospitals. Patients were diagnosed according to DSM-IV criteria, using the Comprehensive Assessment of Symptoms and History (CASH). The distinction between deficit and non-deficit forms of schizophrenia was made using the Schedule for the Deficit Syndrome (SDS). In the 127 patients diagnosed with non-deficit schizophrenia, the distribution of variations at the three loci deviated significantly from the expected distribution ($p=0.00002$). The combination of the three at-risk variations was observed in 30.1% of patients, whereas 21.7% would have been expected by chance. Our data suggest that specific combinations of variations across multiple genes are associated with clinical schizophrenia subtypes. Analyzing combinations of susceptibility genes, or gene interactions, rather than single genes, may therefore facilitate the detection of disease-related genetic variants. Ultimately, it may be possible to define specific genetic at-risk profiles, associated with different symptoms or disease course. We are currently studying this possibility by relating the combination of at-risk variants with specific symptoms in our entire sample.

CHANGES IN THE PROTEIN STRUCTURE OF PROTOCADHERINX/Y GENE PAIR IN HOMINID EVOLUTION—A PUTATIVE BASIS FOR CEREBRAL ASYMMETRY

T. J. Crow,* N. A. Williams
SANE POWIC, Oxford, United Kingdom

Through a translocation approximately 3 million years ago (close to the Australopithecus/Homo boundary) the brain-expressed genes ProtocadherinY and X are represented on the human Y and X chromosomes respectively whereas there is a single gene (ProtocadherinX) in other mammals. On the basis of the neuropsychological and radiological deficits associated with sex chromosome aneuploidies we argue that the sequence of events is relevant to the evolution of the sexual dimorphism of cerebral asymmetry, a putative correlate of language. Sequence comparisons with the great apes reveal that in contrast to earlier purifying selection there is evidence of phases of positive selection, on the ProtocadherinX ectodomain and the ProtocadherinY cytoplasmic domain in the hominid lineage (Crow & Williams, 2004). That the changes in the PCDHY cytoplasmic domain are of functional significance is supported by analyses of the number of conservative to radical changes of amino acids estimated to have changed during hominid and chimpanzee/bonobo (CB) evolution. Compared to branch CB where both cytoplasmic amino acid changes are wholly conservative none of the 8 amino acid substitutions identified along hominid branch Y in the PCDHY cytoplasmic domain are in this class. One PCDHY amino acid substitution is entirely radical in terms of change in charge, polarity and volume; 2 substitutions alter 2 of these categories and the remaining 5 residues change one category. Of particular note are the five changes in the PCDHX ectodomain. Two of these X branch-specific changes (located 164 amino acids apart) yield a cysteine residue with the unique ability to form a disulphide bridge with another cysteine residue within or between polypeptide chains. Such bridges may affect the strength of homophilic binding between two PCDHX molecules and/or the strength of heterophilic binding to PCDHY doublets on adjacent cells. (No loss or gain of cysteine residues is found along the PCDHY-specific branch). Notably three of the changes in PCDHX are located within 26 amino acids of each other, in ectodomain cadherin repeat 5. We note that four of the Y substitutions are in the proximal region of the ectodomain (in cadherin motifs 4-7) in which four of the substitutions on the X have also occurred. We conclude that the concomitant changes in protein conformation and interaction are in some way related to the cerebral torque that is characteristic of the human brain.

SNPS IN THE CODING REGION OF THE HUMAN 5-HT2A RECEPTOR ARE ASSOCIATED WITH ALTERATIONS IN THE PHARMACODYNAMICS OF ATYPICAL ANTIPSYCHOTIC DRUGS IN HEK-293 CELLS

M. A. Davies,* V. Setola, D. J. Sheffler, E. Salay, S. J. Hufeisen, R. Strachan, B. L. Roth
Psychiatry, Case University, Cleveland, OH, USA

Rationale: Drug therapy for shcizophrenia includes atypical antipsychotic drugs, which target G-protein coupled receptors (GPCRs), particularly the dopamine and serotonin receptors. Atypical antipsychotic drugs demonstrate a weaker affinity for D2-dopamine receptors and a higher affinity for 5-HT2A-serotonin receptors than typical antipsychotic drugs. The atypical antipsychotic drugs are effective treating both the positive and negative symptoms of schizophrenia, and their use is associated with less extrapyramidal side effects (EPS) and prolactin level elevation than the traditional antipsychotic drugs. Because the 5-HT2A-serotonin receptor is a major molecular target for atypical antipsychotic drugs, pharmacogenetic investigators are now examining whether naturally occurring variations in genes (called single nucleotide polymorphisms or SNPS) encoding the 5HT2A receptor gene (HTR2A, 13q14-21) are associated with alterations in the pharmacodynamics of selected agonists and antagonists at the 5-HT2A receptor. Seven SNPs are located within the coding region of the human 5HT2A receptor gene (ref. ncbi.gov). Two of the seven SNPS (T102C and C516T) are silent mutations and do not cause a change in the protein, whereas five SNPs (T25N, I197V, A447V, S421F and H452Y) result in a change

in an amino acid. Objective: In this study we performed site-directed mutagenesis and conducted functional and binding assays to examine the pharmacodynamics of six atypical antipsychotic drugs (aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone) that function as antagonists at the 5HT2A receptor in HEK-293 cells. Results of the assays were compared for the wild type and four functional SNPs (T25N, I197V, A447V and H452Y). Conclusion: Functional SNPs in the coding region of the 5HT2A receptor were associated with variations in the pharmacodynamics of atypical antipsychotic drugs at 5HT2A receptor in HEK-293 cells. This information is important since these SNPs occur naturally in the population and the 5HT2A receptor is a primary target of drug therapy for schizophrenia and other behavioral disorders and these variations likely result in individual variations in drug response. Supported by RO1MH57635,KO2MH01366 and the NIMH Psychoactive Drug Screening Program.

FOUR QUANTITATIVE TRAIT LOCI FOR THALAMIC VOLUME IN BXD RECOMBINANT INBRED MICE

H. Dong,* M. V. Martin, J. Colvin, Z. Ali, L. Wang, L. Lu, R. W. Williams, G. D. Rosen, J. G. Csernansky, J. M. Cheverud

Psychiatry, Washington University School of Medicine, St. Louis, MO, USA

Decreases in thalamic volume have been observed in schizophrenia patients and hypothesized to represent an early event during the pathogenesis of the disease. However, whether this neuroanatomical abnormality is under genetic control and reflects the influence of susceptibility genes in patients with schizophrenia is unknown. In this study, we determined the heritability of thalamic volume and mapped quantitative trait loci (QTLs) related to genetic variation using BXD recombinant inbred (RI) strains of mice. Digital images of coronal sections from 193 (101 male and 92 female) mice representing 35 BXD RI strains and two parental strains (C57BL/6J and DBA/2J) were obtained from the Mouse Brain Library (www.mbl.org). We then determined the volume of the entire thalamic complex in each animal using point counting and Cavelieri's rule. Two series of sections were used for each animal; the values were averaged, and then adjusted for shrinkage using previously reported methods (Lu, et al, 2001). Heritability was calculated using ANOVA, and QTL analysis was carried out with WebQT (http://www.webqtl.org). The volumes of the thalamus in the B6 and D2 parental strains were 19.19±0.77 mm^3 and 16.10±0.45 mm^3, respectively, which was significantly different (p=0.0055). There was no effect of sex or age on thalamic volume. The heritability of thalamic volume was estimated to be 38%, and four QTLs were identified on chromosomes 10, 11, 13 and 16. One of these QTLs (i.e., on chromosome 13) was also found to be associated with the volume of the ventral hippocampus, as reported in a separate study conducted by our group. The genetic correlation between the volumes of the thalamus and the ventral hippocampus was 0.63 and the predicted shared variance for these traits was estimated at 0.40. Also, a QTL on chromosomes 11 has been previously associated with overall neuron number in BXD and BXH mice (Williams, et al, 1998). The remaining QTLs are, to our knowledge, uniquely associated with the volume of the thalamus in BXD strains of mice. These results suggest that thalamic volume is a heritable trait in mammals. Further fine-mapping of these QTLs will be needed to select candidate genes, and to examine the association of these candidate genes with schizophrenia. Supported by MH71616.

SEARCH FOR PSYCHOSIS LIABILITY GENES ON CHROMOSOME 6Q IN SCHIZOPHRENIA, BIPOLAR, AND ALZHEIMER'S DISORDERS

V. C. Kodavali,* L. Pless, J. Wood, R. A. Sweet, V. L. Nimgaonkar

Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

Several reports suggest linkage and associations at chromosomal 6q12-26 region in Schizophrenia, Bipolar Illness and Late On-set Alzheimer Disease (LOAD) patients, particularly with the short tandem repeat marker, D6S1021. We have investigated two chromosomal regions, namely, D6S1021 (1Mbp) and FYN/WISP3/Laminin genes (0.5Mbp). We screened these two regions in two phases. In phase I, the DNA pooling method was employed to estimate the allele frequency differences between cases and controls. We have screened 200 Single Nucleotide Markers (SNPs) in these two regions using 125 DNA samples from patients with Schizophrenia, Bipolar I, LOAD with and without psychotic symptoms (LOAD+P and LOAD-P, respectively) and a community control group. In phase II, SNPs were genotyped individually using SnapSHOT assay method, if they showed approximately 10% allele frequency differences between cases and appropriate comparison groups. Twenty such SNPs were genotyped and using the trends test, only LOAD+P and LOAD-P group comparisons revealed significant associations for SNPs, rs1365683 and rs2841685 at a p value of 0.00011 and 0.004, respectively. The haplotypes at these two markers, showed significant associations in LOAD+P compared to LOAD-P group (SNP-EM Omnibus likelihood ratio test; p = 0.0007). SNPs rs7769774, rs2895568, rs4946271, and rs1050349 showed a trend for associations (p value 0.03-0.04). Thus, we have suggestive evidence for association with psychosis among Alzheimer disease patients with markers rs1365683 and rs2841685. We are continuing analysis of other markers in this region.

NEUREGULIN-1 EXPRESSION IS DECREASED IN PRIMARY SKIN FIBROBLASTS OF SCHIZOPHRENIC SUBJECTS

S. Leonard,* S. Mexal, R. Berger, R. Freedman

Psychiatry, UCHSC at Fitzsimmons, Aurora, CO, USA

Neuregulin-1 (NRG1) has been implicated as a candidate gene for schizophrenia in both linkage (8p) and association studies. The NRG1 gene has 15 exons, transcribed as three main isoforms, Type I, Type II and Type III. These three NRG1 isoforms showed similar mRNA expression in postmortem hippocampus of schizophrenics (n=12)and controls (n=12), as determined by Affymetrix Hu95Av2 oligonucleotide arrays and quantitative RT-PCR. NRG1 expression was also unchanged in postmortem hippocampus of the smokers in each group. Skin fibroblasts, cultured postmortem from the same subjects, were assayed utilizing U133 Plus 2.0 arrays. Use of cultured fibroblasts removes most of the potential confounding effects of pre- and postmortem parameters, such as brain pH, postmortem interval, cause of death, and medical and recreational drug use. Fibroblasts were cultured at the same passage and conditions for all subjects. Two independent probe sets on the U133 Plus 2.0 arrays, specific to NRG1 Type I, indicated reduced expression in skin fibroblasts from patients (n=12) as compared to the non-mentally ill subjects (n=12). Quantitative RT-PCR confirmed this decrease in NRG1 Type I expression in schizophrenics (-1.4 fold, P = 0.045). The results show that levels for a candidate gene in schizophrenia can be readily assayed in a surrogate tissue, suggesting that cultured skin fibroblasts may be a useful tool for disease assessment and drug development.

This research was funded by NIH grants DA09457, MH44212, NARSAD, and the Veterans Affairs Medical Research Service.

INVESTIGATING THE INFLUENCE OF CHAT GENE POLYMORPHISMS ON OLANZAPINE AND RISPERIDONE THERAPY IN SCHZIOPHRENIA

D. Mancama,* M. Arranz, J. Munro, I. Mata, M. Beperet, R. Kerwin
Psychological Medicine, Institute of Psychiatry, London, United Kingdom

Choline acetyltransferase (ChAt) is responsible for synthesizing acetylcholine, the neurotransmitter that mediates muscarinic and nicotinic cholinergic activity. Widely distributed throughout the brain, ChAt modulates levels of acetylcholine to play important roles in sleep, movement, and cognitive functions including attention, learning and memory. Recent studies have provided salient evidence pointing to significant alterations in the physiological integrity of ChAt among patients with schizophrenia. Most notably these include significant reductions in ChAt levels within the pontine tegmentum of such subjects, further to which these changes have been found to correlate with measures of cognitive decline in the disorder. The underlying mechanisms for this are unknown, and the extent to which they influence the disorders susceptibility and treatment remain uninvestigated. However, we believe genetic variants of ChAt may be important in determining susceptibility to schizophrenia. Moreover, such mechanisms may significantly influence the outcome of such patients to antipsychotic treatment; to investigate this potential we screened the ChAt gene for polymorphisms of potential interest, and investigated two of these (designated ChAtPP1/RsaI and ChAtPP3/TaqI) for influence on treatment outcome in our sample of schizophrenia patients of Basque and Spanish origin undergoing olanzapine and risperidone therapy. Drug response was prospectively rated according to GAF and PANSS scales, and statistical analyses performed using chi-square tests and regression analysis. When each polymorphism was examined in relation to olanzapine and ripseridone outcome among the Basque patients, no evidence for association was found. Lack of association was also observed when the Basque and Spanish patient groups were combined and examined under stratified analysis. Further analyses did not find any influence of ChAt variants on improvement in positive symptoms, negative symptoms, and general psychotic symptoms during treatment with either of these drugs. We conclude from our findings that the polymorphisms ChAtPP1/RsaI and ChAtPP3/TaqI do not significantly influence olanzapine or risperidone outcome in our sample population of Basque and Spanish patients. Further studies however are required to investigate these findings in other populations, while we cannot rule out the potential presence of other polymorphisms in this gene of more significant importance.

QUANTITATIVE TRAIT LOCI FOR VENTRAL HIPPOCAMPAL VOLUME IN BXD RECOMBINANT INBRED MICE

M. V. Martin,* H. X. Dong, D. Vallera, M. Meltzer, L. Lu, R. W. Williams, G. D. Rosen, J. G. Csernansky, J. M. Cheverud
Psychiatry, Washington University School of Medicine, St. Louis, MO, USA

Hippocampal volume reductions, especially involving the anterior portion of the hippocampus, have been reported in schizophrenia patients and their siblings. These findings suggest that changes in hippocampal structure may be related to genetic influences that increase susceptibility to schizophrenia. In this study, we used RI strains of mice to find quantitative trait loci (QTLs) with an effect on the volume of the ventral hippocampus, the subregion of the hippocampus in the mouse analogous to the anterior hippocampus in the human. We examined the heritability and mapped QTLs for ventral hippocampal volume in 33 strains of BXD recombinant inbred mice and BXD parental strains. We measured the volume of the ventral hippocampus in a total of 135 mice, using digital images of sections obtained from the Mouse Brain Library (www.mbl.org). Two parallel series of sections were used per animal and volume measurements were obtained using point counting and Cavalieri's rule. Average volumes using the available series for each animal were adjusted for shrinkage and corrected for age-related variation. The heritability was calculated using ANOVA and QTL analysis was carried out with WebQTL (http://www.webqtl.org). The heritability of ventral hippocampal volume was estimated to be 0.49, and 3 QTLs were identified on chromosomes 8, 13, and 15. These findings are consistent with a previous study of BXD RI mice, which found QTLs for the volume of the entire hippocampus and the architecture of the dentate gyrus on chromosomes 15 and 13, respectively (Lu, et al, 2001). However, we found a high LRS on a region of chromosome 8, which was not reported in the previous QTL analysis related to total hippocampal volume and dentate gyrus architecture. Thus, a gene in this region may have a more specific role in regulating ventral hippocampal development. Interestingly, a marker on chromosome 13 (D13Mit248) was found to be associated with both the ventral hippocampal volume and total thalamus volume, which was measured in a separate study conducted by our group. The genetic correlation between the volumes of these structures was 0.63 and the predicted shared variance for these traits was estimated at 0.40. These findings suggest that a gene with a more general role in neurodevelopment may exist in this region of chromosome 13 in neuroanatomical structure volume and may be implicated in the functional interactions between these brain regions. Supported by MH71616.

CELL CULTURE AND GENE EXPRESSION ANALYSIS SHOW CELL CYCLE ALTERATIONS IN BIOPSIED OLFACTORY NEUROEPITHELIUM FROM ADULTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER

R. McCurdy,* F. Feron, C. Perry, D. McLean, J. J. McGrath, N. K. Hayward, A. Mackay-Sim
Clinical Genetics Research Program, Centre for Addiction and Mental Health, Toronto, ON, Canada

Pathological evidence suggests that schizophrenia may result from altered brain development. The adult olfactory epithelium provides an available "window" on neuronal development because new neurons are formed there throughout life. Previously we demonstrated several differences from controls in olfactory cultures from schizophrenic patients. The present study aimed at replicating these findings concerning schizophrenia, extending the analysis to bipolar disorder and investigating gene expression levels in biopsied olfactory mucosa with a focus on cell cycle-related genes. Biopsies of olfactory mucosa were collected under local anaesthetic from three groups: schizophrenia (n=11), bipolar (n=10), control (n=11). Tissue was cultured for 3 weeks in serum-free medium. Cell nuclei were stained with bisbenzimide and counts made of total cells, mitotic figures, and apoptotic/necrotic cells. An additional biopsy was obtained

for RNA extraction and microarray hybridization. RNA samples (n=7 for schizophrenia and n=5 for the other two groups) underwent antisense amplification prior to hybridization. Our current findings show in schizophrenia a two-fold increase in proliferation of neural cells compared to controls and bipolars. In bipolar cultures there was a 3-fold increase in cell death compared to controls and schizophrenia. Microarray analysis showed 146 and 139 differentially expressed genes in schizophrenia and bipolar disorder respectively, compared to controls. Consistent with increased mitosis in schizophrenia biopsy cultures three genes that function to positively influence cell cycle had increased expression. In the bipolar disorder group a dysregulation of the phosphatidylinositol-signalling pathway was seen; five genes that either directly function within or interact with this pathway had decreased expression. There is speculation that the therapeutic effect of antipsychotic drugs acting upon this pathway in bipolar disorder involves reduction of neuronal cell death. Increased mitosis of neural cells has now been observed in two separate groups of schizophrenic patients indicating a robust finding. This study provides strong evidence for a neurodevelopmental aetiology of schizophrenia and bipolar disorder acting at the level of cell cycle control. Subtle changes in the timing of cell cycle regulation could account for the brain pathologies observed in these diseases.

ASSOCIATION STUDY BETWEEN THE VAL-66-MET POLYMORPHISM IN THE BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) GENE AND SCHIZOPHRENIA

L. Michelon,* Q. Cordeiro, H. Vallada
Department of Psychiatry, School of Medicine, University of Sao Paulo, Sao Paulo, Brazil

Brain-derived neurotrophic factor (BDNF) is abundantly expressed within the brain and has been demonstrated to promote the survival, differentiation, proliferation, plasticity and maintenance of a broad variety of central nervous system neurons. Recent studies have suggested its contribution in the pathophysiology of schizophrenia (SCZ). In the present study we investigated the genetic association between the BDNF Val-66-Met gene polymorphism and SCZ. We investigated the distribution of the studied polymorphism in 118 patients with DSM-IV SCZ and in 252 controls. No significant differences were found in allelic (p=0.069, X2=3.30, OR=1.51 0.94<OR<2.40) and genotypic (p=0.11, X2=4.36, 2d.f.) distributions. No evidence of association between the Val-66-Met polymorphism of the BDNF gene and SCZ was found in our Brazilian sample.

LARGE-SCALE TRANSCRIPTOME ANALYSES OF SCHIZOPHRENIC BRAINS USING SERIAL ANALYSIS OF GENE EXPRESSION (SAGE)

E. B. Ojopi,* D. M. de Souza, A. Schmitt, W. F. Gattaz, E. Dias Neto
Psychiatry, University of Sao Paulo, Sao Paulo, Brazil

Schizophrenia (SCZ) is a complex disease caused by a conjunction of environmental and genetic components. It is probable that the genes that modify the dynamics of the central nervous system, causing SCZ, may act during diverse stages of the brain development modifying other genes, in a cascade of effects. The genetic components involved are likely to be a sum of series of alterations in genes of 'small effect', being most adequately studied collective by large-scale projects. Due to the great difficulty in obtaining adequate biological material to evaluate gene expression, current genetic approaches to study genes involved in SCZ are basically dependent on the identification and association studies using DNA polymorphisms. In this work, we are evaluating the transcriptome of schizophrenic-derived brains using SAGE (Serial Analysis of Expression Gene). This powerful methodology is being used here for the first time to the study of this disease, and it should allow the evaluation of virtually all the transcripts active in the diseased brains, generating quantitative data from transcripts differentially regulated in SCZ. More than 50,000 SAGE tags have been already produced from pre-frontal cortex of patients with SCZ, enabling the analysis of more than 20,000 transcripts. Ninety-two of these seem to be upregulated whereas fourty-five transcripts are downregulated when compared with non-schizophrenic brains. Genes that seem to be differentially expressed will be subsequently evaluated in individual brains by using Real-time PCR. The application of SAGE followed by a confirmation of differential expression using real-time PCR should enable the identification of a series of genes whose transcription is consistently altered in SCZ. The identification these markers should have an important effect in the diagnosis, treatment and the better understanding of SCZ. Acknowledgements: ABADHS, FAPESP.

POLYMORPHISMS IN THE DOPAMINE D2 RECEPTOR GENE: A STUDY OF ASSOCIATION WITH SCHIZOPHRENIA IN A SPANISH POPULATION ISOLATE

M. Parsons,* M. J. Arranz, I. Mata, M. Beperet, F. Iribarren-Iriso, B. Arroyo, R. Sainz, R. W. Kerwin
Clinical Neuropharmacology, Institute of Psychiatry, London, United Kingdom

Numerous lines of evidence have highlighted the D2 receptor as a possible candidate gene in the pathophysiology of schizophrenia. However, association studies investigating D2 polymorphisms and schizophrenia have produced contradictory results. Disease heterogeneity has been mentioned as one of the significant reasons for discordant results. Different genetic factors may be contributing to disease aetiology in different heterogeneous populations. Human isolate populations show lower heterogeneity that large heterogeneous populations and can help to identify genes involved in complex disorders. We have used a sample from a human isolate from Navarra (North Spain) of Basque origin, one of the oldest isolates in Europe (Calafell et al., 1994) to clarify previous discordant results regarding D2 polymorphisms. We investigated two D2 polymorphisms (TaqI A1/A2 and −141−C Ins/Del) polymorphisms in a clinical sample from the Navarra isolate consisting of 165 controls and 167 patients with psychotic disorders, of which 119 are schizophrenic. The results show that the TaqI A2 allele was more frequent in schizophrenic patients than in controls (c2=9.9, df= 1, p=0.002). A similar association was found for the TaqI A2/A2 genotype (c2=13.33, df=1, p=0.0003). No similar association was found for the −141C Ins/Del polymorphism. Conclusions: There was a strong association between a potentially functional polymorphism in the 3′ region of the DRD2 gene and schizophrenia, suggesting that this or other genetic factors in linkage with it may play a role in the pathophysiology of schizophrenia.

ASSOCIATION OF PERICENTRIN 2 (PCNT2) WITH SCHIZOPHRENIA

A. A. Pillai,* K. Nakamura, K. Yamada, Y. Iwayama-Shigeno, T. Toyota, N. Takei, Y. Minabe, K. Suzuki, Y. Sekine, Y. Iwata, M. Nakajima, S. Moriwaki, J. McGrath, K. Miyoshi, A. Honda, K. Baba, T. Katayama, M. Tohyama, T. Yoshikawa, N. Mori
Dept. of Psychiatry & Neurology, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan

A centrosomal protein of pericentrin 2 (PCNT2) has been found to be essential for the centrosomal localization of DISC1 (disrupted-in-schizophrenia 1), a potential candidate gene for major psychiatric disorders. It has been hypothesized that a signaling cascade involving several molecules interacting with DISC1 may explain the pathophysiology of schizophrenia. PCNT2, constituting an integral component of the pericentriolar material, is pivotal to microtubule organization and assembly of mitotic spindle apparatus during mitosis. Abnormalities of PCNT2 can affect microtubule dynamics, and thus may cause alterations in neuronal migration and neural circuitry, leading to neurodevelopmental disorders such as schizophrenia. We investigated the association of PCNT2 allelic variants with schizophrenia in a case-control study of Japanese subjects (125cases and 125 controls), by analyzing 20 SNPs evenly distributed throughout the 121.6 kb gene. A significant between-group variation (p=.037) was observed in the distribution of allele frequencies for the SNP rs2249057 (A/C) in exon 10 (silent mutation). In addition, there was significant variation between the two groups in the frequencies of two-SNP and three-SNP haplotypes, involving rs2249057. The linkage disequilibrium (LD) pattern was found to be similar in the two groups, with substantial LD between adjacent SNP pairs. We also analyzed PCNT2 gene expression in lymphocytes with samples of drug-na?ve schizophrenics (n=27) and controls (n=59). A significant group difference was observed in the PCNT2 expression in lymphocytes. However, no variation was observed in PCNT2 expression in fibroblasts with samples of schizophrenics (n=10) and controls (n=10). The allelic and haplotypic associations, as well as the gene expression analysis, suggest that PCNT2 may be a potential candidate gene for schizophrenia, harboring a susceptibility region around rs2249057. Although the functional role of PCNT2 in schizophrenia needs be elucidated, PCNT2 might have its own effect by intervening in the neurodevelopmental process. Alternatively, the effect may be mediated through a signal transduction pathway involving DISC1 and other cytoskeletal and centrosomal proteins.

EPIGENETICE OF X CHROMOSOME: SKEWED X INACTIVATION AS POSSIBLE SOURCE OF DISCORDANCE TO SCHIZOPHRENIA AND BIPOLAR DISORDER IN MONOZYGOTIC FEMALE TWINS

A. Rosa,* M. Picchioni, S. Kalidindi, I. W. Craig, R. M. Murray
SGDP, Institute of Psychiatry, London, United Kingdom

The contribution of genetic factors to schizophrenia (SZ) and bipolar disorder (BD) has been largely recognised from twin, family and adoption studies. However, to date no genes have been unambiguously identified in the origin of these disorders. Monozygotic (MZ) twins discordant for psychiatric disorders have provided an intriguing paradigm for investigating the aetiology of these complex conditions and are thought to frequently reflect the influence of environmental factors. Recently, however, several authors have suggested the possible involvement of epigenetic factors operating during initial neurodevelopment (Petronis et al 2001). Epigenetic changes can modify the primary DNA sequence and can result in heritable changes in gene function. Epigenetic phenomena, such as differential methylation of DNA, may result in altered patterns of gene expression and may, therefore, have relevance for the understanding of the phenotypic discordance of MZ twins for disorders including SZ and BD. We tested this hypothesis by investigating concordant and discordant SZ and BD female twin pairs. To this end, we employed an inactivation assay based on the discrimination between active and inactive X chromosomes as reflected by their methylation patterns at the human androgen receptor locus. To date, we have examined mouth swab and/or blood samples from 4 MZ pairs discordant and 5 concordant for SZ; 5 pairs discordant and 4 pairs concordant for BD and compared their inactivation skewing with 25 healthy control pairs. The results obtained so far, although generally reflecting a consistency in skewing estimates obtained with blood and with buccal swabs, do not suggest a significant contribution from X linked loci to the phenotypic differences observed for the discordant pairs affected by SZ. However, the discordant BD twins showed to be more discordant in the methylation of the maternal and paternal X alleles. Since significant evidence of linkage for BD to chromosome X has been previously reported (Baron et al 1987; Ekholm et al 2002), at the moment, we are expanding the number of twin pairs investigated, which will enable a more robust investigation into the hypothesis of discordant skewing in X chromosome inactivation contributing to phenotypic differences in these female twin pairs.
Acknowledgments: This work was supported by the Wellcome Trust and the Stanley Medical Research Institute. We also thank AGAUR (Generalitat de Catalunya) and Fundacio Seny (Barcelona).

NICOTINIC ACETYLCHOLINE RECEPTOR EXPRESSION AND DIVERSITY IN SCHIZOPHRENIA AND BIPOLAR DISORDER

E. G. Severance,* F. Leister, R. H. Yolken
Pediatrics, Stanley Div., Johns Hopkins University, Baltimore, MD, USA

Cognitive dysfunction, sensory gating deficits and nicotine addiction in schizophrenia implicate neuronal nicotinic acetylcholine receptors (nAChRs) in the etiopathogenesis of this disorder. Decreased expression of the α7 nAChR in schizophrenia has been inferred from immunohistochemistry and α-bungarotoxin binding studies in post-mortem brain samples. Previous analyses of mRNA transcripts of the α7 gene have revealed a high level of transcriptional diversity including duplications, SNPs and splice variants. In the present study, we measured the degree of mRNA transcription of the major nAChR subtypes in post-mortem cortical samples from the Stanley Array Collection and sought to investigate the role of alternative splicing as a genomic mechanism of dysfunction in schizophrenia and bipolar disorder. cDNA from the prefrontal cortex of 105 post-mortem brains (35 each of schizophrenia, bipolar disorder and controls) from the Stanley Neuropathology Consortium was generated by reverse transcription and subjected to real-time PCR quantification. Alternatively spliced isoforms were amplified with primers designed to span intron-exon boundaries using endpoint PCR, and resulting products were cloned and sequenced. Preliminary analyses reveal a trend towards decreased expression of both α4 and α7 subunit-containing nAChRs in the brains of individuals with schizophrenia ($p<0.08$). A variant of the α7 gene that contains a partial

duplication of exons 5-10 (CHRFAM7) was associated with a significantly reduced expression in the brains of individuals with bipolar disorder ($p<0.01$). Numerous splice variants were identified, including a previously unreported isoform that incorporates a 123 base pair insert in the ligand binding region of the α7 receptor. In a pilot endpoint PCR analysis, the novel transcript was strongly amplified in the prefrontal cortex of the samples from individuals with schizophrenia, and weakly amplified in the samples from individuals with bipolar disorder and controls. These findings suggest that the altered expression of nicotinic receptors in disease states and subsequent defective cholinergic neurotransmission are likely due to the high level of transcriptional diversity that results in truncated receptor products. The authors thank Maree Webster, Michael Knable, E Fuller Torrey, Serge Weis, and the Stanley Neuropathology Consortium for providing the brain samples.

DELINEATING THE INFLUENCE OF ANKK1 AND DOPAMINE 2 RECEPTORS IN SCHIZOPHRENIA

O. Skrobot,* D. Mancama, M. Arranz, I. Mata, M. Beperet, R. Kerwin
Psychological Medicine, Institute of Psychiatry, London, United Kingdom

Dopamine is thought to be involved in the aetiology and pathology of psychiatric disorders such as psychosis and depression. Atypical antipsychotics only become effective at doses over 65% of dopamine 2 (D2) receptor occupancy, implicating the importance of these receptors. Consequently, variability in treatment response in patients with schizophrenia may be explained by genetic factors affecting the density or function of these targets. Due to findings that the Taq1 A1/A2 polymorphism, located within the ANKK1 gene, affects the regulation of expression of the D2 receptor, it was hypothesized that other polymorphisms in the ANKK1 gene may be associated with effects on D2 expression and function. Four polymorphisms spanning the ANKK1 gene (1240C/A, 19878 G/C, -8882 G/C, -2099 A/G) were genotyped in a sample of psychiatric patients and control participants of Spanish ethnicity and a human isolate of Basque origin from Navarra, Northern Spain using a case/control association study design. Subsets of the patients were treated with the atypical antipsychotics olanzapine and risperidone, which have a varying degree of affinity for dopaminergic receptors. Several associations were found between these polymorphisms and psychiatric illness. In addition, associations were also observed relating genetic variants in the ANKK1 gene to variation in symptomatology after antipsychotic treatment. In summary, this study has demonstrated that genetic variants in the ANKK1 gene may contribute to the aetiology of psychiatric disorders and variation of response to atypical antipsychotic drug treatment. Replications of this study in other populations are required to confirm these findings.

THE SCHIZOPHRENIA AND FRAGILE SITE CONNECTION

C. L. Smith,* N. Nguyen, G. Nguyen, M. Boselli, M. Schultz, H. Abdolmaleky, A. Bolton
Center for Advanced Biotechnology, Boston University, Boston, MA, USA

Our previous results on twins led us to propose that schizophrenia is associated with global genomic instability. The goal of this research was to explore the relationship between schizophrenia and fragile sites. There are 119 fragile sites spread throughout the human genome. These regions of the genome are prone to mutation and generally associated with genomic remodeling and plasticity. For instance, retroviruses insert into the genome within these regions, many genes within these regions are subjected to epigenetic regulation and these regions are frequent sites for deletions, translocations and other rearrangements. The sequence of about 13 fragile sites is known and at least one site ranges up to 3.2 megabases in size. The relationship between schizophrenia and fragile sites was explored by comparing the chromosomal addresses of fragile sites and genes and chromosomal abnormalities linked to schizophrenia. Databases were constructed for fragile sites, for genes linked to schizophrenia and for chromosomal abnormalities linked to schizophrenia. The information in these databases was collected from published reports. The chromosomal addresses between fragile sites and genes linked to schizophrenia, and between fragile sites and chromosomal abnormalities were compared. The results showed that 73% of the genome is not known to contain any fragile sites. A larger than expected number of genes and chromosomal abnormalities linked to schizophrenia co-localize to regions of the genome containing fragile sites (Chi Square, $P = 0.001$). Negative controls showed no associated with fragile sites. One control consisted of all the known human genes available in Genbank. The second negative control consisted of genes tested but not linked to schizophrenia. These results link schizophrenia to multiple fragile sites and support the hypothesis that schizophrenia is linked to genomic instability. Cancer is linked to multiple fragile sites and associated with genomic instability and there is one report of an anti-correlation between cancer and schizophrenia. We speculate genomic instability in Schizophrenia accounts for seemingly disparate biological and environmental factors that influence this disease by increasing genomic instability. If this hypothesis is correct, the prevention and/or minimization of schizophrenia can be achieved by stabilizing the genome.

9. Neurochemistry, Clinical

KETAMINE DISRUPTION OF FEARFUL FACIAL EMOTION PROCESSING IN HEALTHY WOMEN

K. M. Abel,* J. Hallak, T. Russell, J. Lees, S. Dursun, J. W. Deakin, M. L. Phillips
Centre for Women's Mental Health Research, Manchester University, Manchester, United Kingdom

Background: Most women with schizophrenia have children, but their inability to relate emotionally to their infants is associated with consistently poor parenting outcome. Schizophrenia shows deficits in processing of facially expressed emotions. We have suggested that ketamine reliably mimics these deficits and as part of a series of studies exploring poor mother-infant interaction in schizophrenia, we used ketamine in healthy women to model abnormal emotion processing. Methods: 15 healthy, young women were tested during menses in a placebo-controlled, randomised, blinded, crossover design. Subjects received an infusion of ketamine (0.23mg/kg bolus; 0.5mg/kg infusion over 1 hour) or saline placebo while completing non-facial stimuli (shapes and colours) and facial stimuli (5 different emotions and 4 different intensities of emotion) in a two-choice matching task. Results: There was a significant difference in change from baseline scores between ketamine and placebo in CADSS ($p<0.001$) and BPRS ($p<0.001$). Subjects were significantly slower on ketamine compared to placebo ($p=0.04$). There was a trend for subjects on ketamine to make more errors ($p=0.07$). In general, compared to non-face tasks, reaction times for face tasks were significantly slower($p=0.02$); and significantly more errors were made ($p=0.001$).On Ketamine subjects took longer to complete Face tasks only ($p=0.02$)and made more errors($p=0.08$). Ketamine effects on emotions considered most relevant to mother-infant interaction were explored ie: fear/happy/sad. A main effect of emotion ($p=0.01$), and an interaction between emotion and condition ($p=0.04$) were found: On ketamine subjects made more errors compared to placebo on the emotion matching task only ($p=0.05$). Although subjects found sad emotions most difficult, posthoc analysis showed ketamine only slowed RT in fear ($p=0.02$) and at the highest intesnities of emotion ($p=0.001$). Conclusions: Ketamine may have specific effects on negative facial emotion processing most apparent at the highest intensities of emotion. The capacity for mothers with schizophrenia to interpret and respond appropriately to their infant's facial emotions may be compromised in particular with negative emotional cues.

ABNORMAL EXPRESSION OF POSTSYNAPTIC PROTEINS ASSOCIATED WITH AMPA RECEPTOR TRAFFICKING IN THE PREFRONTAL CORTEX IN SCHIZOPHRENIA

M. Beneyto,* V. Haroutunian, K. L. Davis, J. H. Meador-Woodruff
Mental Health Research Institute. Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA

Ampakines, positive AMPA receptor modulators, improve cognitive function in schizophrenia, and enhancement of AMPA receptor-mediated currents by these compounds potentiates the activity of antipsychotics. Recently, in vitro studies have revealed that the dynamic redistribution of AMPA receptors in and out of the synaptic membrane is an important mechanism for certain forms of long lasting synaptic modification at the glutamatergic synapse. Trafficking of AMPA receptors is mediated by specific interactions of a complex network of proteins that also target and anchor them at the postsynaptic density (PSD). These proteins modulate and maintain cell surface expression, and regulate AMPA receptors response to glutamate and subsequent signaling cascades, as these proteins link AMPA receptors to critical intracellular effector molecules. The aim of this study was to clarify if there are abnormalities in the trafficking and localization of AMPA receptors at the PSD in the prefrontal cortex in schizophrenia by analyzing both at transcript and protein levels the expression of NSF (regulates the "constitutive pool" for recycling of AMPA synaptic receptors), GRIP1, ABP, and PICK1 (linked to vesicular trafficking in the NMDA-dependent "regulated pool", modulating the intracellular "storage" of AMPA receptors), SAP97 (traffics GluR1-containing newly synthesized AMPA receptors) and stargazin (binds to all four AMPA subunits and sweep them laterally into postsynaptic sites). In situ hybridization in postmortem samples, with region and cell level analysis, showed minimal changes in the expression of AMPA receptor subunit mRNA in schizophrenia, while expression of some of the intracellular AMPA trafficking proteins was altered. Specifically, we found increased expression of mRNA for stargazin, decreased expression of PICK1, and no change in the expression of NSF. Preliminary data from western-blot experiments show less dramatic changes, although GRIP1 is abnormally increased in schizophrenia, suggesting increased intracellular storage of AMPA receptors. These data suggest that AMPA receptors are dysregulated in schizophrenia, not at the level of receptor expression, but rather at varius locations in intracellular pathways associated with AMPA receptor targeting, trafficking, and recycling. Supported by MH53327.

CLINICAL CORRELATES OF REPRODUCTIVE HORMONE ABNORMALITIES IN WOMEN WITH SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

M. Chakos,* N. Dargani, J. Tropnas, M. Ranganathan, C. Ansi-Boldur, B. Sheitman, J. A. Lieberman
Psychiatry, SUNY Downstate Medical Center, Brooklyn, NY, USA

Background: Gonadal hypofunction in the form of subnormal estrogen levels, in addition to high androgen levels, has been previously reported in female patients with schizophrenia and schizoaffective disorder. Association of low estrogen levels and symptom exacerbation has also been reported. This study examines the clinical correlates of reproductive hormonal abnormalities in female patients who were persistently symptomatic despite stable treatment with antipsychotic medication. Methods: Twenty one women between the age of 18 to 50 treated with antipsychotic medications for schizophrenia or schizoaffective disorder and who were not taking oral contraceptives were recruited to for the study. Patients who participated in the study had been treated with a stable regimen of antipsychotic medication for at least one month and were still experiencing persistent psychotic symptoms with a PANSS score equal to or greater than 60. The subjects completed questionnaires about their menstrual history, were assessed for clinical symptoms including the deficit syndrome, and provided blood samples for measurement of a range of reproductive hormones including estradiol, DHEA, DHEAS, free testosterone, prolactin, progesterone and oxytocin. Results: The mean age of study participation was 42 years of age, the mean duration of illness was 16 years and the mean PANSS score was 79. Four of the 20 participants met criteria for the deficit syndrome. Across the sample, mean hormone levels for estrogen were below normal values and mean DHEA, DHEAS, and free testosterone levels were

above normal values. After controlling for age, lower estrogen levels were associated with greater psychopathology in the form of higher total PANSS scores (r = -0.479, p=0.032) and the PANSS general psychopathology subscale scores (r = -0.55, p=0.014). Lower oxytocin levels were also associated with higher total PANSS scores (-0.487. p=0.047) and higher scores on the general psychopathology subscale (-.502, p=.040). Greater severity of the deficit syndrome was associated with lower estrogen levels (p=0.002). Significance: The role of neurosteroids in the pathophysiology of psychiatric illness is rapidly becoming an important focus of investigation. These findings suggest that women with schizophrenia have abnormalities that involve several reproductive hormones and that these abnormalities are associated with illness severity.

INCREASED IL-12 AND DECREASED IL-18 PLASMA LEVELS IN DRUG NAIVE PATIENTS WITH A FIRST EPISODE OF PSYCHOSIS DURING TREATMENT: CLINICAL IMPLICATIONS

B. Crespo-Facorro,* E. Carrasco-Marin, J. M. Pelayo Teran, R. Perez Iglesias, C. Pena, M. L. Ramirez, F. Leyva-Cobian, J. L. Vazquez-Barquero
Unidad de Investigacion Psiquiatria. Dept. Psychiatry, University of Cantabria, Hospital Marques de Valdecilla, Santander, Cantabria, Spain

Patients with psychosis may have a dysfunction in the normal Th1/Th2 balance with an impaired production of Th1 cytokines and also an overactivation of the Th2 system. Nonetheless, the biological mechanisms that may lead to the proposed dysfunctional Th1/Th2 balance are still unclear. It is of note that a key step in the development and regulation of the Th1 response is exerted by IL-12 and IL-18 cytokines that plays a key role in bridging the Th1-Th2 balance. The aims of the present study were to investigate in a large sample of first episode psychotic patients, who had not been previously taken antipsychotic medication, (1) whether there is a change in IL-12 and IL-18 plasma levels during the acute phase of the illness and after 6 weeks of treatment and (2) whether these changes in cytokine levels are related to the severity of symptomatology. 52 (36M) drug-naive individuals with a first psychotic episode from a larger ongoing prospective Study of Early Phases of Psychosis (PPEP), University Hospital Marques de Valdecilla, in Santander were included. The patients had not received any dose of antipsychotics in their lifetime, or only a single bed-time dose of neuroleptics previous blood sample was obtained. For this study measures of psychopathology included SANS, SAPS and BPRS. There was a significant increased in plasma IL-12 levels (54.63 (21.59) vs 68.46 (28.85); t=4.306;p< 0.001) and a discrete decreased in plasma IL-18 levels (80.05 (61.11) vs 59.88 (30.76); t=2.008; p=005) after six weeks of treatment compared to cytokine levels at baseline. The correlation analysis shows that there is a significant inverse relationship between the increase in IL-12 levels and the severity of positive symptoms (SAPS total) (r= -0.372, p= 0.007) (i.e., the higher the increase in IL-12 level, the smaller the severity of psychotic symptoms). No significant correlations between IL-18 levels and psychopathology were found. Thus, our results suggesting that the anomalies of the IL-12 and IL-18 function may be relevant to understand the TH-1/TH-2 imbalance described in schizophrenia and additionally, showing the relevance of examining the relation between of the immune system and clinical features of the illness.

GENE EXPRESSION DEFICIT IN GLUTATHIONE SYNTHESIS: ROLE IN THE DISCONNECTIVITY SYNDROME OF SCHIZOPHRENIA

K. Q. Do,* M. Tosic, P. Bovet, J. H. Cabungcal, P. Deppen, F. Gheorghita, J. P. Hornung, M. Preisig, M. Sagara, F. Schenk, A. Solida, M. Cuenod
Center for Psychiatric Neuroscience, Lausanne University, Prilly-Lausanne, Switzerland

Glutathione level ([GSH]) and that of its metabolite *γ-Glu-Gln are decreased in the cerebrospinal fluid of drug-naive schizophrenics. [GSH] measured by magnetic resonance spectroscopy was diminished by 52% in medial prefrontal cortex (Do et al, 2000). A decrease in mRNA levels, analyzed by quantitative RT-PCR, was also observed in fibroblasts for two GSH synthesizing enzymes (glutathione synthetase and the modulatory subunit of glutamate-cysteine ligase, GCLM). Moreover, the level of GCLM expression correlates negatively with some PANSS scores (positive symptoms and abstract thinking). Thus, depression of gene expressions is likely causes of low brain [GSH] and is related to psychopathology. GSH is an important endogenous redox regulator and neuroactive substance, protecting cells from damage by reactive oxygen species generated, among others, by dopamine. GSH deficit induced oxidative stress would lead to lipid peroxidation and micro-lesions in the surrounding of catecholamine terminals, affecting the synaptic contacts on dendritic spines of cortical neurones, thus causing a structural disconnectivity. GSH deficit could also lead to functional disconnectivity by depressing NMDA neurotransmission. Decreasing pharmacologically [GSH] in experimental models, with or without blocking DA uptake (GBR12909), induces morphological and behavioral changes similar to those observed in patients. In developing rats (p5-p16), [GSH] deficit and GBR induce a decrease of spines in prefrontal pyramids and of parvalbumine but not of calretinine immunoreactivity in anterior cingulated GABA neurons. GSH depletion in hippocampal slices impairs long-term potentiation through an NMDA mediated mechanism (Steullet et al. 2004). Developing rats with low [GSH] and GBR have deficit in cognitive functions (Castagne et al 2004). GSH system deficit during development constitutes a vulnerability factor for schizophrenia.

PLASMA HOMOVANILLIC ACID IN SCHIZOPHRENIA

R. Freedman
Psychiatry, University of Colorado, Denver, CO, USA

The dopamine theory of schizophrenia is perhaps the most notable achievement of schizophrenia research and is still the guiding principle of current therapeutics. The measurement of dopamine metabolites as a guide to the diagnosis and treatment of schizophrenia has a long history in our field, but a Medline search on plasma homovanillic acid, the last of the metabolite measures to receive attention, revealed just one report in 2004. Problems with variance in the measure, concern about the relative contribution of peripheral and central nervous system sources for catecholamine metabolites, and the failure to observe values in schizophrenia that were outside the range of normal contributed to the loss of interest in this measure. A retrospective review, however, shows that reproducibility can be achieved with relatively modest experimental control. Furthermore, the measure correlates well with several measures of psychopathology in schizophrenia, although it does not distinguish per-

sons with schizophrenia from others. Changes in plasma homovanillic acid during neuroleptic withdrawal, for example, significantly predict the clinical course over the next several years: patients with higher plasma homovanillic acid levels are much more likely to require longer-term institutional treatment than patients with lower levels. Plasma homovanillic acid is also a particularly revealing measurement when considered in the context of other aspects of risk in schizophrenia. Recent genetic and neurobiological data have led to the conceptualization of schizophrenia as the outcome of more than one pathophysiological deficit. From this perspective, the usefulness of peripheral dopamine metabolites as measures of the contribution of altered dopaminergic neurotransmission to schizophrenia may have been prematurely discounted.

A NEUROCOMPUTATIONAL MODEL OF THE DYNAMICS AT THE SUBCORTICAL DOPAMINE RECEPTORS IN THE CONTEXT OF SCHIZOPHRENIA

H. Geerts,* A. Spiros, R. Carr, J. Dani, M. Kramer
In Silico Biosciences, Berwyn, PA, USA

Dopamine D2-Receptor antagonism in the striatum is still the cornerstone of neuroleptic therapy in schizophrenia (SZ). However, increasing evidence suggests a role for the D1 receptor in regulating the output of the ventral striatum, which is related to the discrimination of salient stimuli. In addition, the Dopamine D3-receptor is also involved in dopamine clearance. This computer model incorporates the latest data on schizophrenia pathology, dopamine (DA) dynamics on D1D2 and D3-R in the basal ganglia and the effect of neuroleptic drugs, The model takes into account the capacity of the dopaminergic neurons to switch from tonic to burst firing and the competition between endogenous dopamine and the different neuroleptics. A major readout of this computer model is a signal-to-noise ratio (S/N), defined by the neurotransmission of a model striatal neuron in conditions of burst vs tonic dopaminergic firing. This can be linked to the discrimination of salient compared to irrelevant stimuli. In particular, when results from imaging studies and postmortem analysis in schizophrenia patients are introduced in the model, a decreased capability of stimulus discrimination in the SZ pathology becomes apparent. The reduction in this S/N ratio can be corrected by both a D1-R and a D2-R modulation, is dependent upon D3-R antagonism and upon the koff rate of the neuroleptic relative to dopamine, as both enter into competition for the same binding site. The model explains the beneficial effect of neuroleptics with a large range of D2-R inhibition, such as clozapine and risperidone on the S/N ratio and is compatible with the recent findings of nicotine receptor stimulation on dynamics of the dopaminergic system. This computational model allows testing certain hypotheses about the pathophysiology of schizophrenia in silico and evaluating different pharmacology of novel neuroleptics.

EXPRESSION OF EXCITATORY AMINO ACID TRANSPORTER INTERACTING PROTEINS IN THE THALAMUS IN SCHIZOPHRENIA

I. Huerta,* R. E. McCullumsmith, K. L. Davis,
V. Haroutunian, J. H. Meador-Woodruff
Mental Health Research Institute, University of Michigan, Ann Arbor, MI, USA

The excitatory amino acid transporters (EAATs) are a family of plasma membrane proteins that maintain synaptic glutamate concentration by removing glutamate from the synaptic cleft. EAATs are expressed on glia (EAAT1 and EAAT2) and neurons (EAAT3 and EAAT4) throughout the brain. EAAT-mediated glutamate reuptake is regulated, in part, by several EAAT interacting proteins that modulate subcellular localization and glutamate transport activity of the EAATs. Several lines of investigation support the hypothesis of the glutamatergic abnormalities in the thalamus in schizophrenia, including previous work in our laboratory demonstrating increased expression of EAAT1 and EAAT2 transcripts in the thalamus in schizophrenia, suggesting that alterations in synaptic glutamate levels may contribute to the pathophysiology of schizophrenia. Since EAAT interacting proteins regulate EAAT function, directly impacting glutamatergic neurotransmission, we hypothesized that expression of EAAT interacting proteins may be altered in schizophrenia. Using in situ hybridization in subjects with schizophrenia and a comparison group, we detected increased expression of JWA and KIAA0302, molecules that regulate EAAT3 and EAAT4, respectively, in the thalamus in schizophrenia. In contrast, we did not find changes in the expression of ARHGEF11 transcripts in the thalamus in schizophrenia. Studies on the EAAT2 interacting protein GPS1 are presently underway. These findings suggest that regulation of glutamate reuptake is abnormal in this illness, supporting the hypothesis of altered thalamic glutamatergic neurotransmission in schizophrenia.
Supported by MH53327.

IMPAIRED GLUCOCORTICOID NEGATIVE FEEDBACK IN SCHIZOPHRENIC PATIENTS WITH HIPPOCAMPAL PATHOLOGY

N. N. Hussain,* M. B. Goldman
Harvard Longwood Psychiatry, Beth Israel Deaconess Medical Center, Boston, MA, USA

Hippocampal pathology is the most localizing finding in schizophrenia, but its significance is unclear. Polydipsic schizophrenic patients, especially those who are hyponatremic, have hippocampal volumes that are diminished relative to matched schizophrenic patients. Polydipsic patients also exhibit resistance to dexamethasone which could reflect impaired hippocampal-mediated glucocorticoid negative feedback. To further address this interpetation, plasma cortisol levels (CORT) were first lowered by blocking 11-beta-hydroxylation with metyrapone, and then the drop in adrenocorticotropin (ACTH) was determined in response to a 150 min cortisol infusion. Hippocampal influences were accentuated by conducting the study in the evening, and by utilizing CORT levels that occupy primarily hippocampal mineralocorticoid receptors. Schizophrenic subjects were 7 hyponatremic polydipsic (HPS), 7 normonatremic polydipsic (NPS), and 8 normonatremic nonpolydipsic (NNS) plus 10 healthy controls (HC). Normals were studied on two occasions, once with cortisol and once with saline, to delineate the normal response. To enhance statistical power, we relied on apriori Helmert contrasts, comparing H1: the HC to the three schizophrenic groups; H2: the NNS to the two polydipsic groups (HPS,NPS); and H3:the NPS to HPS. CORT levels prior to, during, and following the infusion changed similarly across groups. Basaeline ACTH was marginally lower in HC than the three patient groups (H1:P=.06), which in turn resembled each other. ACTH levels began to fall in HC at 60 min into the infusion and fell throughout the remaining 180 min of the study. ACTH in NNS remained lower than HC (H1:P<.03), but showed a similar pattern of response. In contrast, ACTH response was delayed in NPS (H2 X Time:P<.02), and markedly blunted in HP (H3 X Time: P<.03). At the end of the study ACTH levels were HP=15.6±8.9, NP = 7.9±5.8, NN = 7.2±2.6, and HC =5.2±3.1 pg/ml

(H3: P<.05). Hippocampal regulation of HPA function thus appears to be impaired in direct proportion to hippocampal volume loss in schizophrenia. Converging evidence indicates that the hippocampal pathology in schizophrenic patients with water imbalance accounts for their impaired neuroendocrine function. Furthermore, this pathology may cause schizophrenia by disrupting stress responses in more complicated neurosystems. Clarifying the pathophysiology in simpler systems may reveal mechanisms in more complicated systems underlying psychosis.

ALTERED EXPRESSION OF NMDA RECEPTOR SUBUNITS AND RELATED NMDA ANCHORING PSD PROTEINS IN SCHIZOPHRENIA

L. V. Kristiansen,* M. Beneyto, V. Haroutunian, K. L. Davis, J. H. Meador-Woodruff
Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA

Excitatory neurotransmission in the CNS predominantly depends on glutamate signaling. Glutamatergic synaptic transmission is mediated through specialized metabotropic G-protein coupled receptors as well as through ionotropic receptor channels including the kainate, NMDA and AMPA receptors. Several lines of investigation suggest that alterations in the expression of glutamatergic signaling molecules are involved in the pathophysiology of schizophrenia. Research from our laboratory has previously described abnormal expression of transcripts that encode N-methyl-D-aspartate (NMDA) receptor subunits as well as several NMDA-related intracellular signaling molecules of the postsynaptic density (PSD) in subcortical regions of schizophrenic patients. In this study, we have analyzed by western blot analysis the expression of NMDA receptor subunits as well as of intracellular PSD molecules in two prefrontal cortical brain regions in postmortem tissue from elderly schizophrenic patients and a comparison group. At the level of protein expression, we found a splice variant of the NR1 NMDA receptor subunit to be significantly decreased in the schizophrenic patients, whereas NR2A-D receptor subunits in these same individuals were unchanged. We additionally have studied the expression of the NMDA related PSD proteins, PSD-93, PSD-95, SAP-102 and NFL in schizophrenia. These are all proteins that selectively interact with either one or both of the NR1 and NR2 subunits of the NMDA receptor. Using both in-situ hybridization and western blotting we analyzed the expression of these PSD proteins in prefrontal cortical areas BA9 and BA32 in schizophrenia. While there is no effect of illness on the expression of the PSD-93, SAP-102 and NFL proteins, transcript as well as protein expression levels of the key NMDA anchoring protein, PSD-95 are significantly increased in schizophrenia. These results indicate that the NMDA receptor and its related intracellular proteins are abnormally expressed in the prefrontal cortex in schizophrenia. This work was supported by MH53327 and a grant from the Stanley Foundation.

CUMULATIVE EXPOSURE TO ESTROGEN AND PSYCHOSIS: A PEAK BONE MASS, CASE-CONTROL STUDY IN FIRST-EPISODE PSYCHOSIS

N. P. Maric,* V. Popovic, M. Jasovic Gasic, N. Pilipovic, J. van Os
Institute of Psychiatry, Belgrade, Yugoslavia

Background. The organizational structural effects of estrogen may be cumulative and permanent by impacting on neurodevelopment, giving rise to neuroprotective effects and eventually reduction of psychosis risk. Reduction in Bone Mineral Density (BMD in g/cm2), as a biological marker of reduced cumulative exposure to estrogen, may be a marker of increased psychosis risk. BMD at any age is the end result of peak bone mass density and subsequent loss and thus bone mass in later life depends upon peak BMD achieved. In order to avoid the influence of aging, various hormone-deficiency syndromes and disease-related insults which affect BMD, only young female patients with first episode of psychotic disorder were included, in whom it was assumed that peak bone mass had been achieved. Methods. A sample of 19 first-episode female psychosis patients with minimal previous antipsychotic exposure (mean 10 weeks) and 20 female controls underwent advanced fan-beam dual X-ray absorptiometry (DEXA) to assess lumbal spine BMD (L1-L4). Controls were frequency-matched for age (patients: mean age 23.7, SD=3.1; controls mean age 24.5 SD=3.8, p=0.49), education and residence. In addition, all subjects were screened for conditions and habits known to cause BMD loss such as smoking, polydipsia and family history of osteoporosis in first and second-degree relatives. None of the subjects had known medical conditions such as Cushing syndrome, hyperthyroidism or metabolic bone disorders that could account for any bone loss. None had been taking drugs that affect BMD. Information was recorded on age at menarche, current menstrual status, use of oral contraceptives and previous gynaecological and obstetrical history. Results. Mean BMD was around one standard deviation lower in patients (1.13, SD=0.10) than in controls (1.25, SD=0.12; P=0.0021), and 84% of patients scored below the median value of the controls (OR=5.3, 95% CI: 1.2, 24.2). In the patients, the association between duration of antipsychotic therapy and BMD was neither large nor significant (standardized effect size: -0.01, P=0.65). Conclusions. Female patients with first episode schizophrenia had accrued less peak bone mass than age matched healthy women i.e. had evidence of relative osteopenia. The results are compatible with the hypothesis that psychosis in women may be associated causally with a reduced protective effect of estrogen over the course of development.

EXPRESSION OF EXCITATORY AMINO ACID TRANSPORTER 1-3 TRANSCRIPTS IN THE PREFRONTAL CORTEX IN SCHIZOPHRENIA

R. E. McCullumsmith,* D. S. Gupta, V. Haroutunian, K. L. Davis, J. H. Meador-Woodruff
Mental Health Research Institute and Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA

Postmortem morphometric, stereological, imaging, and gene expression studies have implicated dysfunction of the prefrontal cortex (PFC) in schizophrenia. These findings, taken together with abnormalities of glutamate transmission demonstrated in pharmacological, postmortem, and imaging studies, indicate that alterations in synaptic glutamate levels may contribute to schizophrenic symptomatology. Synaptic glutamate levels are determined, in part, by the reuptake of glutamate by a family of excitatory amino acid transporters (EAATs). These molecules perform a critical function in glutamate synapses because glutamate reuptake, not enzymatic breakdown, determines the rate of glutamate clearance from the synapse. Given the pivotal function of EAATs in glutamate synapses and converging evidence of abnormalities of both cortical function and glutamate transmission in schizophrenia, we hypothesize that the expression and EAATs is altered in the PFC in this illness. Accordingly, we measured the transcripts encoding EAAT1, EAAT2 and EAAT3

in Brodmann areas (BA) 9 and 32 in subjects with schizophrenia and a control group. We detected increased expression of EAAT1 and EAAT2 in the gray matter of BA32, but not BA9. Results from studies of EAAT3 mRNA expression in the PFC in schizophrenia, as well as EAAT1-3 expression in rats treated with antipsychotics, will also be presented. Our findings of altered cortical expression of molecules critical for neurotransmission in glutamate synapses highlight abnormalities in the schizophrenic brain that can be more profitably targeted for the generation of novel treatment modalities for this disabling illness. This work was supported by MH53327 (JHMW), and a Pfizer Postdoctoral Fellowship (REM).

NMDA RECEPTOR SUBUNIT AND ASSOCIATED PSD PROTEIN TRANSCRIPTS IN HIPPOCAMPUS IN SCHIZOPHRENIA AND BIPOLAR DISORDER

J. Meador-Woodruff,* M. Beneyto, L. V. Kristiansen, R. E. McCullumsmith, E. Scarr, B. Dean
Mental Health Research Institute, Univerisity of Michigan, Ann Arbor, MI, USA

Schizophrenia has been associated with dysfunction of glutamatergic neurotransmission, particularly abnormalities of the NMDA subtype of glutamate receptor. Recent data suggest involvement of the NMDA receptor-signaling complex, which includes NMDA receptor subunits as well as associated interacting proteins that are critical for normal NMDA receptor assembly, trafficking, insertion in the plasma membrane, and activation. The interacting proteins are selective for NMDA receptor subunits, the most well characterized being PSD-93, PDS-95, SAP102, CIPP, NF-L and yotiao. Previously, studies from our lab have detailed changes in glutamate receptor subunit transcript expression in schizophrenia in postmortem brain tissue. In the present work, we have expanded the scope of our studies to now focus on the expression of these molecules in hippocampus in both schizophrenia and bipolar disorder. We performed in situ hybridization to assess the expression of the transcripts encoding NMDA receptor subunits NR1, 2A, 2B, 2C and 2D, and the transcripts for the NMDA receptor associated PSD proteins PSD-95, PSD-93, NF-L and SAP102 in from subjects with schizophrenia, bipolar disorder and a comparison group. There was a significant decrease in the expression of both NR1 subunit transcripts and SAP102 in the schizophrenic subjects. On the other hand, all five NMDA subunits and PSD-95, SAP102, and NF-L were significantly decreased in bipolar disorder. We propose that both schizophrenia and bipolar disorder have glutamatergic components involving alterations in the NMDA receptor signaling complex including the intracellular machinery that is coupled to the NMDA receptor subunits. These data suggest that schizophrenia is associated with abnormal intracellular signaling, and points to novel targets for innovative drug discovery. Supported in part by MH53327.

A CONTROLLED STUDY OF CSF LEVELS OF CASPASES 1, 3, 8 AND 9 IN SCHIZOPHRENIA: EVIDENCE OF APOPTOTIC OVEREXPRESSION

H. A. Nasrallah
Psychiatry, University of Cincinnati, Cincinnati, OH, USA

Background: The pathophysiology of progressive brain tissue loss in schizophrenia remains unknown, but as with other neurodegenerative disorders, overexpression of cortical apoptotic pathways is a leading model. To test this hypothesis, we examined CSF concentrations of several caspases, a family of cysteine proteases that play central roles in apoptosis, in schizophrenia patients with good and poor response to antipsychotics as well as in healthy controls. Methods: The CSF of 63 drug-free relapsed patients with schizophrenia (mean age = 34.2 ± 8.9 years) and 13 healthy control subjects were assayed for the levels of caspases 1, 3, 8 and 9. The patients were classified into rapid responders, delayed responders and nonresponders based on 60% reduction in psychosis scores (SAPS) after 6 months. Results: ANOVA showed no significant differences between all schizophrenics and all controls. However, there were significant increases in caspase 3 (p=.05) and caspase 8 (p=.05) in nonresponders compared to rapid responders. There was no difference in caspase 9 but a significantly lower level of caspase 1 was found in rapid responders compared to healthy controls (p=0.011) and between healthy controls vs. delayed responders (p=0.033). Discussion: These data are consistent with increased cortical apoptosis in the schizophrenia group with non response to antipsychotic medications. The implications for further research into apoptotic mechanisms to elucidate the neurobiology of brain tissue loss in schizophrenia are discussed.

COMPETITIVE DISPLACEMENT OF CLOZPINE FROM PLASMA PROTEINS IN NORMOLIPIDEMIC AND HYPERLIDEMIC PLASMA SAMPLES: THE CLINICAL IMPLICATIONS

R. Procyshyn,* T. Ho, K. M. Wasan
Department of Research, Riverview Hospital, Port Coquitlam, BC, Canada

The objective of this study is to assess whether dyslipidemia affects clozapine's overall plasma distribution when it is in the presence of another highly protein bound drug that competes for plasma protein binding sites. In doing so, we performed in vitro studies in which warfarin sodium was pre-incubated in normolipidemic and hyperlipidemic plasma samples in varying concentrations. Following the pre-incubation with warfarin, [3H]clozapine mixed with unlabeled clozapine was added to the plasma samples. The plasma was separated into its lipoprotein and lipoprotein deficient fractions by density gradient ultracentrifugation and clozapine distribution was determined. Our results indicated that when normolipidemic plasma was pre-incubated with various concentrations of warfarin no significant redistribution of clozapine was noted among the various plasma lipoprotein fractions. However, in the case of the hyperlipidemic plasma, pre-incubating with warfarin resulted in a significant redistribution of clozapine from the lipoprotein-deficient fraction to the very-low-density and low-density fractions of lipoproteins. Despite the differences observed in the redistribution of clozapine, pharmacokinetic principles would predict that in vivo the steady state unbound concentration of clozapine in both normolipidemic and hyperlipidemic plasma remains unchanged. With no change in the steady state unbound (active) concentration of clozapine one would expect that there would be no change in clinical status. However, it may be that this is only true for those individuals with a normal lipid profile and not for those individuals with dylipidemia. We discuss the possibility that clozapine's redistribution and association with lipoproteins may actually increase its effectiveness.

CLINICAL, PSYCHOSOCIAL, AND COGNITIVE IMPLICATIONS OF ESTRADIOL AND PROGESTERONE IN FIRST BREAK SCHIZOPHRENIA

S. E. Purdon,* P. G. Tibbo, T. I. Prior
Psychiatry, University of Alberta, Edmonton, AB, Canada

The diagnostic and syndrome specificity of estradiol and progesterone in schizophrenia was examined in 28 first episode and 9 early phase general psychiatry patients with measures of clinical, psychosocial, and cognitive status. Participants were unmedicated and within 18 months of illness onset. The schizophrenia sample exhibited more severe positive, negative, and general symptoms of psychosis (PANSS), as well as more severe general impairment (CGI), more cognitive impairment (General, Visual, Executive, Memory), and poor post-morbid psychosocial status (HQLS), relative to the general psychiatry patients. The groups did not differ on measures of depression (BDI, CDI), anxiety (STAI, HAMA), mania (BRMS), obsessive ideation (YBOCS), compulsive behavior (YBOCS), or premorbid psychosocial status (PAS). The two groups did not differ on estradiol or progesterone levels. Although estradiol and progesterone abnormalities were not specific to the diagnosis of schizophrenia, syndrome specificity was apparent in the inverse relation between estradiol and the positive symptoms in schizophrenia, and the direct relations between progesterone and both positive and negative symptoms in schizophrenia. Also, several symptoms suggesting a disorganized syndrome were related to the combination of estradiol and progesterone levels. This syndrome specificity was unique to the schizophrenia sample. In the general psychiatry control sample, estradiol was inversely related to general psychopathology, anxiety, depression, and obsessive ideation. Estradiol and progesterone did not demonstrate predictive power in relation to psychosocial status, premorbid status, or cognitive impairment in either group. Although there appears to be no diagnostic specificity of estradiol or progesterone levels in schizophrenia, and the hormones are not related to correlates of poor outcome, the syndrome specificity of the two hormones is remarkable and may be relevant to onset and severity of illness.

Standardized Beta from Regression of PANSS on Estradiol and Progesterone in Schizophrenia and Non-Schizophrenia Psychosis

a p<.05 with E or P alone.
b p<.05 remains after entry of alternate hormone.

DISEASE-SPECIFIC POLYPEPTIDE-PATTERNS IN CSF IN SCHIZOPHRENIA AND ALZHEIMER DISEASE

T. J. Raedler,* S. Wittke, H. Mischak, H. Jahn, K. Wiedemann
Psychiatry, University Hospital Hamburg-Eppendorf, Hamburg, Germany

Introduction: Due to methodological limitations, the current analysis of CSF-proteins is limited to total protein content and a few selected polypeptides. However, many more proteins are secreted into the CSF. These CSF-proteins may carry disease-specific information for neuropsychiatric disorders, as pathological brain-processes are more likely to be represented in CSF than in other body-fluids. CE-ESI-TOF-MS (capillary electrophoresis on-line coupled to an electrospray ionisation time of flight mass spectrometer) is a new technique that permits the comprehensive analysis of polypeptides in biological fluids. We applied this novel analytical technique to the analysis of CSF. Methods: CSF-samples from seven patients with schizophrenia and eight patients with Alzheimer Disease were analysed with CE-ESI-TOF-MS. In addition, the CSF from four healthy controls with no known psychiatric or neurological disorders was analysed under similar conditions. Results: Using the current application of this method, over 450 different polypeptides can be detected in the CSF with a detection-threshold in the fmol-range. These proteins formed a specific protein-pattern in the healthy controls. Patients with schizophrenia and Alzheimer Disease show disease-specific protein-patterns that differ from the healthy controls. Conclusion: Our results suggest that CE-ESI-TOF-MS provides a useful tool for the analysis of CSF-proteins. Further studies are needed to establish specific protein-patterns in larger samples of patients suffering from schizophrenia and Alzheimer Disease as well as well-matched healthy controls.

METABOLIC VARIATIONS ON FIRST EPISODE PSYCHOSIS AFTER ONE YEAR TREATMENT WITH TYPICAL AND ATYPICAL ANTIPSYCHOTIC TREATMENT

M. Ramirez,* J. M. Pelayo-Teran, I. Martinez-Gonzalez, O. Martinez-Garcia, M. T. Garcia-Unzueta, J. A. Amado Senaris, J. L. Vazquez-Barquero, B. Crespo-Facorro
Hospital Universitario Marques de Valdecilla, Santander, Spain

The aim of the current work was to assess variations on different metabolic variables on first episode psychosis after one year treatment with either Haloperidol, Olanzapine or Risperidone. 70 first episode psychotic patients were included (70% male, 30% female). Age ranged from 15 to 50 years old (m 25,8). None of them had received previous pharmacological treatment. Patients were randomly assigned to three treatment groups: Haloperidol (N=13), Olanzapine (N=26) and Risperidone (N=31). Administered doses were flexible (maximum dose Haloperidol 9 mg/d, Olanzapine 20 mg/d, Risperidone 6 mg/d). Serum levels of glucose, cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, leptin, and insulin were determined initially and one year after treatment. Paired sample t tests were performed for within group comparison. Increases in cholesterol (p<0,001), triglycerides (p= 0,01) and leptin (p<0,001) were found for the whole group of patients. Olanzapine group had an increase in cholesterol (p=0,005), glucose (p=0,009) and leptin (p= 0,012) levels whereas Risperidone group had increases in cholesterol (p=0,005) and Haloperidol group in leptin levels (p=0,010). Changes in other variables did not reach significance. These results suggest that long term treatment with atypical antipsychotic drugs may increase glucose and cholesterol levels. Olanzapine presents a higher risk of increasing serum levels of glucose and cholesterol than Haloperidol and Risperidone.

PREVALENCE OF HYPERANDROGENISM IN PERSISTENTLY SYMPTOMATIC FEMALE SCHIZOPHRENIC PATIENTS ON ANTIPSYCHOTIC MEDICATIONS

M. Ranganathan,* S. S. Bangalore, C. Ansi-Boldur, N. Dargani, J. Tropnas, M. H. Chakos
Psychiatry, SUNY Downstate Medical Center, Brooklyn, NY, USA

Background: Hyperandrogenism has been reported in a number of psychiatric diagnoses including schizophrenia and bipolar disorder. This study examines the prevalence of hyperandrogenism and menstrual cycle irregularities in female patients with chronic schizophrenia or schizoaffective disorder who had persistent symptoms of psychosis despite treatment with antipsychotic medications. Methods: Twenty one women with schizophrenia or schizoaffective disorder who were between the ages of 18 to 50 being treated with antipsychotic medications and not on oral contraceptives were recruited for the study. In order to participate patients had to be on a stable regimen of antipsychotic medication for one month and to be experiencing persistent psychotic symptoms with a PANSS score equal to or greater than 60. The subjects completed questionnaires about their menstrual history and provided blood samples for measurement of DHEA, DHEAS, and free testosterone. Results: The mean age of study participants was 42 years of age, the mean duration of illness 16 years and the mean PANSS score was 79. The mean DHEA, DHEAS and Free Testosterone levels were above normal. Thirty three percent of the women had irregular menstrual cycles. Eighty one percent of subjects had an increase in androgens. Twenty nine percent of the sample had both irregular menstrual cycles and had increased androgen levels, which suggest a diagnosis of PCOS. Clinical and neuropsychological correlates associated with these findings will be presented. Significance: Hyperandrogenism with menstrual irregularities seen in PCOS has been linked to metabolic syndrome, with an increased risk of cardiovascular disease and diabetes. We noted a high prevalence of both hyperandrogenism and menstrual irregularities in persistently symptomatic female schizophrenic patients. These findings might reflect an increased incidence of PCOS and warrant further study to determine the prevalence and clinical significance of PCOS and the metabolic syndrome in this patient population.

INVESTIGATION OF THE CCK-B SYSTEM IN INDIVIDUALS WITH SCHIZOPHRENIA ALONE AND IN THOSE WITH A COMORBID ANXIETY DISORDER

Y. Shulman,* J. M. Le Melledo, J. Bradley, P. Tibbo
Neuroscience, University of Alberta, Edmonton, AB, Canada

The cholecystokinin-B (CCK-B) system plays a role in the pathophysiology of schizophrenia and anxiety disorders (ADs), separately, and may explain the high comorbidity rates of the two disorders. In this preliminary study, a double blind, cross-over, placebo controlled design was used to determine the effects of a 50 microgram i.v. bolus injection of pentagastrin (CCK-5) (a CCK-B receptor agonist) on subjective levels of anxiety, rated by the Panic Symptom Scale (PSS) and Visual Analogue Scale for maximum change in anxiety (VAS-A max) in three age and sex matched study groups: individuals with schizophrenia (SZ) (n=7; mean age=34.14 years), individuals with schizophrenia and a comorbid AD (SZ+AD) (n=4; mean age=35.75 years) and healthy control individuals (HC) (n=11; mean age=32.36 years). All three groups reported significantly higher VAS-A max and PSS scores post CCK-5, compared to post placebo (SZ: p=0.003 and p=0.003; SZ+AD: p=0.021 and p=0.027; HC: p=0.000 and p=0.001, for VAS-A max and PSS scores, respectively). The SZ+AD group reported significantly higher PSS scores (p=0.019) and VAS-A max scores (p=0.030) than the HC group, post CCK-5. The SZ+AD group also reported significantly higher VAS-A max scores (p=0.008) than the HC group, and significantly higher PSS scores (p=0.000) than both the SZ group and the HC group, post placebo administration. Preliminary results indicate that individuals with schizophrenia, regardless of whether they have a comorbid AD, are more anxious following CCK-5 administration, compared to placebo. Further, while the HC group and the SZ group respond in a similar manner behaviorally to both CCK-5 and to placebo, the SZ+AD group responds differently to the same challenge paradigm, compared to the other groups. Further investigation of the CCK-B system, with more individuals per group may establish biological differences between the three groups.

THE ROLE OF THE ASTROCYTE IN GLUTAMATERGIC DYSFUNCTION IN SCHIZOPHRENIA

A. E. Steffek,* V. Haroutunian, K. L. Davis, J. H. Meador-Woodruff
Mental Health Research Institute, University of Michigan, Ann Arbor, MI, USA

Converging data suggest that abnormalities in molecules that transport, metabolize and bind glutamate occur in schizophrenia. Since astrocytes sustain intimate contact with synapses and express multiple receptors, transporters and enzymes crucial for excitatory neurotransmission, we hypothesize that astrocytes may contribute to glutamatergic dysfunction in schizophrenia. Astrocytes terminate glutamatergic neurotransmission and prevent excitotoxicity by removing glutamate from the synapse. They express high affinity uptake sites and contain enzymes such as glutamine synthetase (GS) that converts glutamate to glutamine so that it may be transported back to the presynaptic neuron. Previous studies in our laboratory found increased mRNA expression of astrocytic excitatory amino acid transporters (EAAT) 1 and 2 in the thalamus and increased EAAT2 levels in the prefrontal cortex in schizophrenia. Additionally, we found increased GS mRNA expression in thalamus in schizophrenia. In the present work, transcript expression by in situ hybridization of GS in postmortem prefrontal cortex from elderly schizophrenic patients and a comparison group revealed no significant changes. In addition, examination at the protein level using western blot analysis found no significant changes of GS protein levels. We are also investigating whether these abnormalities are limited to astrocytic molecules associated with glutamatergic transmission or reflect a more global astrocytic lesion. Therefore, we have examined the expression of genes associated with astrocytic function. We have found significantly decreased mRNA expression of the intermediate filament protein, GFAP, and the calcium binding protein, S100β, in the prefrontal cortex in schizophrenia. Western blot analysis of GFAP did not reveal any significant changes. Protein studies of S100β are underway. These data reflect that astrocytic abnormalities occur in schizophrenia, and abnormalities which contribute to glutamatergic dysfunction may be region-specific. Supported by Scottish Rite Schizophrenia Fellowship (AES) and MH53327 (JHMW).

ATYPICAL ANTIPSYCHOTICS AND RECEPTOR BINDING: ENHANCING COGNITION AND MOOD

L. Warrington,* S. M. Stahl, D. K. Shayegan
Pfizer Inc, New York, NY, USA

Schizophrenia is characterized by a diversity of symptoms that hypothetically arise from heterogeneous neuroanatomical and neurochemical malfunctions. This review profiles the unique portfolio of receptor-binding actions for each of the five first-line atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole), and discusses the theoretical implications that these binding properties hold for potentially improving cognition and mood in schizophrenia. Articles characterizing the receptor-binding properties of the atypical antipsychotics were selected by means of a MEDLINE search. These articles indicated that all antipsychotic agents target the key hypothetical neurochemical disturbance in psychosis—excessive dopamine neurotransmission at dopamine-D2 receptors in the mesolimbic pathway of the brain—presumably responsible for the positive symptoms of schizophrenia. All atypical antipsychotic agents are serotonin-2A (5-HT2A)/dopamine-D2 antagonists or D2 partial agonists, properties that contribute to reduced motor side effects. Interaction with 5-HT2C, 5-HT1D, and 5-HT1A receptors, and serotonin and norepinephrine reuptake sites, in human brain tissue predict cognitive improvement, heightened negative symptom relief, and enhanced modulation of mood. Affinity for alpha1-adrenoceptors, histamine H1 receptors, and muscarinic M1 receptors predicts orthostatic hypotension, sedation, cognitive disturbance, or weight gain. In conclusion, our research indicates that receptor-binding properties other than serotonin-2A/dopamine-D2 occupancy may explain the cognitive and affective symptom improvement associated with atypical antipsychotic therapy.

TYROSINE TRANSPORT IN SCHIZOPHRENIA

F. Wiesel,* G. Edman, L. Flyckt, A. Eriksson, H. Nyman, N. Venizelos, L. Bjerkenstedt
Neuroscience, Psychiatry, Uppsala University, Uppsala, Sweden

Tyrosine is the precursor to dopamine synthesis. There is evidence that tyrosine availability to the brain will influence dopamine function and thereby cognitive functioning. The availability is regulated by facilitated (L-system) or active (A-system) transport across plasma membranes. The importance of tyrosine for dopamine function motivated us to study tyrosine kinetics in schizophrenia. Amino acids were measured in plasma and monoamine metabolites in CSF from un-medicated patients with schizophrenia and controls. Tyrosine kinetics (transport velocity, Vmax and affinity to transport sites, Km) was determined in vitro using fibroblasts as a model. With PET we determined in vivo kinetics across the blood-brain barrier at baseline and after a loading dose of tyrosine. Finally cognitive functioning was analysed with neuropsychological tests. Plasma and CSF studies indicated that less tyrosine was transported across the blood brain barrier in patients with schizophrenia. Tyrosine kinetics in the fibroblast model demonstrated a reduced transport capacity and increased affinity to the transport sites in the patients. In vivo it was found that tyrosine transport was differently regulated in patients and controls. Cognitive functioning was worse in patients with increased affinity (low Km) to tyrosine transport sites. The findings give strong evidence that tyrosine transport is different from healthy controls. In the in vitro studies there were several cell passages before the experiments were made which suggests that the differences observed may be due genetic factors rather than to environmental causes. There may be a polymorphism of the genes that processes the transport proteins probably those of the A-system. The connection between cognitive functioning and tyrosine kinetics validates the significance of the finding as well as the in vivo data with PET. It may be speculated that the underlying mechanism is a change in membrane functioning that in turn influence the neuron network and cognitive functioning. Reference: Wiesel F-A, Edman G, Flyckt L, Eriksson A, Nyman H, Venizelos N, Bjerkenstedt L. Kinetics of tyrosine transport and cognitive functioning in schizophrenia. *Schizophrenia Research*, 2004 (in press).

PROTEOMIC ANALYSIS OF ANTIPSYCHOTIC RESPONSE

Z. Zimolo,* D. C. D'Souza, E. Perry, K. H. Stone, T. Wu, K. Williams, J. H. Krystal
Psychiatry, Yale University, New Haven, CT, USA

Schizophrenia continues to be an illness only partially responsive to treatment. In contrast to positive symptoms, its negative and cognitive symptoms seem particularly treatment refractory. There are several theories about possible pathophysiology of schizophrenia; in addition to dopaminergic system, glutamatergic system became a focus of interest for various treatment approaches. Glutamatergic system might prove to be particularly useful for treatment of negative and possibly cognitive symptoms. Development of better treatment strategies may be further enhanced by developing objective biological state markers, which are lacking in assessments of schizophrenia severity. The goal of this study was to identify candidate peripheral molecular markers of schizophrenia in response to various treatments: classic antidopaminergic, as well as experimental glutamate system modulating agents such as D-serine and riluzole. Serum was collected from patients (n=22) who were undergoing several clinical studies and were being treated with regular antidopaminergic agents or with experimental treatment agents (riluzole 50 mg bid, D-serine 30mg/kg/day or placebo). Positive, negative and cognitive symptom clusters were assessed. Serum samples were compared before and after 6 week treatment utilizing proteomic techniques (2D differential fluorescence gel electrophoresis-DIGE). The differences between the samples were analyzed and grouped by treatment category. METHODS: Blood was collected 8-9 AM and centrifuged at 4 degrees C. Serum was frozen at -80 degrees C until further analysis. Prior to DIGE analysis, serum was depleted from albumin and immunoglobulin and the samples were labeled with fluorescent dyes Cy3 or Cy5. The comparison sample pairs of before and after treatment were performed in a single gel and differential protein expression was analyzed (Amersham platform). RESULTS: In a preliminary analysis, DIGE comparison before and after 6 weeks of treatment with the antidopaminergic or glutamate modulating agents revealed over 30 proteins that significantly changed (>3 fold) in serum. Protein changes in response to treatment category will be presented and identification of the most consistently changed proteins will be attempted by mass spectroscopy. The ultimate goal of these preliminary studies is to investigate candidate marker molecules in the periphery which may be used in tracking schizophrenia severity in addition to characterizing medication response.

10. Neurochemistry, Animal

ELECTROPHYSIOLOGICAL INVESTIGATION OF AUDITORY SENSORY INFORMATION PROCESSING AND SELECTIVE ATTENTION IN NMDA RECEPTOR HYPOMORPHIC MICE

S. Bickel,* H. P. Lipp, R. Nitsch, D. Umbricht
Psychiatry Research, University, Zurich, Switzerland

Neurocognitive deficits are recognized as a major limiting factor for rehabilitation and functional outcome in schizophrenia. They include deficits in attention, episodic, and working memory, as well as deficits in information processing at automatic, preattentive stages such as auditory information processing. Deficient signaling through the NMDA receptor has been implicated in these deficits. We investigated the electrophysiological manifestations of auditory sensory information processing in mice with a reduced expression of the NR1 subunit of the NMDA receptor. We examined the N1-recovery function, steady-state-gamma-response, mismatch negativity and electrophysiological indices of selective attention, functions known to be altered in schizophrenia. The NR1 hypomorphic mice (N=7) showed a normal N1-recovery (i.e. increase of N1 with longer interstimulus intervals) compared to the control group (N=10). However, the latency of N1, which normally demonstrates a decrease with longer ISI, was significantly prolonged—corresponding to similar observations in some schizophrenic patients and mimicking the effects of acute ketamine administration in healthy volunteers. In the steady-state-oscillatory-response paradigm in which trains of clicks at specific frequencies (60/40/30/20 and 10Hz) were delivered the index-group demonstrated significantly enhanced responses at stimulation frequencies of 10 and 60 Hz, but normal power at 40 Hz compared to wild-type mice. In addition, they showed different time-dependent changes in power of the response at stimulation frequencies of 30 and 40 Hz. In a preliminary analysis of the SA-paradigm, the index-group showed a decreased positive enhancement, indicating a deficient learning and/or attentional ability. In conclusion, the NR1 hypomorphic mice modeled only parts of the characteristics of the ERP-alterations shown in schizophrenic patients. Supported by National Alliance for Research on Schizophrenia and Depression (NARSAD).

MODULATION OF CENTER-SURROUND INTERACTIONS IN CORTICAL VISUAL AREA MT OF THE ALERT MACAQUE MONKEY

R. T. Born,* C. C. Pack, J. N. Hunter
Neurobiology, Harvard Medical School, Boston, MA, USA

Many schizophrenics have deficits in smooth pursuit eye movements and motion perception that are likely to be caused by changes in relatively low-level visual motion computations. One such operation, characterized in the middle temporal visual area (MT) of the macaque monkey, is known as "center-surround antagonism," and it is believed to be important for, among other things, using motion cues to discriminate figure from background. A psychophysical signature of this process has recently been described (Tadin et al., 2003), and found to be perturbed in schizophrenia patients (Kim et al., 2003). In normal controls, for low-contrast stimuli, motion discrimination performance improves with increased stimulus size, whereas, for high-contrast stimuli, performance actually worsens as the stimulus is made larger. This counterintuitive decrease in performance in normal observers has been attributed to the presence of antagonistic surrounds in the receptive fields of low-level motion processing neurons. People with schizophrenia, however, show improved performance with increasing stimulus size, even for high-contrast stimuli, suggesting an impairment in center-surround antagonism in their brains. If these psychophysical findings are indeed the product of impaired center-surround interactions, then stimulus contrast should have a profound effect on this property as measured from neurons. To test this prediction, we recorded extracellularly from MT neurons in alert macaque monkeys and characterized their responses to moving stimuli of different sizes and contrasts. As previously reported, with high-contrast stimuli we found that many MT neurons had antagonistic surrounds that rendered them less responsive to large fields of moving random dots than to small fields (Allman et al., 1985). At low contrast, however, the same neurons actually increased their responses as the dot fields were made larger. Thus at low contrast antagonistic surrounds became weaker or, in some cases, disappeared entirely. This result is consistent with the perceptual studies of Tadin et al. (2003) and supports the notion that some of the deficits found in patients with schizophrenia may result from a dysmodulation of center-surround interactions. From this perspective, it may also be interesting to study the effects of neuromodulators, such as dopamine, on center-surround interactions.

NMDA RECEPTOR HYPOFUNCTION BY MK-801 OR NEONATAL 6-HYDROXYDOPAMINE LESION INHIBITS NICOTINE-INDUCED UPREGULATION OF THE HIGH AFFINITY NEURONAL NICOTINIC RECEPTORS: THEORETICAL IMPLICATIONS FOR SCHIZOPHRENIA

C. R. Breese,* S. Birru, D. J. Knapp, G. R. Breese, D. Overstreet, J. Vaglenova, T. Mayo, T. Gustman, J. E. Hubbard
Pharmacal Sciences, Auburn University Harrison School of Pharmacy, Auburn, AL, USA

Previous results have shown an attenuated upregulation of high affinity neuronal nicotinic receptors following tobacco use in schizophrenic postmortem brain (Breese et al., *Neuropsychopharmacology*, 23:351, 2000). Since it has been theorized that some of the symptoms observed in schizophrenia may be related to hypoglutamatergic function, we hypothesized that NMDA glutamatergic receptor hypofunction may modulate the expression of neuronal nicotinic receptors following chronic nicotine exposure. In these studies, we examined nicotinic receptor regulation in two hypothetical NMDA receptor hypofunction models in rats, including animals pretreated with low dose MK 801, or in adult animals which had received a neonatal 6 hydroxydopamine (6-OHDA) lesion (Moy et al., *Psychopharmacology*, 161:255, 2002). Lesioned or intact adult rats were either treated with saline, 1.0 mg/kg nicotine, 0.2 mg/kg MK-801, or MK 801 followed 8 hours later with 1.0 mg/kg nicotine. Animals were treated for 21 days, sacrificed, and cortices dissected and homogenized for [3H] epibatidine binding. Results indicate that nicotinic receptor binding was not different between saline, MK 801, or saline treated 6 OHDA lesioned control animals (all $p>0.05$), but was significantly increased in intact and sham nicotine treated animals ($p<0.001$). Consistent with the NMDA receptor hypofunction hypothesis, nicotinic receptor binding in animals co-treated with MK-801 and nicotine was comparable to saline treated controls, and

was significantly reduced compared to nicotine treated animals ($p<0.001$). In addition, binding in nicotine treated 6-OHDA lesioned animals was also significantly reduced compared to the nicotine treated sham animals ($p<0.002$). Scatchard analysis showed that these differences were not a result of a change in binding affinity. The changes in nicotinic receptor binding in these NMDA receptor hypofunction model systems were similar to that observed in the postmortem brains of schizophrenics that smoked (Breese et al., 2000). These results suggest that NMDA receptor blockade or hypofunction is capable of affecting nicotine-induced neuronal nicotinic receptor upregulation, and provides a theoretical basis for the potential influence of NMDA glutamate receptor hypofunction on the abnormal regulation of nicotinic receptor expression observed in schizophrenic postmortem brain. Support: NARSAD Young Investigator Award and an Auburn University Biogrant.

THE MEK/ERK MAP KINASE PATHWAY IN ANTIPSYCHOTIC ACTIONS

J. L. Browning,* K. A. Young, P. B. Hicks
Neuropsychiatry Research Program, Scott & White Hospital, Temple, TX, USA

We previously reported that clozapine administration dose-dependently increases phosphorylation of the MEK/ERK MAP kinase pathway components in the rat prefrontal cortex and that the 5-HT2a agonist, DOI, reverses this increased phosphorylation. Furthermore, in conditioned avoidance responding (CAR), a behavioral assay of antipsychotic activity, we observed that suppression of CAR by clozapine (10 mg/kg) or haloperidol (0.1 mg/kg) is reversed by administration of MEK inhibitors, but not inhibitors of the p38 or JNK MAP kinase pathways. We now report that the increase in MEK/ERK pathway phosphorylation observed in the prefrontal cortex does not occur in the striatum. We further report that inhibitors upstream of MEK also prevent clozapine-induced suppression of CAR. The i.c.v. administration of inhibitors of PKC (bisindolylmaleimide), PI3K (Wortmannin and LY294002), and CaMKII (KN-62) were effective at reversing suppression of CAR by clozapine. Taken together, these data support a role of the MEK/ERK pathway in the antipsychotic actions of clozapine.

EFFECTS OF LONG-TERM HALOPERIDOL EXPOSURE ON N-ACETYLASPARTATE AND OTHER NEUROMETABOLITES MEASURED WITH H-MRS AT 11.7T IN RATS

J. R. Bustillo,* R. Barrow, N. Perone-Bizzozero, J. Lauriello, R. Paz, M. Galloway
Psychiatry, University of New Mexico, Albuquerque, NM, USA

Proton magnetic resonance spectroscopy (1H-MRS) studies of schizophrenia suggest an effect of the disease or of antipsychotic medications on brain N-acetyl aspartate (NAA), a marker of neuronal viability and function. We studied in the rat the effect of haloperidol on NAA, choline, creatine, glutamate and glutamine in several brain regions where metabolite reductions have been reported in chronically medicated patients with schizophrenia. Two groups of sixteen rats each were treated with haloperidol depo (0.38 mg/kg/month), and vehicle for 6 months and were sacrificed. Concentrations of metabolites were determined by high resolution magic angle proton magnetic resonance spectroscopy (HR-MAS 1H-MRS) at 11.7 Tesla in ex-vivo punch biopsies (2 cubic mm)from the following brain regions: medial frontal and cingulate cortex, striatum, nucleus accumbens, dorsal and ventral hippocampus, amygdala, and temporal cortex. There were no differences in NAA between the haloperidol and vehicle treated animals accross any of the regions of interest studied ($p>0.05$). Likewise, there were no statistically significant differences in choline, creatine, glutamine and glutamate, metabolites often measured in schizophrenia populations. A prolonged exposure to the dopamine D2 receptor blockade effects of haloperidol does not result in changes in NAA, glutamate, glutamine and other metabolites in the proton spectrum. These results are consistent with the only other two studies of the effect antipsychotic drugs on NAA in the rat brain. The documented lower NAA in chronically treated schizophrenia patients is most likely not a simple effect of antipsychotic medications.

CHRONIC DOPAMINERGIC HYPERACTIVITY LEADS TO PROGRESSIVE DEGENERATION VIA ACCUMULATION OF ΔFOS B—RELEVANCE TO SCHIZOPHRENIA

R. T. Cantrup,* W. J. Rushlow, N. Rajakumar
Graduate Program in Neuroscience, University of Western Ontario, London, ON, Canada

A progressive neurodegenerative process may contribute to the poor clinical outcome in a sub-set of schizophrenic patients. Recently, our laboratory has described that disruption of subplate function in the developing prefrontal cortex in rats leads to adult-onset behavioral changes characteristic of subcortical dopaminergic hyperactivity and several neuropathological changes similar to those described in schizophrenic brains. Interestingly, these animals also show a progressive, delayed-onset neurodegenerative changes in the hippocampus. Here we demonstrate that BDNF levels are decreased in the hippocampus and the nucleus accumbens in these animals. Decreased BDNF levels have been observed in schizophrenic brains. It was hypothesized that chronic dopaminergic hyperactivity leads to accumulation of ΔFos B, a transcription factor, in the nucleus accumbens, and increased levels of ΔFos B in turn down regulate BDNF mRNA. Our pilot studies indicate increased levels of ΔFos B in D1-containing neurons of the nucleus accumbens. Currently, we are employing *in situ* hybridization and western blotting to quantify the changes in BDNF and ΔFos B levels in these animals. Supported by the Ontario Mental Health Foundation.

MODELING HYPOFRONTALITY AND COGNITIVE INFLEXIBILITY IN SCHIZOPHRENIA

S. Cochran,* A. Egerton, L. Reid, S. McGregor, B. Morris, J. Pratt
YRING, University of Glasgow, Glasgow, United Kingdom

In schizophrenia, hypofrontality of the prefrontal cortex is associated with deficits across several cognitive domains, including the capacity to effectively transfer attentional set between abstract properties of complex stimuli (Weinberger et al., (1986) *Arch Gen Psychiatry*. 43(2):114-24). Although cognitive deficits are highly debilitating to schizophrenic patients, antipsychotic drugs have limited efficacy in the treatment of these symptoms. Effective animal models should aid the understanding and treatment of cognitive dysfunction in schizophrenia. We have recently developed a model of schizophrenia in which rats develop hypofrontality and reductions in

parvalbumin mRNA expression following chronic intermittent PCP treatment, mirroring prefrontal cortex deficits seen in schizophrenia (Cochran et al., 2003 *Neuropsychopharmacology* 28: 265-275). The aim of the present study was to determine whether this treatment regime also reproduces the cognitive deficits observed in the disease. Cognitive flexibility was investigated using the attention set-shifting task in rats (Birrel and Brown (2000) *J Neurosci* 20: 4320-4) that is formally equivalent to the human Wisconsin Card Sort Test. In a single session rats perform a series of seven two-choice discriminations, at the core of which is the extra-dimensional shift (EDS) test that necessitates a shift of attention between perceptual dimensions. Seventy two hours after the final PCP treatment, Long Evans rats exhibited a significant deficit in their ability to shift attention between, but not within, perceptual dimensions (ANOVA: drug x discrimination test interaction $F6,48 = 8.02$, $p = 0.02$, followed by planned contrasts: EDS test $t(10) = -2.37$, $p < 0.05$). These findings suggest that repeated intermittent administration of PCP produced a persistent selective deficit in ability to transfer attentional set, but not in ability to reverse stimulus-reward associations. Together with our previous metabolic imaging studies, these results suggest that chronic intermittent administration of PCP in the rat models both the neuropathological and executive dysfunction aspects of prefrontal cortical deficits in schizophrenia. This model should aid the characterisation of the neurobiological processes contributing to schizophrenic pathology, and provide a platform for investigation of the potential reversal of these deficits by novel antipsychotic compounds.

EFFECTS OF HALOPERIDOL, CLOZAPINE, AND QUETIAPINE ON DEFICITS IN SENSORIMOTOR GATING IN A GENETIC MODEL OF REDUCED NMDA REXEPTOR FUNCTION

G. E. Duncan,* S. S. Moy, J. A. Lieberman, B. H. Koller
Psychiatry, University of North Carolina, Chapel Hill, NC, USA

Reduced NMDA receptor function is hypothesized to contribute to the pathophysiology of schizophrenia. In order to model chronic and developmental NMDA receptor hypofunction, a mouse line was developed that expresses low levels of the NMDA R1 subunit (NR1) of the NMDA receptor. These mice show increased acoustic startle reactivity and deficits in prepulse inhibition (PPI) of acoustic startle (Duncan et al. *Behav. Brain Res*. 53:507, 2004). The present study tested the hypothesis these altered acoustic startle responses in the NR1 hypomorphic (NR1 -/-) mice would be affected by antipsychotic drug treatment. Haloperidol (0.5 mg/kg) did not attenuate the increased startle reactivity in the NR1 -/- mice but did increase PPI in both the mutant and wild type mice. Clozapine (3 mg/kg) and quetiapine (10 and 20 mg/kg) reduced startle magnitude and increased PPI in both the wild type and mutant mice. For the mutant mice the effects of clozapine and quetiapine on both startle and PPI was to essentially normalize the response parameters to levels seen in the vehicle-treated wild type mice. The antidepressant drug imipramine (10 and 20 mg/kg) had minimal effects on startle amplitude in NR1 -/- or wild type mice. No effect of impramine on PPI was apparent at 10 mg/kg in either genotype. At 20 mg/kg imipramine increased PPI in the wild type but not in the mutant mice. These data demonstrate that clozapine and quetiapine exhibit a similar profile in the PPI paradigm with this genetic model of reduced NMDA receptor function. The NR1 hypomorphic mice may represent a model to explore new treatment strategies to counteract behavioral abnormalities associated with chronic and development NMDA receptor hypofunction. Support Contributed By: MH-063398 and by a grant from the Investigator Sponsored Studies Program of AstraZeneca.

DNA MICROARRAY STUDIES OF CHRONIC OLANZAPINE-TREATED RAT BRAINS

S. H. Fatemi,* T. Reutiman, C. Bell, P. Fried, L. Nos, D. Pearce, A. I. Brooks
Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA

Recent emerging biochemical data indicate that several important neuroregulatory genes and proteins may be involved in etiology of schizophrenia (Costa et al 2002). Additionally, the same genes appear to be targets of several psychotropic medications which are used to treat schizophrenia and mood disorders. Recent DNA microarray studies show that genes involved in myelination, synaptic neurotransmission, signal transduction, apoptosis and glutamate/GABA regulation may be differentially regulated in brains of subjects with schizophrenia (Marcotte et al 2003; Tkachev et al 2003). We hypothesized that chronic administration of olanzapine to rats would alter expression of various genes that may be involved in etiology of schizophrenia and mood disorders. Rats were administered olazapine (N=20, 2 mg/kg/day) or sterile saline intraperitoneally (N=20) daily for 21 days. Control (N=4) and olanzapine (N=4) treated frontal cortices were analyzed using cDNA microarray technology spanning approximately 40,000 genes using established protocol (Elshatory et al 2003). The results showed significant downregulation of 24 genes and upregulation of 28 genes by greater than two fold in the drug treated brains vs controls. The identity and implications of alterations in these genes will be discussed. These results show for the first time that olanzapine causes permanent changes in levels of several important genes that may be involved in etiology of schizophrenia and other psychiatric disorders. The generous support by Kunin Fund of St. Paul Foundation and the Stanley Medical Research Institute is greatly appreciated.

LACK OF WORKING OR LONG-TERM MEMORY IMPAIRMENT IN AMPHETAMINE SENSITIZED ANIMALS

R. E. Featherstone,* S. Kapur, P. J. Fletcher
Biopsychology, Centre for Addiction and Mental Health, Toronto, ON, Canada

Developing a convincing animal model of schizophrenia remains a major challenge for modern neuroscience. Previous work in our lab has centered upon amphetamine sensitization as a potentially useful animal model of schizophrenia. Exposure to an intermittent, escalating dose amphetamine regime induces a sensitized state that, both behaviourally and neurochemically, mirrors that found in schizophrenia. To date, amphetamine sensitized rats have shown impairments on a number of behavioural tasks known to be similarly disrupted in human schizophrenics, such as prepulse inhibition, latent inhibition and attentional set-shifting. In the following series of experiments, we sought to assess the effects of amphetamine sensitization on both working and long-term memory, two cognitive domains in which schizophrenic patients show robust deficits. Rats were exposed to an intermittent, escalating dose regimen of amphetamine (1 to 5 mg/kg amphetamine, three times a week, for five weeks), or a similar

number of saline injections. In experiment 1, animals were tested on an operant version of the delayed non-match to sample task (working memory), using location of response as the item to be remembered. Experiment 2 used a standard fixed-platform location water maze task (long-term memory), while experiment 3 used a variable-platform location water maze task (long-term memory). Amphetamine sensitized animals were not impaired on any of these tasks. Subsequent tests revealed greatly elevated rates of locomotion in the sensitized group in response to a challenge with a low dose of amphetamine (0.5 mg/kg), demonstrating that sensitization to amphetamine had occurred. These results suggest that amphetamine sensitization does not produce similar memory impairments as are seen in schizophrenia, and, thus, might not be an adequate model of this aspect of schizophrenic cognition.

HIPPOCAMPUS-DEPENDENT COGNITIVE COORDINATION IN RATS

A. A. Fenton,* M. Wesierska, D. Klement, A. V. Olypher
Physiology and Pharmacology, SUNY, Downstate Medical Center, Brooklyn, NY, USA

Cognitive coordination, defined as the set of processes that alter the timing of neuronal responses without changing what they signal about receptive field stimuli, is inferred from behaviors requiring the dynamic grouping of stimuli (Phillips and Silverstein, 2003, *Behav Brain Sci* 26:65). Impaired cognitive coordination is hypothesised to be a core deficit in the disorganization syndrome of schizophrenia but inadequate experimental models impede investigations of this hypothesis and potential mechanisms. We present 1) behavioral evidence of hippocampus-dependent cognitive coordination in rat and 2) electrophysiological evidence that the intrahippocampal injection of tetrodotoxin (TTX) that impaired cognitive coordination also changed spike time correlations of hippocampal neurons without altering firing rates. Dynamic grouping of dissociated stimuli into cognitive representations was tested in the Room+Arena− place avoidance task. Rats had to avoid a room-defined place using distal visual room stimuli that were dissociated from local olfactory arena stimuli by continuously rotating the arena at 1 rpm. Dynamic grouping was not required in three control tasks because room and arena stimuli were not dissociated. The arena rotated but room cues were hidden by darkness in one task and arena cues were hidden by water in the second. The arena was stable in the third. Injecting TTX (5ng/ul) into one hippocampus 1 hr before training abolished the Room+Arena− place avoidance requiring dynamic grouping. Since the control tasks were not impaired, a specific deficit in cognitive coordination, but not deficits in performance, memory, navigation, or behavioral inhibition account for the data. Electrophysiological field potentials and discharge of ensembles of single cells were recorded from the injected and uninjected hippocampi of urethane-anesthetized rats to identify the TTX-induced changes. TTX injection abolished action potential discharge in the injected hippocampus for hours. The loss of commisural excitation in the uninjected hippocampus caused changes there. Excitatory pyramidal cell but not inhibitory interneuron firing rates transiently increased for 15 min. The correlated discharge at the timescale of gamma oscillations (25-50 ms) was persistently increased in initially weakly correlated pyramidal cell pairs. We suggest that potentiated excitatory-excitatory connectivity may underlie cognitive coordination in the rat model and possibly in psychosis.

THE ACETYLCHOLINESTERASE INHIBITOR GALANTAMINE EXHIBITS FUNCTIONAL DOPAMINE ANTAGONISM IN CEBUS APELLA MONKEYS

A. Fink-Jensen,* M. Andersen, T. Werge
Psychiatry, Rigshospitalet University Hospital, Copenhagen, Denmark

Muscarinic receptor agonists are known to exhibit functional dopamine antagonism in rodents and the muscarinic M1/M4 receptor agonist xanomeline exhibits antipsychotic-like effect in a Cebus apella monkey model of psychosis as well as in schizophrenic patients. Galantamine is an acetylcholinesterase inhibitor, which is primarily used to improve cognitive deficits in Alzheimers Disease (AD) patients. This group of compounds has also been reported to decrease psychotic-like behaviors in AD patients and antagonize dopaminergic effects in rodents. In order to further explore the antipsychotic potential of acetylcholinesterase inhibitors, we investigated the effects of galantamine (0.1, 0.3, 0.6 and 1.0 mg/kg s.c.) on behavior induced by the indirect dopamine receptor agonist d-amphetamine in Cebus apella monkeys. Antipsychotic compounds antagonize d-amphetamine-induced motor unrest and stereotypies in monkeys, a model used routinely in our laboratory to evaluate antipsychotic potential of test compounds. Galantamine inhibited d-amphetamine-induced motor unrest, stereotypies and arousal in Cebus apella monkeys. Galantamine did not induce extrapyramidal side effects but caused sedation and emesis at high doses. These data show that galantamine, despite it lack of affinity for dopamine receptors, exhibit functional dopamine antagonism. The data further substantiate that cholinergic receptor agonists may serve as new tools in the pharmacological treatment of psychosis.

EFFECT OF ANTIPSYCHOTIC DRUGS ON THE MONOAMINERGIC ABERRATION CAUSED BY EXPOSURE TO METHYLAZOXYMETHANOL ON GESTATIONAL DAY 17

P. Flagstad,* J. Arnt, M. Didriksen, J. Kullingsjo, S. Waters, E. Ljung, N. Waters
Pharmacology Target Research, H. Lundbeck A/S, Copenhagen-Valby, Denmark

Rats with disrupted hippocampal and neocortical development, through methylazoxymethanol (MAM) exposure on gestational day 17 have been suggested as a developmental model of schizophrenia. The MAM exposed rats show behavioral changes relevant to the positive and negative symptoms of schizophrenia as well as deficits in some relevant cognitive functions. In the present experiment we examined the levels of monoamines and their metabolites in seven different brain areas of rats exposed to MAM on gestational day 17. Furthermore, we investigated the effect of three weeks of treatment with a classical (haloperidol, D2 antagonist) and of an atypical (sertindole, D2 / 5-HT2A / α1-NA antagonist) antipsychotic compound on the monoaminergic indices. The brains were dissected into the frontal cortex, remaining cortex, limbic region, hippocampal region, striatum, brain stem and the thalamus. The major morphological effect (only weights evaluated) of the MAM treatment identified in this study was a significantly reduced weight of the hippocampal region (~13 %). The main effect of the MAM treatment was an increase in monoamines, in particular noradrenaline and serotonin in the hippocampal and cortical regions. The increases in monoamines were negatively correlated to the weights of the dis-

sected structures, as no clear differences were seen on total amount of monoamines in the structures. This suggests a suppressed, but spared monoamine system in the atrophic areas. Using the present preclinical model we found that when treating with haloperidol or sertindole the main effect was not on the dopaminergic-, but on the serotonergic-measures (a lowering of serotonin turnover across structures) and of importance for future investigations the effect was seen in the MAM treated rats, but not in the controls. Furthermore, a separate analysis showed that whereas both haloperidol and sertindole decreased the serotonin turnover, the effects on other measures (dopamine and noradrenaline metabolism) separated the effect of the two compounds. The finding of a state-dependent (in MAM treated vs. controls) effect of antipsychotic compounds could be of importance for future investigations into the mode of action of antipsychotic compounds as the effects of antipsychotic compounds might be missed if experiments are only performed in normal animals.

AMPHETAMINE SENSITIZATION DISRUPTS ATTENTIONAL SET-SHIFTING AND SUSTAINED VISUAL ATTENTION IN THE RAT: REVERSAL BY A D1 RECEPTOR AGONIST IN THE PREFRONTAL CORTEX

P. J. Fletcher,* C. C. Tenn, Z. Rizos, V. Lovic, J. Sinyard, S. Kapur
Centre for Addiction and Mental Health, Toronto, ON, Canada

Previous work has shown that amphetamine (AMP) sensitization results in neurochemical and behavioural abnormalities, including disrupted prepulse inhibition of the startle reflex and latent inhibition, similar to those seen in schizophrenia. The present experiments examined the effect of AMP sensitization on two, more complex forms of attention. The first set of experiments used a set-shifting task (SST) that measures the ability to shift attention from one perceptual dimension of a stimulus to another (analogous to the Wisconsin Card Sorting Test). The second set used the 5-choice serial reaction time (5-CSRT) test to measure sustained visual attention (analogous to the continuous performance test). Rats received injections of AMP, or saline 3 days per week for 5 weeks. Testing on the SST began 4-weeks later. Rats were trained to dig in bowls for food; bowls, differing in odour and texture were presented in pairs, only one of which was baited. They were tested on a series of discriminations involving the dimensions of odour and texture. The discriminations included simple and compound discriminations, an intradimensional shift, an extradimensional shift (EDS), and their reversals. AMPH-sensitized rats performed as well as controls on the simple and compound discriminations but exhibited a marked deficit on the EDS. This effect was reversed by injecting the D1 receptor agonist SKF38393 (0.06 ug) into the medial prefrontal cortex (mPFC). For the 5-CSRT test rats were trained to respond to a brief (1s) light stimulus presented randomly in one of 5 spatial locations, with 100 trials per session. Rats were then sensitized to AMP and testing was continued on non-drug days, and for several weeks of withdrawal. In AMP-sensitized rats response accuracy was not affected, but the number of errors of omission was increased. Increasing the stimulus duration abolished this effect. Reducing the stimulus duration resulted in a decline in accuracy that was more marked in AMP-sensitized rats than in controls. The reduced accuracy and the increase in omissions seen in AMP sensitized rats was reversed by injecting SKF38393 into the mPFC. AMP sensitization markedly disrupts two form of attentional behaviour, indicating that this procedure may be useful for modelling attentional deficits in schizophrenia. The reversal of these effects by a D1 receptor agonist suggests that the behavioural effects of AMP result from a dysregulation of dopamine function in the mPFC.

EFFECTS OF CHRONIC ANTIPSYCHOTIC TREATMENT ON PRESYNAPTIC PROTEIN MRNAS IN RAT BRAIN

X. Gao,* H. W. Wang, K. Struckhoff, C. A. Tamminga
Psychiatry, The University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA

Neurotransmitter release from nerve terminals is facilitated by the docking and fusion of synaptic vesicles involving presynaptic trafficking proteins. The interaction between the vesicular membrane proteins, the target membrane proteins, and signal proteins play a critical role in the triggering of events in CNS associated with information transfer. Chronic treatment with antipsychotic drugs, haloperidol or risperidone, blocks dopamine-mediated transmission in animals and alters regional neurotransmitter release particularly in striatum. Therefore, haloperidol or risperidone treatment may alter presynaptic trafficking protein concentrations.. To elucidate the long-term effect of antipsychotics on synaptic proteins, we treated rats chronically with two antipsychotics, a traditional drug, haloperidol, and a new agent, risperidone. The rats were given drinking water containing either no drug, haloperidol (1.5mg/kg/day), or risperidone (1.5mg/kg/day or 6mg/kg/day) for 6 months in a blinded design. We analyzed the treated tissue for mRNA of six presynaptic proteins, synaptotagmin1, synaptotagmin4, synaptophysin, complexin 1, complexin 2, and GAP-43 mRNAs using in situ hybridization. We will demonstrate which of the drugs, if any; alter levels of mRNA for these presynaptic trafficking proteins. The quantification of all six presynaptic protein mRNAs across drug groups will be reported. This knowledge will be important when analyzing human postmortem brain tissue to distinguish differences between drug-induced or disease-associated molecular changes.

BEHAVIOURAL AND NEUROCHEMICAL INVESTIGATION OF A PUTATIVE MODEL OF SCHIZOPHRENIA: BRATTLEBORO RATS

J. Gartlon,* J. Cilia, C. S. Shilliam, S. M. Staveley, L. A. Dawson, D. N. Jones
Psychiatry CEDD, GlaxoSmithKline, Harlow, Essex, United Kingdom

Brattleboro (BB) rats are a mutant variant of the out-bred Long Evans (LE) strain that possess a single nucleotide deletion in the gene for the neuropeptide/neurohormone vasopressin. Homozygotic BB rats have no detectable plasma vasopressin and develop a condition analogous to diabetes insipidus. BB rats also display a number of behavioural changes relevant to schizophrenia, including cognitive deficits (Jentsch, 2003, *J Neurosci* 23:1066) and a haloperidol/clozapine-sensitive deficit in pre-pulse inhibition (PPI) (Fiefel et al., 2004, *Neuropsychopharm* 29:731). The aims of this study were to (a) confirm the PPI deficit and investigate additional behavioural phenotypes, (b) investigate reversal of the PPI deficit following acute and chronic clozapine administration, and (c) measure changes in levels of dopamine, 5-HT and their metabolites in pre-selected brain regions. All studies used male homozygous BB rats and LE controls. Initial behavioural characterisation revealed enhanced startle reactivity to acoustic stimuli and elevated levels of motor activity in response to

a novel environment (e.g. BB = 547±37, LE = 1094±60 s mobile time; P<0.05). In agreement with Fiefel and Priebe (Biol Psychiatry 50:425, 2001) BB rats showed a deficit in PPI. However, in contrast to Fiefel and Priebe (2001), PPI was significantly reduced only under variable inter-stimulus interval (ISI) (30-600 msec) conditions (e.g. 300 msec ISI, BB = 39±5, LE = 71±3 %PPI; P<0.05) and not when the intensity (75-85 dB) or the duration (10-30 msec) of the pre-pulse was varied. Clozapine reversed the PPI deficit in BB rats following acute (1 day) and chronic (14 and 21 days) administration. Clozapine also elevated PPI in LE controls following 7, 14 and 21 days administration. Measurement of steady state ex-vivo neurochemistry revealed altered parameters of dopamine function in the frontal cortex (region II) of BB rats with decreased levels of both dopamine and its metabolite (DOPAC). The 5-HT system was not affected. These findings confirm and extend evidence for BB rats as a genetic model of schizophrenia. The sensitivity of the PPI deficit to a range of atypical antipsychotic drugs will be determined in further studies.

MATERNAL POLY I:C EXPOSURE DURING PREGNANCY REGULATES TNFα, BDNF, AND NGF EXPRESSION IN NEONATAL BRAIN AND THE MATERNAL-FETAL UNIT OF THE RAT

J. H. Gilmore,* L. F. Jarskog, S. Vadlamudi
Psychiatry, University of North Carolina, Chapel Hill, NC, USA

Maternal infection during pregnancy is associated with increased risk for schizophrenia. Animal models of maternal infection during pregnancy include the use of polyriboinosinic-polyribocytidilic acid (poly I:C), a synthetic double stranded RNA that stimulates an immune response. Maternal exposure to poly I:C during pregnancy causes long-lasting behavioral changes in the offspring consistent with schizophrenia, including impaired pre-pulse inhibition. We have proposed that induction of inflammatory cytokines and alterations of neurotrophic factors represent a final common pathway for the variety of maternal infections associated with increased risk for schizophrenia. Therefore, poly I:C or saline was administered to E16 pregnant rats to model maternal infection; levels of TNFα, BDNF, and NGF were determined by ELISA. TNFα was significantly increased in maternal plasma, placenta, and amniotic fluid, while significantly decreased in fetal liver/spleen and neonatal brain (approx 15%, $p < 0.0001$). Prenatal exposure to lipopolysaccharide also caused a similar decrease in TNFαin neontal brain. NGF and BDNF were significantly decreased in placenta and fetal liver/spleen. There was no change in BDNF or NGF in fetal or neonatal brain. Changes in TNFα, BDNF, and NGF after maternal exposure to poly I:C represents a potential mechanism through which maternal infection alters brain development and increases risk for schizophrenia.

NEONATAL NEUROSTEROID ADMINISTRATION RESULTS IN DEVELOPMENT-SPECIFIC ALTERATIONS IN PREPULSE INHIBITION AND LOCOMOTOR ACTIVITY IN JUVENILE AND ADULT RATS

S. S. Gizerian,* J. A. Lieberman, A. C. Grobin
Curriculum in Neurobiology, University of North Carolina School of Medicine, Chapel Hill, NC, USA

Maturation of the mammalian brain continues into early adulthood, including cortical pruning and the initiation of DA signaling in the prefrontal cortex (PFC) near the time of puberty. Many neuropsychological disorders manifest at this time, including schizophrenia; the onset of symptoms may be linked to the changes occurring in the developing brain. These changes alter the function of the mesocorticolimbic system as well. In the normal adult brain, inhibition by DA and GABA in the PFC regulates this circuitry, while disinhibition of the mesocorticolimbic system is associated with behavioral changes relevant to human psychosis, including reduced prepulse inhibition (PPI, a measure of sensory gating) and increased locomotor response to amphetamine. A single neonatal injection of the neurosteroid ALLO (3α-hydroxy-5α-pregnane-20-one, 10 mg/kg, i.p.), a potent, positive modulator of $GABA_A$ signaling, alters the localization of PFC interneurons and the volume and cell number of the medial dorsal thalamus in adulthood, changes that are consistent with disinhibition in the PFC. We investigated behavior across development after administration of ALLO during the first postnatal week to determine if there is a critical window in which ALLO levels may impact the development and mature function of the mesocorticolimbic circuitry. PPI and total locomotor activity after amphetamine exposure were assessed at P21 (pre-puberty), P40 (puberty), P60 (post-puberty), and P80 (adulthood). Administration of ALLO on P2 resulted in reduced PPI (P21, 25.6%, F=3.06, p=0.049) and increased locomotor response (P21, 16.2%, F= 5.339, p=0.0098) to amphetamine by P21, while administration of ALLO on P5 resulted in reduced PPI (P80, 39.6%, F=4.382, p= 0.0373) and increased locomotor response to amphetamine post-pubertally (P80, 37.9% F=8.07, p<0.0001). Because ALLO levels rise in response to stress, these data indicate that the behavioral consequences of a perinatal stress event vary according to the timing of the insult. There may be a critical window during which aberrant neurosteroid levels could impact brain maturation, resulting in an increased susceptibility to the development of a schizophrenia vulnerable phenotype. Supported by: Stanley Scholars Grant (SSG), MH065470 (ACG), and Silvio Conte Center.

EFFECT OF ANTIPSYCHOTIC DRUGS ON THE G PROTEIN-COUPLED RECEPTOR DESENSITIZATION MACHINERY

E. V. Gurevich,* M. R. Ahmed, O. Nichols, J. L. Benovic, V. V. Gurevich
Pharmacology, Vanderbilt University, Nashville, TN, USA

Previous studies have implicated G protein-coupled receptors (GPCRs) in the pathophysiology of schizophrenia and the action of antipsychotics. Typical antipsychotics are potent antagonists of D2/D3 dopamine receptors. Atypical antipsychotics have lower affinity to D2/D3 receptors and higher affinity to serotonin 5-HT2A and other GPCRs. Upon stimulation, GPCRs undergo rapid desensitization. The desensitization involves activation-dependent receptor phosphorylation by G protein-coupled receptor kinases (GRKs) followed by the binding of arrestins. Arrestin binding precludes further signal transduction and induces receptor internalization. The internalized receptor can either be recycled back to plasma membrane or degraded, which leads to the receptor down-regulation. Molecular events unleashed by antipsychotic treatment are likely to include modifications in the intracellular trafficking of GPCRs. We examined the expression of two arrestins (arrestin2 and arrestin3) and four GRKs (GRK2, GRK3, GRK5, and GRK6) in the rat brain following chronic (21 days) treatment with haloperidol (1 mg/kg/day) or clozapine (20 mg/kg/day). The expression was measured in 11 brain regions by quantitative Western blotting using subtype-specific antibodies

and purified proteins as standards. The results show that treatment with a typical or atypical antipsychotic differentially affected the expression of arrestins and GRKs in the brain. The expression of arrestin2 in the dorsolateral striatum was significantly elevated (by 62%) following treatment with haloperidol but not clozapine. Conversely, in the ventrolateral striatum the arrestin2 concentration was increased by clozapine (by 40%) but not haloperidol. In the dorsal hippocampus, the arrestin2 expression was significantly decreased following the clozapine treatment (by 30%), whereas haloperidol had no effect. The expression of GRK2, one of two major GRK subtypes in the brain, was selectively increased in the prefrontal cortex by both clozapine and haloperidol. The data show that chronic antypsychotic treatment alters the expression of the key components of the GPCR trafficking machinery. Typical antipsychotic haloperidol and atypical drug clozapine induce markedly different patterns of changes, which may be important for their typical or atypical profile. These changes in GPCR regulatory machinery by antipsychotics may be essential for their therapeutic action or responsible for the unwanted side effects.

BIFEPRUNOX: A NEW AND DIFFERENT ANTIPSYCHOTIC

P. Hertel,* C. K. Olsen, M. Didriksen, J. Arnt, K. Marquis, J. van der Heyden, A. McCreary, M. B. Hesselink
Psychopharmacology, H. Lundbeck A/S, Valby-Copenhagen, Denmark

The effect of bifeprunox was evaluated in a number of preclinical models which have been useful in predicting antipsychotic action in man: conditioned avoidance response and antagonism of amphetamine and phencyclidine-induced hyperactivity. Haloperidol, clozapine, risperidone, olanzapine and aripiprazole were used as reference agents. Bifeprunox was shown to have potent antipsychotic like effects in a therapeutic model sensitive to all antipsychotic agents (suppression of conditioned avoidance behavior in rats, MED of 0.25 mg/kg sc). Interestingly, clozapine, aripiprazole and bifeprunox caused only a partial suppression of the conditioned avoidance response, while all other antipsychotic agents tested completely blocked this response. Administration of phencyclidine [PCP, a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptors] results in a psychotomimetic state that has been suggested to be a valid pharmacological model of schizophrenia. In rats and mice, PCP administration leads to hyperactivity and stereotypy, as well as cognitive deficits. Bifeprunox inhibited the PCP-induced hyperactivity in mice (ED50=0.00096 mg/kg sc), while inhibition of baseline activity was seen only at much higher doses (ED50=0.083 mg/kg sc). The high potency and degree of selectivity compared to base-line activity, of bifeprunox against PCP-induced hyperactivity, is unique compared to known antipsychotic drugs. Bifeprunox more potently antagonized overt behavior stimulated by d-amphetamine (ED50=0.005 mg/kg and 0.02 mg/kg sc versus low dose (0.5 mg/kg) and high dose (2.0 mg/kg) amphetamine, respectively) as compared to the doses needed for affecting baseline activity (ED50=0.036 mg/kg sc) in rats. The selectivity, between inhibition of amphetamine (0.5 mg/kg)-induced hyperactivity and baseline activity, was highest for aripiprazole, followed by bifeprunox and risperidone. These data indicate that bifeprunox has antipsychotic like activity in a wide range of animal models.

BIFEPRUNOX: *IN VIVO* CHARACTERIZATION OF A NOVEL PARTIAL AGONIST FOR THE D_2 RECEPTOR

M. B. Hesselink,* A. C. Mc Creary, J. C. Glennon, K. L. Marquis, P. Hertel, J. Arnt, M. Didriksen, S. K. Long
Preclinical Drug Validation Unit, Solvay Pharmaceuticals Research Laboratories, Weesp, Netherlands

The effects of bifeprunox and reference dopaminergic drugs (the full dopamine agonist quinpirole, the partial agonists preclamol and aripiprazole and the antagonist haloperidol) were investigated in a number of *in vivo* mechanistic models predictive of modulation of dopamine-mediated behavior. In rats with unilateral 6-OHDA lesion of the dopaminergic input into the striatum, quinpirole and preclamol induced contralateral turning behavior, induced by stimulation of lesion-induced supersensitive postsynaptic D_2 receptors. Bifeprunox induced comparable turning behavior (ED_{50} 0.026 mg/kg, sc). Aripiprazole however induced minimal turning behavior and did not reach the criterion of 50% compared to apomorphine (ED_{50}>2.5 mg/kg, sc). In microdialysis studies in the nucleus accumbens of the freely moving rat, bifeprunox (0.01-1 mg/kg ip) dose-dependently decreased both extracellular dopamine and serotonin levels to 80 % of control levels. This effect is believed to be a consequence of presynaptic D_2 receptor and 5-HT_{1A} receptor activation, respectively. The D_2 receptor partial agonist preclamol and the full dopamine agonist quinpirole induced a decrease in extracellular dopamine levels, while aripiprazole was without effect on dopamine and 5-HT levels. The D_2 receptor antagonist haloperidol induced a clearly different effect, increasing dopamine levels without affecting 5-HT levels. In addition to inducing dopamine agonistic behaviors, bifeprunox acted as a dopamine partial agonist *in vivo* since it was able to inhibit dopamine agonist mediated behavior, eg. inhibition of apomorphine-induced climbing in mice (ED_{50} 0.14 mg/kg, po) and amphetamine-induced hyperactivity in rats (ED_{50} 0.02 mg/kg, sc; see also Hertel et al). The dopamine partial agonist aripiprazole and the antagonist haloperidol showed a comparable effect, while the partial agonist preclamol was able to inhibit amphetamine-induced locomotor activity (ED_{50} 2.2 mg/kg, sc) but not apomorphine-induced climbing behavior (ED_{50}>30 mg/kg, po). In conclusion, bifeprunox shows a profile that on one hand is consistent with that of existing antipsychotic agents, ie an ability to antagonize behaviors induced by dopamine agonists, and on the other hand strongly contrasts with dopamine antagonists in that it is able to stimulate dopaminergic receptors in situations where the dopaminergic tone is low or dopamine receptors are supersensitive.

CLOZAPINE AND HALOPERIDOL DIFFERENTIALLY MODULATE THE BASAL RATE AND PATTERN OF NEURONAL FIRING AND THE EFFECTS OF NMDA ANTAGONISTS IN AWAKE RAT PREFRONTAL CORTEX

H. Homayoun,* B. Moghaddam
Neuroscience, University of Pittsburgh, Pittsburgh, PA, USA

Mechanisms responsible for the superior efficacy of clozapine in the treatment of schizophrenia remain poorly understood. Prefrontal cortex (PFC) is a critical target for the therapeutic actions of antipsychotics, particularly for treatment of cognitive and negative symptoms. We used ensemble single unit recording to determine whether clozapine and haloperidol influence the pattern of activity of neurons in the tonically active PFC of behaving animals. Our recent findings indicate that psychotomimetic NMDA antagonists disrupt the

pattern of activity of PFC neurons (Jackson et al., PNAS, 2004); therefore, we also examined the effect of haloperidol and clozapine in modifying the disruptive effects of the NMDA antagonist MK801 on PFC neuronal activity. Clozapine altered the spontaneous firing rate of 50% of the neurons in a state-dependent manner: it increased the firing rate of the neurons with low baseline firing rates and decreased the activity of neurons with higher firing rates. Clozapine also increased the frequency and duration of spontaneous bursts and the percentage of spikes in bursts. Administration of MK801 at doses that led to behavioral stereotypy increased the rate but decreased burst activity of most PFC neurons. Clozapine reduced the number of neurons that increased their firing rate in response to MK801. In the remaining (MK801-responsive) neurons, clozapine dose-dependently reduced the effects of MK801 on bursting and on the magnitude and duration of firing rate increases. Haloperidol, when injected alone, influenced the firing rates of 45% of neurons in a state-independent manner and had no effect on burst activity. Haloperidol reduced the number of neurons that responded to MK801. However, it did not change the magnitude and duration of MK801 effects on firing rate and burst activity in the remaining neurons. Both drugs attenuated MK801-induced behavioral stereotypy but only the effect of clozapine had a high correlation with changes in PFC firing activity. These findings indicate that while both clozapine and haloperidol can influence the firing rate of PFC neurons under baseline or disrupted conditions, clozapine effects are state-dependent and involve modulation of burst activity. This suggests that clozapine has the capacity to *normalize* PFC neuronal activity and to increase signal transmission efficiency of PFC neurons. This mechanism may underlie the superior clinical profile of clozapine compared to typical antipsychotics.

IN RATS TREATED ACUTELY OR CHRONICALLY WITH CLOZAPINE, THE CLOZAPINE-INDUCED INCREASE IN PREFRONTAL CORTEX DOPAMINE AND NOREPINEPHRINE LEVELS IS INFLUENCED BY TYROSINE AVAILABILITY

G. E. Jaskiw,* B. Kirkbride, R. Bongiovanni
Psychiatry Service, Louis Stokes Cleveland VAMC, Cleveland, OH, USA

Brain dopamine (DA) transmission can be affected by availability of the precursor amino acid tyrosine. Administration of a tyrosine and phenylalanine-free amino acid mixture ((NAA(-)) can reduce brain tyrosine levels. To examine the precursor dependence of clozapine (CLZ) induced DA levels in medial prefrontal cortex (MPFC) we treated male rats with vehicle (VEH) or CLZ (10mg/kg/d in drinking water) for 21d. A cannula was surgically implanted and a microdialysis probe inserted (AP +1.2, ML +3.2, VD -5.5) on days 18 and 20 respectively. On day 21 microdialysis collection began. Rats received IP vehicle (VEH) or NAA(-) (total 1g/kg, two IP injections, 1 hr apart) and 60 min later IP CLZ (10mg/kg) or VEH. Six (chronic/acute/acute) treatment groups were studied: VEH/VEH/VEH, VEH/NAA(-)/CLZ, CLZ/VEH/VEH, CLZ/NAA(-)/VEH, CLZ/VEH/CLZ, CLZ/NAA(-)/CLZ. Basal DA levels were not different between groups. NAA(-) did not affect MPFC DA or NE in CLZ/NAA(-)/VEH animals. Peak DA (370% of baseline) and norepinephrine (NE) (510% of baseline) in the CLZ/VEH/CLZ group were significantly greater than peak DA (220% of baseline) and NE (330% of baseline) in VEH/NAA(-)/CLZ and CLZ/NAA(-)/CLZ groups ($p < 0.01$). Thus, after acute or chronic treatment with CLZ, the CLZ-induced increase in MPFC DA as well as NE levels depends on the availability of tyrosine. Given that schizophrenia is associated with abnormalities in mesocortical catecholamine transmission and in tyrosine transport across the blood brain barrier, pharmacological manipulation of brain tyrosine levels may provide a useful probe as well as a mechanism for enhancing psychotropic drug actions. Support Contributed By: Department of Veterans Affairs Medical Research Service.

ALPHA-2 RECEPTOR AGONISTS ABOLISH DEFICITS OF COGNITION TRIGGERED BY NMDA RECEPTOR HYPOFUNCTION: COMPARISON OF ALPHA-2A AND -2C MECHANISMS

J. Jentsch
Psychology, UCLA, Los Angeles, CA, USA

Alpha-2 agonists are highly effective at preventing NMDA-antagonist induced cognitive deficits in rats, and this set of effects may be predictive of their pro-cognitive effects in schizophrenia patients. Studies have been undertaken to characterize the role for alpha-2A, 2B and 2C receptor subtypes in higher cognitive functions because subtype specific agonists may bear the cognitive, but not sedating and hypotensive, agonist effects. Research has focused mainly on the 2A and 2C subtypes because these are the receptors found in the forebrain. To address these issues directly, we used receptor subtype specific agonists and antagonists to transiently and dose-dependently alter activation of either the 2A or 2C subtypes in rats pre-trained to perform an operant delayed non-match-to-sample task. Clonidine and guanfacine, both alpha-2A+B+C agonists, (0.001-0.01 mg/kg and 0.05-1.0 mg/kg, respectively) blocked deficits of spatial working memory produced by phencyclidine (PCP), while the alpha-2A+B+C antagonist atipamezole (0.1-0.5 mg/kg) augmented PCP-induced impairments at a dose that had no measured effect on its own. Pre-synaptic noradrenergic fibers are required for the atipamezole effects. BRL-44408 (<5.0 mg/kg), an alpha-2A selective antagonist, was without measured effect on performance when given alone or in combination with PCP. By contrast, the alpha-2C receptor antagonist MK-912 (0.3-1.0 mg/kg) impaired spatial working memory performance on its own. In addition, the alpha-2A receptor antagonist failed to attenuate the cognitive enhancement by clonidine or augment the effects of PCP. These results force a reappraisal of the view that alpha-2A receptors alone mediate the neurocognitive effects of broad spectrum alpha-2 receptors, such as clonidine and guanfacine. They also suggest that alpha-2C receptors should not be ignored in the design of new agents meant to improve working memory and attention in schizophrenia and attention deficit disorder.

GENOMIC SPECTRUM OF ESTROGEN ACTIONS IN RAT BRAIN: RELEVANCE TO ESTROGEN THERAPY IN PSYCHIATRIC DISORDERS

M. M. Khan,* K. M. Dhandapani, L. D. Sevilla, V. B. Mahesh, D. W. Brann
Institute of Molecular Medicine and Genetics, Medical College of Georgia, Augusta, GA, USA

Estrogen (E2) has been implicated in the pathophysiology and sex differences in onset, prognosis and treatment response of schizo-

phrenia and other CNS disorders. E2 has thus been hypothesized to have an important role in brain development and protection against psychiatric insults. Work from our group using gene chip analysis revealed that 7-day treatment with E2 had a significant stimulatory effect on the expression of a variety of genes relevant to beneficial effects of estrogen in psychotic patients. The gene which were up regulated fall under various categories, the most important are those related to; a) synaptic plasticity (pre and postsynaptic genes e.g. syntaxins, SAP97, PSD-93, SAP102, synaptotagmin, N-cadherin); b) neurotransmission (GABA receptor/transporters, glutamate (GluR1), muscarinic (M4), dopamine (D4) and nicotinic (alpha-7) receptors) and; c) regeneration and growth (growth factors, stem cell factor and various cell adhesion molecules). Some of these genes have been implicated in the pathophysiology of schizophrenia and other neurodevelopmental disabilities. Stimulatory effects of E2 on the synaptic plasticity, was also confirmed by measuring the number of spines and protein density using golgi impregnation, silver-enhanced nanogold and immunofluorescence staining. Results from this analysis showed, a significant increase in the number of dendritic spines and proteins density for PSD-95, spinophilin and synaptotagmin in the temporal-parietal and prefrontal cortex. Altogether, these observations suggest that E2 regulates expression of synaptic, neurotransmission and regeneration/growth-related genes/proteins in the cerebral cortex, which could have implications for understanding the beneficial effects of estrogen in psychiatric disorders. Grant support to DWB: NIH/NICHD HD028964.

IMAGING OF HERPES VIRUS INFECTIONS OF THE BRAIN BY POSITRON EMISSION TOMOGRAPHY (PET): A NEW TOOL FOR SCHIZOPHRENIA RESEARCH?

H. C. Klein,* A. R. Buursma, J. Garssen, D. Kegler, W. Vaalburg, E. F. de Vries
Centre for Mental Health, Winschoten, Netherlands

The cause of psychotic exacerbations in patients suffering from schizophrenia is not known. Some schizophrenic like psychoses occur in the early course of herpes encephalitis. Herpes simplex virus (HSV-1) has been detected in many post-mortem human brain samples. These two facts have reactivated the hypothesis that some schizophrenic psychoses are linked to viral reactivation. To test this hypothesis we need a non-invasive "virus imaging" technique in humans. This study will show the validation of a PET method to image the presence of replicating herpes viruses in the living rat brain. Replication of all herpes viruses in non-dividing brain tissue requires the activity of the viral enzyme thymidine kinase. In our gene therapy work we found that the activity can be monitored using PET with the tracer 9-[(1-[18F]fluoro-3-hydroxy-2-propoxy)methyl]guanine ([18F]FHPG). The aim of this study is to determine the feasibility of the method to monitor cerebral herpes infection in-vivo. Eight male Wistar rats were infected intranasally with 1*10E7 pfu of human strain of HSV-1 and three saline inoculated rats served as controls. Clinical signs of disease were scored daily. After 7 days, [18F]FHPG (20.0±16.4 MBq) was injected intravenously and a dynamic PET scan was acquired for 1 hour. To discriminate small brain regions ex-vivo autoradiography was performed on brain slices. Some infected brain samples were analyzed for phosphorylated [18F]FHPG metabolites using HPLC and for HSV sequences by PCR. The PET imaging results showed a significant accumulation of the tracer in the infected rats of 6.6±3.6*10E-2 percent of the injected dose per gram tissue (%ID/g). Brain radioactivity in control animals was at background level (-0.36±1.1*10E-2 %ID/g). Ex-vivo autoradiography showed high tracer uptake in the olfactory bulbs, motor cortex, somatosensory cortex and substantia nigra of HSV infected rats (levels were 3.2, 2.2, 2.1 and 1.8 times higher than controls). HPLC analysis showed 15% phosphorylated fraction of the tracer in the infected rat and PCR analysis confirmed the presence of HSV-1. Clinical signs invariably preceded enhanced tracer uptake. We conclude that PET imaging of thymidine kinase activity with [18F]FHPG is feasible for imaging of severe HSV infections of the brain. The sensitivity of the method seems sufficient to detect mild HSV infections of the brain. We hope that these results are a step forward towards application in human schizophrenia research.

GONADAL HORMONE MODULATION OF PERFORMANCE IN OPERANT TASKS MEASURING PREFRONTAL CORTICAL FUNCTION IN ADULT MALE RATS

M. Kritzer,* A. Brewer, F. Montalmant, M. Davenport, J. Turvin, J. K. Robinson
Neurobiology and Behavior, Stony Brook University, Stony Brook, NY, USA

Previous studies in this lab have shown that gonadectomy (GDX) selectively and significantly increases dopamine (DA) axon density in the prefrontal cortex of adult male rats in an androgen reversible manner. Behavioral studies in similarly manipulated rats also reveal impairments in open field and delayed T-maze alternation tasks that are consistent with supranormal prefrontal DA. To explore these behavioral consequences further we tested GDX and hormone replaced rats on a series operant tasks designed to examine rule learning, behavioral flexibility, impulsivity and reward strength— constructs often viewed as mediated by prefrontal DA. For all tasks rats were tested in two lever operant chambers with cue lamps placed over each response lever; rats were water restricted, with 0.1ml of water delivered to a front aperture serving as reward. To maximize study sensitivity, we used regression analyses to correlate performance with the quantitative variable of bulbospongiosus muscle (BSM) weight, a standard, sensitive indicator of circulating androgens in rats. What was revealed were deficits in some but not all of the tasks. Specifically, after pre-training on bar pressing, in learning a simple alternating response rule, low BSM weight, i.e., GDX and GDX- estrogen treated rats, was significantly correlated with increased numbers of training sessions needed to reach criterion performance. In the following light/dark discrimination task, deficits in learning to press the cued lever were significantly correlated with low BSM weight on the first day of testing, but thereafter no relationship was evident. Likewise, when next trained on a match to position rule and upon acquiring that a non-match to position rule, no significant correlations between hormone levels (muscle weight) and performance were observed. Impulsivity, measured by a differential reinforcement of low rate of responding task, was also unrelated to hormone status. However, animals with low BSM weights did cease to respond on a progressive ratio schedule of reinforcement task significantly sooner than controls. Thus, androgen-sensitivity was observed for only some of the constructs predicted to be impaired based on the striking effects of GDX on prefrontal DA. Nonetheless, these data suggest that the hormone modulation of prefrontal DA systems may also extend to some of the DA-dependent prefrontal functions that are vulnerable, often in sex-specific ways, in schizophrenia. RO1NS41966.

ALPHA 2 NORADRENERGIC AGONISTS INCREASES CORTICAL EXCITABILITY

A. Lavin,* G. D. Andrews
Physiology, Medical University of South Carolina, Charleston, SC, USA

The role of noradrenaline (NE) in cognition, working memory and attention has been well recognized. It is known that NE exerts its actions on prefrontal cortex (PFC) by acting on alpha and beta-adrenergic receptors. Furthermore, evidence from different laboratories indicates that NE can improve PFC function by acting through a particular subtype of noradrenergic receptor (NER): the alpha2 NER. The alpha2 receptors are located pre- and postysnaptically and improvements in cognition following administration of alpha2 agonists have been reported in aged monkeys and in young monkeys with depletions of NE. Moreover, specific alpha 2A agonists have been used to treat disorders related with dysfunctions in working memory and attention. However, there is scant data regarding the cellular mechanisms that mediated the clinical effects of alpha2 agonists. Using rat slices and whole-cell recordings we assessed the intrinsic and evoked excitability (eEPSP) of pyramidal cells located in infralimbic and prelimbic cortices. Clonidine (specific alpha2 agonist, 10 μM) was either bath-administered or puffed into the soma or in the apical dendrites (300-800 μM from the soma). Bath-administration of clonidine increased significantly the amplitude of the eEPSP in 16/26 cells (38.5%). Moreover, clonidine increased significantly intrinsic excitability in 9/23 cases (39%) in intact preparations. Furthermore, in 4/8 cells clonidine increased both synaptic excitability and eEPSP. In contrast, in a catecholamine-depleted preparation, clonidine increased significantly only intrinsic excitability (4/4 cells) without affecting eEPSPs. Our results show that alpha2 agonists can modulate cortical activity by differentially affecting either synaptic or intrinsic activity and furthermore, the regulation will depend on the levels of catecholaminergic tone.

RESPONSE TO NOVELTY CORRELATES WITH DOPAMINE RECEPTOR AVAILABILITY IN STRIATUM OF LIVING PIGS

N. M. Lind,* A. Moustgaard, A. K. Olsen, S. B. Jensen, S. Jakobsen, A. K. Hansen, S. M. Arnfred, R. P. Hemmingsen, A. Gjedde, P. Cumming
Department of Psychiatry, University Hospital of Copenhagen, Bispebjerg, Copenhagen, Denmark

The novelty seeking (NS) personality trait is linked to brain dopamine (DA) neurotransmission. Assessment of response to novelty is often part of animal models of schizophrenia. In this context, we have hypothesized that amphetamine-evoked changes in the binding of [11C]raclopride to dopamine D2/3 receptors in the brain of living pigs should correlate with individual NS score. Twelve adult Gottingen minipigs (Dalmose, Denmark) of mixed sexes were tested for response to a novel object. The number of contacts and the total time spent in contact with the object was recorded, and a mean time per contact was calculated as the index of NS. Dynamic positron emission recordings were made (Siemens ECAT) after intravenous bolus injection of 500 MBq [11C]raclopride, first in a baseline condition, and again after challenge with d-amphetamine sulphate (1 mg/kg). Maps of the binding potential (*pB; Bmax/Kd*) of [11C]raclopride were calculated using the reference tissue method of Logan. Correlations between novelty scores and striatal [11C]raclopride *pB*s were assessed with Pearson's Partial Correlation Coefficient with gender and rank partialled out. The NS scores correlated significantly with baseline [11C]raclopride *pB* ($r = 0.88$; $p = 0.01$) and the amphetamine-evoked decrease in [11C]raclopride *pB* ($r = 0.91$; $p = 0.005$) in striatum. Baseline [11C]raclopride *pB* is understood to be reduced tonically by competition from endogenous dopamine. The present correlation analysis therefore suggests that the pigs showing greater exploration of novel objects had lower basal dopamine levels than did pigs with less exploration of a novel object. The correlation between novelty scores and amphetamine-evoked declines in striatal [11C]raclopride *pB*, confirms previous animal and human studies showing a relationship between novelty-seeking behaviour and individual DA response to amphetamine. In conclusion, the results support the link between novelty-seeking and increased neurochemical response to psychostimulants. This study was financially supported by unrestricted grants from the Lundbeck Foundation and the Copenhagen Hospital Corporation Research Foundation.

THE HIPPOCAMPUS MODULATES DOPAMINE NEURON RESPONSIVITY BY REGULATING THE INTENSITY OF PHASIC NEURON ACTIVATION

D. Lodge,* A. A. Grace
Neuroscience, Psychiatry, and Psychology, University of Pittsburgh, Pittsburgh, PA, USA

The tonic/phasic model of dopamine release was first posited in 1991 and presented a foundation for investigating the regulation of dopamine (DA) system responsivity. Since this time there has been increasing evidence for functionally related but independent afferent systems regulating either tonic or phasic dopamine release. Using in vivo extracellular recordings and microdialysis in chloral hydrate anaesthetized rats we now report that although individual manipulations of afferent pathways exert independent control over DA neuron firing characteristics, simultaneous activation of multiple regions can result in a supra-phasic increase in dopaminergic transmission. Specifically the present study demonstrates that infusions of NMDA into the ventral subiculum (vSub) induce an increase in the number of spontaneously active DA neurons (population activity), while having no affect on firing rate or average bursting activity. In contrast, NMDA activation of the pedunculopontine tegmental nucleus (PPTg) resulted in a significant increase in DA neuron burst firing without affecting population activity. Interestingly, the simultaneous excitation of the vSub and PPTg induced a significant increase in both DA neuron population activity and burst firing resulting in a ~3-fold increase in the number of high-bursting neurons observed per electrode track. These data suggest that dopamine neuron population activity is not simply associated with the tonic release of DA in forebrain regions but rather represents a recruitable pool of dopamine neurons that can be further modulated by excitatory inputs to induce a graded phasic response. Since the vSub is a major output of the hippocampal formation, these data suggest that the hippocampus can regulate the intensity of a phasic signal via recruitment of previously quiescent dopamine neurons. Taken as a whole, we hypothesize that the synchronous activity of select afferent inputs to the VTA are required to induce the most robust DA signal and hence pathologies of afferent systems may result in aberrant DA signaling. It is therefore plausible that hippocampal damage such as that observed in schizophrenia may result in a pathologically increased DA neuron population activity and that this hyper-dopaminergic state may lead to a considerably increased phasic DA signal in response to non-salient events or objects.

L-STEPHOLIDINE: A D_1 AGONIST D_2 ANTAGONIST WITH AN ANTIPSYCHOTIC-LIKE PROFILE

D. C. Mamo,* S. Natesan, S. VanderSpek, S. Kapur
Schizophrenia Division, Centre for Addiction & Mental Health, Toronto, ON, Canada

L-stepholidine is an alkaloid isolated from the root of the Chinese herb *Stephania intermedia* that has been shown to express mixed D_1 agonism and D_2 antagonism properties in rodent behavioural and electrophysiological studies (Jin *et al.* 2002). The primary objectives of this study were to confirm the binding of *l*-stepholidine to dopamine D_1 and D_2 receptors *in vivo*, study its functional characteristics in established rodent models of antipsychotic action, and relate these results to *in vivo* D_2 receptor occupancy. To study striatal dopamine D_2 receptor occupancy, 25 male SD rats were injected s.c. with 1, 3, 10, & 30 mg/kg *l*-stepholidine (EMD Biosciences, San Diego, CA) or normal saline 30 minutes before injection of [^{3}H]raclopride. For striatal dopamine D_1 occupancy, 30 male SD rats were injected with 0.3, 1, 3, 10, & 30 mg/kg of *l*-stepholidine or normal saline 30 minutes before injection of [^{3}H]SCH-23390. 30 minutes after radiotracer injection, the animals were scored for catalepsy and sacrificed by decapitation. To study its efficacy in preclinical models predictive of antipsychotic effects, stepholidine was tested in conditioned avoidance response (CAR), a model predictive of antipsychotic efficacy, and catalepsy (CAT) a model predictive of extrapyramidal side-effects. We found high striatal D_2 occupancy levels even at the lower doses (mean % occupancy ± SD: 1 mg/kg = 41 ± 15 %, 3 mg/kg = 85 ± 1 %, 10 mg/kg = 94 ± 3 %, 30 mg/kg = 90 ± 8 %). The relationship between dose and D_2 occupancy was best described by a rectangular saturating hyperbole, with an estimated ED_{50} (± SE) of 1.0 ± 0.2 mg/kg. We found no catalepsy at doses lower than 10 mg/kg, but the conditioned avoidance response was inhibited by all doses ≥ 1mg/kg. Using [^{3}H]SCH-23390 the striatal D_1 occupancy showed an ED_{50} ± SE = 7.3 ± 1.8 mg/kg (mean % occupancy ± SD: 0.3 mg/kg = 9 ± 6, 1 mg/kg = 13 ± 18 %, 3 mg/kg = 37 ± 7 %, 10 mg/kg = 54 ± 7 %, 30 mg/kg = 77 ± 3 %). The results of this study confirm l-stepholidines central D_1 and D_2 receptor binding *in vivo*, and are consistent with a D_1 agonist and D_2 antagonist profile. The separation between doses producing CAR vs. CAT predicts an antipsychotic profile with limited motor side-effects. The data also predict that *l*-stepholidine may be a promising candidate for the combined treatment of positive (D_2 antagonism) as well as negative and cognitive (D_1 agonism) symptoms of schizophrenia.

BIFEPRUNOX: A NOVEL ATYPICAL ANTIPSYCHOTIC SHARING DOPAMINE D_2 RECEPTOR PARTIAL AGONISM AND SEROTONIN 5-HT_{1A} RECEPTOR AGONISM

K. L. Marquis,* P. Hertel, J. H. Reindeers, M. van der Neut, E. Ronken, M. B. Hesselink
Discovery Neuroscience, Wyeth Research, Princeton, NJ, USA

Bifeprunox (7-[4-([1,1'-biphenyl]-3-ylmethyl)-1-piperazinyl]-2(*3H*)-benzoxazolone, monomethane-sulphonate), a novel putative antipsychotic agent, was investigated in a number of *in vitro* test systems for its receptor binding profile and interaction with the dopamine D_2 receptor. Bifeprunox has high affinity (pKi) for hD_2 receptors (8.5), hD_3 (9.1) and hD_4 (8.0) receptors. Bifeprunox also has high affinity (pKi 8.2) and a partial agonist effect at serotonin 5-HT_{1A} receptors (pD_2 7.0, α 0.7), but virtually no affinity for 5-HT_{2A} and 5-HT_{2C}, noradrenergic α_1 and α_2, muscarinic and histaminergic receptors. In a functional assay (adenylate cyclase activity in CHO cells expressing hD_{2L} receptors), bifeprunox showed highly potent but incomplete antagonism of the effects of the dopamine agonist quinpirole (pA_2 10.1), and weak agonist properties (maximum 28 % agonism at 1 μM, compared to the full agonist quinpirole). Furthermore, bifeprunox inhibited D_2 receptor-sensitive adenylate cyclase activity in rat striatal slices (pD_2 7.9, α 0.6). Finally, in the same preparation, measuring the inhibitory effect on K^+-induced release of [^{3}H]-dopamine, bifeprunox acted as a highly potent antagonist at presynaptic D_2 receptors (pA_2 9.4). Of all reference antipsychotic drugs tested (haloperidol, clozapine, risperidone, olanzapine and aripiprazole), aripiprazole was the only other to show a comparable partial agonist profile *in vitro*. All other reference compounds acted as dopamine D_2 antagonists. Data in these functional assays support the dopamine D_2 partial agonistic properties of bifeprunox and aripiprazole *in vitro*. Indeed, these partial agonists induced agonist-like effects when endogenous dopamine tonus is low, as in the case of the adenylate cyclase activity assays in CHO cells and in striatal slices. However, when the endogenous dopamine level is high, such as with the depolarising potassium concentration used in the [^{3}H]-DA release assay, the partial agonists acted as functional antagonists. This profile could confer a unique antipsychotic profile: in brain regions (n. accumbens) where dopaminergic neurotransmission is believed to be increased in schizophrenia, the partial agonists are expected to act as functional antagonists thus moderating dopaminergic activity. In contrast, in prefrontal cortex, where the dopaminergic system is believed to be hypoactive, the partial agonists are expected to be able to restore dopaminergic neurotransmission.

AV965, A SELECTIVE 5-HT_{1A} SILENT ANTAGONIST AS A CANDIDATE FOR ADJUNCTIVE TREATMENT OF COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

J. F. Mckelvy
Avera Pharmaceuticals, San Diego, CA, USA

There is currently great interest in identifying pharmacologic approaches to modulating cognitive function which might be combined with antipsychotic medications to achieve greater efficacy in the treatment of the schizophrenia syndrome. A potential target for such a pro-cognitive agent is the 5-HT_{1A}receptor. The postsynaptic 5-HT receptor has been shown to mediate an inhibitory current in cortical and hippocampal pyramidal neurons. Both partial agonists and pure (silent) antagonists of this receptor have been shown to enhance cognitive cognitive performance in rodent or primate behavioral models. We are developing a selective 5-HT_{1A}silent antagonist, AV965, which is orally bioavailable, brain penetrating and favorable pharmacokinetics in preclinical models. AV965 exhibits a Kof 4.7 nM against the cloned human receptor and is highly selective with respect to other 5-HT subtypes and other receptor/ion channel sites. *In vivo*AV965 behaved as a full antagonist with no partial agonist properties, antagonizing 8-OH DPAT induced behaviors (ED_{50}<3 mg/kg p.o.) and elevations of serum corticosterone (ED_{50}9 mg/kg p.o.). AV965 administered orally (3 and 10 mg/kg) gave rise to significant increases in hypothalamic extracellular serotonin as determined by $_{\text{in vivo}}$ microdialysis. AV965 was active in the radial arm maze test at 3 mg/kg p.o. AV965 has shown a favorable profile in preclinical safety and pharmacokinetic studies and is ready to begin Phase 1 clinical studies.

CELLULAR AND SUBCELLULAR LOCALIZATION OF PDE10A, A STRIATAL-SPECIFIC PHOSPHODIESTERASE

F. S. Menniti,* A. M. Ryan, T. F. Seeger, D. T. Stephenson, Z. Xie, W. D. Eldred
CNS Discovery, Pfizer Global Research and Development, Groton, CT, USA

PDE10A is a recently identified phosphodiesterase that is highly expressed by the GABAergic medium spiny projection neurons of the mammalian striatum (Seeger et al., *Brain Res*., 985:113-126, 2003). Inhibition of PDE10A results in striatal activation and behavioral suppression, suggesting that PDE10A inhibitors represent a novel new class of antipsychotic agents (Siuciak et al., and Schmidt et al., this meeting). In the present studies we further elucidate the localization of this enzyme in striatum. We find by confocal microscopy that PDE10A like immunoreactivity is excluded from each class of striatal interneuron. Thus, the enzyme is restricted to the medium spiny neurons. Subcellular fractionation indicates that PDE10A is primarily membrane bound. The protein is present in the synaptosomal fraction but is separated from the postsynaptic density upon solubilization with 0.4% Triton X-100. Immuno-electron-microscopy confirms that PDE10A is most often associated with membranes in dendrites and spines. Immuno-gold particles are observed on the edge of the postsynaptic density but not within this structure. These results indicate that PDE10A is localized to the membranes of the dendrites and spines of the medium spiny neurons. This places the enzyme in locations from which it may participate in regulating intracellular signaling at the level of the glutamatergic and dopaminergic inputs to the medium spiny neurons.

COMPARING DOPAMINE D2 STABILIZERS (-)OSU6162 AND ACR16 TO STANDARD ANTIPSYCHOTICS IN ANIMAL MODELS

S. Natesan,* G. Reckless, A. M. Johansson, K. A. Svensson, J. N. Nobrega, S. Kapur
Schizophrenia—PET, Centre for Addiction and Mental Health, Toronto, ON, Canada

A new class of compounds based on their ability to stabilize dopaminergic function in in-vivo models exemplified by (-)OSU6162 (OSU) & ACR16 has been of current interest. Though they lack high binding affinity at dopamine, other monoaminergic, amino acid or peptidergic receptors, they have been demonstrated to counteract both hypo and hyperdopaminergia in-vivo. The mixture of stimulatory and depressant properties on psychomotor function dependent on the prevailing dopaminergic tone led to it being christened by Carlsson et al as dopamine stabilizers. While they show limited in-vitro affinity for the D2 receptors (OSU:Ki 450nM, ACR16:IC50>10-5M), their functional actions are suggestive of interaction with D2 receptors. The objective of this study was to evaluate in-vivo D2 occupancy of these agents in rats using [3H]raclopride over their dose range and correlate it to observed behavioral effects in animal models. OSU showed a dose dependent occupancy of D2 receptors over a range of 3-120mg/kg, SC(42-90% occupancy) with an ED50 of 4mg/kg. ACR16 on the other hand showed a dose dependent occupancy of D2 receptors over a range of 10-240mg/kg, SC (35-90% occupancy) with an ED50 of 19mg/kg respectively, after an hour of administration. Comparing it to haloperidol and clozapine, haloperidol over a dose range of 0.025-1mgkg, SC showed an occupancy range of 53 to 90% with an ED50 of 0.01 mg/kg while clozapine over a dose range of 2.5-60mg/kg, SC showed an occupancy range of 17 to 70% and an ED50 of 19mg/kg. OSU did not show catalepsy in the dose range used for the occupancy study, but in case of ACR16 weak catalepsy was observed in one out of five animals at a dose of 120mg/kg, SC. Also there was significant FOS induction in the nucleus accumbens, the amount of FOS induced by 30mg/kg of OSU & 60mg of ACR16 was equivalent to 0.1mg/kg of haloperidol or 15mg/kg of clozapine. The lack of catalepsy for clozapine and the dopamine stabilizers corresponded to low FOS counts in the dorsolateral striatum. We propose that the behavioral stabilization effects of OSU and ACR16 reported in earlier studies are related to their in-vivo D2 receptor effects. While other possibilities could exist, the current data leads us to hypothesize that drugs with a low affinity and fast-dissociation from the D2 receptor, when given in appropriate doses may show a dopamine stabilization effect while also exhibiting antipsychotic-like effects, with very low motor side-effects, in animal models.

PERINATAL PERTURBATION OF INFLAMMATORY CYTOKINE ACTIVITIES RESULTS IN DISTINCT COGNITIVE / BEHAVIORAL IMPAIRMENTS IN RODENTS; IMPLICATION IN PSYCHIATRIC DISEASES OF NEURODEVELOPMENTAL ORIGIN

H. Nawa,* M. Tohmi, N. Tsuda, Y. Watanabe, T. Someya, M. Mizuno
Molecular Neurobiol., Brain Res Inst., Niigata Univ., Niigata-city, Niigata, Japan

Maternal stress, viral infection, and obstetric complication all induce the production of inflammatory cytokines in amniotic fluids as well as in embryonic/neonatal tissues and are hypothesized to be involved in schizophrenia and its related disorders. Do cytokines mediate such environmental signals that influence brain development and later behavioral traits? Here we show that peripheral cytokine activities in immature animals exert strong and diverse influences on later behavioral/cognitive development and dopaminergic metabolism, depending on cytokine species administered. IL-1α, IL-2, IL-6, interferon-γ, or leukemia inhibitory factor (LIF) was subcutaneously administered to rat pups. These cytokines appeared to penetrate the developing blood-brain barrier to activate their own signaling pathways in the brain. During juvenile stages, neonatal interferon-γ treatment decreased motor activity whereas IL-2 increased motor activity. After adolescence, IL-1α-treated and LIF-treated rats developed cognitive/behavioral abnormalities in startle response, prepulse inhibition, social interaction, and/or working memory, some of which were ameliorated by antipsychotic drug treatment. Gross learning ability of IL-1α-treated and LIF-treated rats was normal in contextual conditioning and two-way avoidance test, however. In parallel, the IL-1α-treated animals displayed neuropathologic alterations including brain weight loss and abnormal dopamine turnover in the frontal cortex without apparent neurodegeneration. These animal experiments illustrate that, during development, inflammatory cytokine activities in the periphery can perturb dopaminergic development and induce future psychobehavioral and/or cognitive impairments. The potential genetic influences and interactions will be tested using different mouse strains receiving IL-1αas neonate.

Behavioral Impact of Perinatal Cytokine Challenges

ND, not determined

DIFFERENTIAL EFFECTS OF A FULL AND A PARTIAL DOPAMINE D2 RECEPTOR AGONIST ON GABA AND GLUTAMATE RELEASE IN THE GLOBUS PALLIDUS OF THE AWAKE RAT

W. T. O,* A. Duffy, J. C. Glennon, G. van Scharrenburg
Physiology, University College Dublin, Dublin, Ireland

Partial dopamine D2 receptor agonists are proposed to be effective antipsychotics and in contrast to classical dopamine D2 receptor antagonists they demonstrate reduced extrapyramidal motor side effects. Striatal dopamine D2 receptor blockade activates striopallidal GABA transmission which disinhibits subthalamic nucleus (STN) glutamate input to the substantia nigra (pars reticulata) (SNr) and via an excitatory feedback loop this also increases glutamate release in the external globus pallidus (GPe). The increase in STN glutamate drive on the SNr increases inhibitory nigral regulation of the motor thalamus resulting in a reduction in the excitatory drive on the (motor) cortex thought to underlie the impairment of movement associated with extrapyramidal motor side effects. In the present study we employed microdialysis in the GPe to investigate the effects of an acute oral administration of two behaviourally active doses of the full and partial dopamine D2 receptor agonists pramiprexole and terguride respectively on local GABA and glutamate release. Basal dialysate GABA and glutamate levels were 16.7±3nM and 1.4±0.3µM (n=27) respectively and remained stable over the course of the experiment (260min). Pramiprexole (0.1 and 0.3mg/kg, p.o.) was associated with a prolonged (180min) dose dependent reduction in both GABA and glutamate levels, which was already evident 20mins after drug administration (for GABA, +7 ±0.1% and -15±0.1% and for glutamate, -1±0.2% and -50±0.05% change from basal levels, respectively). This reduction may reflect a striatal dopamine D2 receptor mediated decrease in striopallidal GABA resulting in a decrease in recurrent STN-GPe glutamate release. In contrast, terguride (10 and 30mg/kg, p.o.) was associated with a short-lasting (20min) and dose dependent increase in both GABA (+19±0.1%, p≦0.005 and +9 ±0.06%) and glutamate levels (+17±0.1% and +38 ±0.02% which there-after reverted to a prolonged reduction until the end of the experiment. The finding that acute administration of terguride but not pramiprexole transiently increases pallidal GABA and glutamate release suggests that (a) partial dopamine receptor agonists such as terguride act at least in the short term, as dopamine D2 receptor antagonists within the striatum and (b) demonstrates that monitoring pallidal GABA and glutamate release may be useful in differentiating full and partial dopamine D2 receptor agonism in intact conscious rat brain.

HYPEREXCITABLE PREFRONTAL CORTEX IN ANIMALS WITH A NEONATAL VENTRAL HIPPOCAMPAL LESION

P. O'Donnell,* K. Y. Tseng, M. Kloc, B. L. Lewis
Ctr. Neuropharmacology & Neuroscience, Albany Medical College, Albany, NY, USA

A neonatal ventral hippocampal lesion (NVHL) in rats and monkeys results in a delayed emergence of behavioral anomalies, typically after puberty. We have recently identified abnormal responses to activating mesolimbic and mesocortical projections in neurons in the medial prefrontal cortex (PFC) and nucleus accumbens recorded in vivo from lesioned animals. PFC and accumbens neurons exhbited an abnormal increase in firing, which also appeared after puberty and was blocked by subchronic treatment with haloperidol. The abnormal cell firing in the nucleus accumbens was also blocked by a prefrontal cortical lesion, suggesting that the prefrontal cortex could be the site in which the absence of proper hippocampal afferents during development (an absence that can cause changes in trophic factors that reproduce conditions present during development that may lead to schizophrenia) may cause delayed deficits. To test whether prefrontal cortical neuron physiology was affected in these animals, we conducted in vitro whole-cell recordings from prefrontal cortical pyramidal neurons and interneurons in slices from adult animals that had a NVHL or a sham operation. Pyramidal neurons in lesioned animals were more excitable, as shown by an increased response to intracellular current injection and to external application of NMDA. Their response to dopamine D1 agonists was also exaggerated and their inhibition by D2 agonists was dampened. Fast-spiking interneurons were less active in lesioned animals and could not be activated by DA agonists, while interneurons from sham-operated animals exhibited the increase in firing reported for the D2 agonist quinpirole in naive animals. It is important to note that the D2 enhancement of interneuron activity seen in normal animals appeared after puberty, indicating that the DA innervation of those neurons matures at that time. These results suggest that a NVHL yields delayed changes in prefrontal cortical local circuit function and particularly in fast-spiking interneurons, which may become evident only after interneurons mature and fail to acquire their normal D2 modulation.

CUSTOM MICROARRAY ANALYSIS OF GENE EXPRESSION PATTERNS IN THE RAT PREFRONTAL CORTEX ASSOCIATED WITH CHRONIC PCP TREATMENT

L. O'Donovan,* S. Cochran, C. Winchester, J. Pratt, B. Morris
Yoshitomi Research Institute of Neuroscience in Glasgow, Glasgow, United Kingdom

Phencyclidine (PCP) is a NMDA receptor antagonist that induces schizophrenia-like symptoms in humans and exacerbates symptoms in schizophrenic patients. Previous work in our group has shown that chronic intermittent PCP treatment in rats produces similar metabolic and neurochemical deficits to those demonstrated in schizophrenia, such as metabolic hypofunction, and decreased expression of parvalbumin mRNA, a marker of chandelier cells, in the prefrontal cortex (PFC) (Cochran et al. 2003; *Neuropsychopharm*. 28: 265-275). It is therefore thought to be a valuable model for schizophrenia and, for microarray analysis, avoids the well-documented problems associated with using human post mortem brain tissue. The aim of this work was to design a custom array to assess changes in gene

expression rapidly in the chronic intermittent PCP and an acute PCP schizophrenia model, as well as observing the effect of clozapine treatment in these models. The custom array comprised more than 200 genes associated with schizophrenia, including reelin, dysbindin, neuregulin, COMT and RGS4. Arrays were spotted with 50mer oligonucleotide probes (MWG-BioTech). Total RNA was isolated from rat PFC and labelled with Cy3 or Cy5 dye using an optimised indirect aminoallyl labelling technique. Experiment and control samples were then mixed in equal amounts and hybridised to arrays. Scanning, quantification and analysis was carried out using Imagene 5.6 and GeneSight 3.2.21 software (BioDiscovery Inc.) and MAVI version 2.6.0 (MWG-BioTech). Statistical analysis allowed the identification of genes differentially regulated with PCP treatment, and also those whose differential expression is reversed by clozapine treatment. The results suggested differential regulation of genes previously implicated in schizophrenia by chronic PCP and clozapine. The data thus provide insight into the genomic changes underlying prefrontal cortex dysfunction in schizophrenia, and demonstrate a rapid approach for detecting efficacy in novel antipsychotic drug candidates. Acknowledgement for support: YRING is a collaborative venture between the Universities of Strathclyde and Glasgow and Mitsubishi Pharma Co.

SELECTIVE SEROTONIN REUPTAKE INHIBITION POTENTIATES THE SUPPRESSIVE EFFECTS OF ANTIPSYCHOTICS ON CONDITIONED AVOIDANCE RESPONDING IN RATS

C. K. Olsen
Psychopharmacology, H. Lundbeck A/S, Valby-Copenhagen, Denmark

Clinical studies have shown increase in efficacy by coadministration of selective serotonin reuptake inhibitors (SSRIs) and antipsychotics in patients with schizophrenia. Furthermore, this drug combination has proven useful within bipolar disorder. The purpose of the present study was to evaluate whether these clinical findings can be reflected in the conditioned avoidance response (CAR) model in rats. Selective suppression of CAR in rats is a method, which is considered as having high predictive validity for antipsychotic efficacy. Rats are trained in a two-way active avoidance procedure to move into the adjacent compartment (avoidance response) within 10 s upon presentation of the conditioned stimuli (tone and light) in order to avoid the appearance of the unconditioned stimulus, a 0.5 mA scrambled electric shock in the grid floor of 10 s in maximal duration. Each test session consists of a 10 trials with intertrial intervals varying randomly between 20 and 30 s. Drug test is preceded by a pre-test the day before. The rats are treated with saline injection 30 min prior to pre-test. We found that citalopram, at doses ineffective on its own (4 or 16 mg/kg, s.c.), significantly potentiated the suppression of CAR induced by threshold doses of risperidone (0.16 or 0.31 mg/kg, s.c.) without causing additional motor disturbances. In the present study citalopram in combination with antipsychotic compounds including classical, atypical as well as the newer generation of partial dopamine agonists were studied. The possible role of pharmacokinetic interactions will be discussed. Originally, the CAR test was considered to be sensitive for the detection of antipsychotic compounds acting primarily as dopamine D2 receptor antagonists. However, the present data extend more recent studies showing that the CAR test is also sensitive to modulation of the serotonergic system. Further suppression of CAR inhibition induced by antipsychotics by selective reuptake inhibition add to the value of the model as having a high predictive validity and consequently a useful tool for supporting add-on strategies.

APLINDORE (DAB-452) EXHIBITS HIGH AFFINITY DOPAMINE D2 RECEPTOR PARTIAL AGONIST ACTIVITY

M. Pausch,* J. N. Heinrich, M. Lai, K. Carroll, G. Hornby, M. Popiolek, L. Jiang, G. Stack, K. L. Marquis, T. H. Andree
Discovery Neuroscience, Wyeth Research, Princeton, NJ, USA

The pharmacological properties of the dopamine D2 receptor (D2R) partial agonist, aplindore (DAB-452), were characterized and compared to other agents in this class. Aplindore exhibited high affinity binding to both D2R short (D2RS) and long (D2RL) isoforms expressed in membranes from stably transfected CHO_K1 cells. Aplindore potently stimulated GTPγ^{35}S binding to D2RS and D2RL containing membranes that was intermediate in efficacy between that produced by the full D2R agonist quinpirole and the weak partial agonist aripiprazole. CHO_K1 cells co-expressing either the D2RS or the D2RL isoform and chimeric Gαq-proteins in which the C-terminal five amino acids of inhibitory Gα-proteins (Gαo, Gαi1, -2, Gαi3) were substituted onto the full length Gαq, facilitated detection of intracellular calcium increase ([Ca^{2+}]i) measured by fluorometric imaging plate reader (FLIPR) technology. Agonist dose-dependent responses were observed with efficacy profile (quinpirole = dopamine = pramipexole > aplindore > (+/-) 3-PPP > (-) 3-PPP > aripiprazole > SDZ-208-912) and rank-order-of-potency (dopamine = quinpirole = pramipexole = aplindore > (+/-) 3-PPP > (-) 3-PPP > aripiprazole > SDZ-208-912) that were similar for both D2R isoforms. The sensitivity and high-throughput capacity of the FLIPR assay provides a convenient approach to explore the partial agonist pharmacology of D2R-ligands and may facilitate discovery of compounds with enhanced therapeutic properties.

A MILD DISRUPTION OF SUBPLATE FUNCTION IN THE DEVELOPING PREFRONTAL CORTEX IS SUFFICIENT TO CAUSE MULTIPLE NEUROPATHOLOGICAL FEATURES OF SCHIZOPHRENIA

R. N. Rajakumar,* B. Rajakumar
Psychiatry, University of Western Ontario, London, ON, Canada

Etiology and pathogenesis of schizophrenia are currently unknown. Subplate neurons are early-generated cells in the cerebral cortex and are critical for the laminar and area specific innervation of thalamocortical fibers. Majority of subplate neurons degenerate at early third trimester in human gestation and the remainder become the NADPH-diaphorase-containing interstitial neurons of the white matter. An abnormal number and distribution of these neurons have been described in schizophrenic brains. We recently observed that in addition to directing thalamocortical fibers, subplate neurons are important for dopaminergic innervation of the cerebral cortex. Ablation of subplate neurons resulted in loss of mesocortical dopaminergic innervation, particularly to the lower layers, a feature described in schizophrenic brains. Here we demonstrate that ablation of less than 10% of subplate neurons in the developing prefrontal cortex leads to adult-onset behavioral changes characteristic of increased subcortical

dopaminergic activity, and a number of neuropathological changes described in postmortem studies of schizophrenic brains, including synaptic abnormality and loss of neuropil in the prefrontal cortex, neuronal loss and disarray in the hippocampus, and progressive ventricular enlargement. In addition, our results indicate that GABAergic synaptic abnormalities of the prefrontal cortex may precede subcortical dopaminergic hyperactivity in schizophrenia. Supported by the Ontario Mental Health Foundation.

DISSOCIATION BETWEEN BLOCKADE AND FUNCTIONAL ANTAGONISM OF D2 RECEPTORS—COMPARING ARIPIPRAZOLE TO OTHER TYPICAL AND ATYPICAL ANTIPSYCHOTICS IN ANIMAL MODELS

G. Reckless,* S. Natesan, J. Parkes, S. VanderSpek, J. Nobrega, S. Kapur
Schizophrenia-PET, Centre for Addiction and Mental Health, Toronto, ON, Canada

In most clinical studies antipsychotic action emerges when antipsychotics block about 60-65% dopamine D2 receptors, and motor side-effects appear when blockade goes beyond 80%. Aripiprazole, a recently introduced clinically effective antipsychotic exhibits EPS comparable to subjects on placebo. The emerging clinical PET data raises two issues: First, it requires much more than 60% D2 occupancy to be clinically effective (doses of 15-30 mg/d result in ~ 90% occupancy); Second, despite an occupancy range that is usually associated with EPS, patients do not show EPS different from placebo. In-vitro assays indicate it to be a partial D2 agonist, while in-vivo, animal studies have shown both presynaptic dopamine autoreceptor agonistic and postsynaptic D2 antagonistic activity. The study objective was to examine the relationship between striatal dopamine D2 occupancy and functional antagonism in rat animal models of amphetamine induced hyperlocomotion (AMPH), conditioned avoidance response (CAR) and catalepsy (CAT). Haloperidol, risperidone and clozapine were used for comparison. The results have been summarized in the table (dose mg/kg/s.c.). In the case of haloperidol and risperidone, CAT was observed at doses that produced D2 receptor occupancy >85%, while they were effective in the CAR model at a lower level [65-85%] of D2 occupancy. Clozapine was effective in the CAR model at occupancies lower than its ED50 for D2 occupancy and did not show catalepsy upto a dose of 60mg/kg (70% occupancy). These results are similar to PET studies performed in schizophrenic human subjects. However in the case of aripiprazole doses >90% did not result in catalepsy, while in the CAR model, inhibition was observed only at D2 occupancies >85%. Furthermore, aripiprazole showed significant selectivity in disrupting pharmacologically induced hyperdopaminergia (AMPH) versus its ability to lower normal endogenous dopamine tone (CAR). The observed dissociation between receptor occupancy and functional antagonism; and the preferential ability to disrupt exaggerated dopamine transmission versus endogenous tone may serve as markers for identifying other partial-agonist antipsychotic agents.

REDUCED INTERNEURON NUMBERS AND ALTERED SYNAPTIC TRANSMISSION IN THE PREFRONTAL CORTEX OF DOPAMINE D2 RECEPTOR NULL MUTANT MICE

B. Roerig,* K. Boukamel, A. Moutanni, B. Chen, J. Kao, A. Puche
Anatomy and Neurobiology, University of Maryland, Baltimore, MD, USA

Alterations in dopaminergic and GABAergic neurotransmission underlie a number of neuropsychiatric disorders. These transmitter systems closely interact in regulating prefrontal cortex function. Despite the importance of inhibitory interneurons in shaping response properties and network behavior, little is known about the factors regulating the development of different interneuron types. Inhibitory interneurons in the cortex show a wide range of morphological and physiological variation. Dopamine and dopamine receptors are involved in the development of cortical GABAergic interneurons, in particular in the prefrontal areas. The D2 receptor appears crucially involved; however its exact role is unclear. Here, we investigate the effect of a dopamine D2 receptor (D2R) null mutation on the development of GABAergic interneurons and synaptic transmission in mouse prefrontal cortex. Mice deficient for D2R show a 40% reduction in the number of interneurons expressing glutamic acid decarboxylase (GAD) and parvalbumin in all cortical layers. The reduction in interneuron number correlates with a dramatic decrease in frequency and amplitude of inhibitory spontaneous synaptic inputs to layer 5 pyramidal neurons. Evoked synaptic inputs, particularly from upper cortical layers, were also reduced in amplitude. In addition, a shift from single IPSC events in wild type to IPSC bursts in dopamine D2 receptor Null mutant (D2KO) mice was observed. Similar, but less prominent effects were also observed in excitatory inputs. To test the effect of absence of the D2 receptor and the resulting alterations in synaptic circuits on the morphological development of interneurons and postsynaptic pyramidal neurons we used particle mediated DiI labeling to measure dendritic processes. The complexity and total length of apical and basal dendrites of interneurons and layer 5 pyramidal neurons was significantly reduced in D2KO mice. In the D2KO animals large basket and chandelier cells were virtually absent, the surviving interneuron types represented mainly small basket and multipolar cells. These results suggest that the dopamine D2 receptor has a selective effect on the development of a subset of cortical interneurons. The development of excitatory neurons and excitatory synapses is also affected, which may be a direct effect or result from the impaired development of inhibitory circuits.

STRIATAL CYCLIC NUCLEOTIDE SIGNALING FOLLOWING PDE10 INHIBITION: COMPARISON TO D1 RECEPTOR ACTIVATION AND D2 RECEPTOR BLOCKADE

C. J. Schmidt,* J. F. Harms, A. Shrikhande, S. K. Wong
CNS Discovery, Pfizer, Inc, Groton, CT, USA

D1 receptor stimulation and D2 receptor blockade are believed to activate the direct (striatonigral) and indirect (striatopallidal) pathways, respectively, by augmenting excitatory corticostriatal or thalamostriatal neurotransmission. Increased striatal activity, primarily within the indirect pathway, is generally considered to be responsible for the antipsychotic activity of D2 receptor antagonists. PDE10 is a newly described cyclic nucleotide phosphodiesterase expressed exclusively by the medium spiny neurons of both the direct and indirect pathways. We have recently described the activity of the PDE10

inhibitor, papaverine, in a range of preclinical models predictive of antipsychotic efficacy. The mechanism responsible for this activity was examined and compared to that of the D2 antagonist haloperidol and the D1 agonist, SKF-81297. Like haloperidol and SKF-81297, papaverine increases tissue levels of striatal cGMP in mice via a nNOS-dependent mechanism. The increase in cGMP produced by either the D2 antagonist or the D1 agonist requires NMDA receptor activation as demonstrated by its sensitivity to MK-801. Unexpectedly, the effect of papaverine on striatal cGMP was not prevented by MK-801 pretreatment. Both dopaminergic agents and papaverine also increased striatal CREB phosphorylation presumably via increases in cAMP and PKA activity. Pretreatment with MK-801 prevented the increase in pCREB due to haloperidol but not that produced by PDE10 inhibition. The effect of all three agents on striatal cGMP was selectively prevented by pretreatment with the AMPA antagonist, CP-465022. Finally, all three agents increased the level of pERK in the striatum however this effect was not prevented by either MK-801 or CP-465022 pretreatment. The results are consistent with previous reports that D2 blockade or D1 stimulation increase striatal activity by enhancing NMDA receptor mediated neurotransmission. In contrast, striatal activation following PDE10 inhibition is not dependent upon NMDA signaling but may involve augmentation of more diverse excitatory signals including but not limited to those mediated by AMPA receptors. These results suggest that the clinical profile of PDE10 inhibitors will be distinct from that of D2 antagonists.

INCREASED STRESS RESPONSIVENESS IN POST-PUBESCENT RODENTS FOLLOWING PARTIAL DEPLETION OF DOPAMINE IN THE PREFRONTAL CORTEX

R. Scornaiencki,* N. Rajakumar
Graduate Program in Neuroscience, University of Western Ontario, London, ON, Canada

Increased responsiveness to stress plays a critical role in the manifestation of schizophrenic symptoms. Neurobiological mechanisms controlling stress responsiveness are not clear. The mesocortical dopaminergic system is highly responsive to stress and is believed to be involved in modulating subcortical dopaminergic activity in response to stress. It was hypothesized that partial loss of dopaminergic fibers in the medial prefrontal cortex (mPFC), a feature described in post-mortem studies of schizophrenia, may lead to increased stress responsiveness, and since D1 receptors are the predominant type in the mPFC, administration of D1 receptor agonists to PFC dopamine-depleted animals would restore the impaired stress responsiveness. Adult rats received bilateral stereotaxic injections of 6-OHDA following desipramine pretreatment into the mPFC to specifically destroy dopaminergic fibers. Two weeks following surgery, they were subjected to forced-swimming for 5 min. One group of rats received pre-treatment of saline, and the other group received subcutaneous injections of a selective D1 agonist, SKF38393. Results indicated that both locomotion and rearing were increased significantly in dopamine-depleted animals that did not receive the D1 agonist. Conversely, dopamine-depleted animals that did receive the D1 agonist behaved similar to sham-operated animals. Recently in a pilot study, we repeated this experiment in prepubertal rats at 5 weeks of age. Interestingly, partial depletion of dopamine in the mPFC failed to alter locomotor or rearing behaviour following acute amphetamine or forced swim stress. This data may shed light on the mechanisms underlying the age-dependent changes in locomotor hyperactivity described in animal models of schizophrenia and in delayed-onset of symptoms seen in schizophrenic patients. Supported by the Ontario Mental Health Foundation.

PHOSPHODIESTERASE 10A (PDE10A) AND PSYCHOSIS: STUDIES USING THE PDE10A INHIBITOR PAPAVERINE AND PDE10A KNOCKOUT MICE

J. A. Siuciak,* D. S. Chapin, S. A. McCarthy
Pfizer, Groton, CT, USA

PDE10A is a recently described cyclic nucleotide phosphodiesterase expressed at high levels in the brain and more specifically in the medium spiny neurons of the striatum and associated nucleus accumbens and olfactory tubercle (Seeger et al., 2003). This localization suggests that PDE10A inhibitors may provide therapeutic benefit in the treatment of diseases involving these brain regions. We have demonstrated that papaverine (PAP) is a potent and selective inhibitor of recombinant rat PDE10A (Schmidt et al., ICOSR 2003). The aim of the present studies was to assess the activity of PAP in animal models of antipsychotic activity. We have previously reported the preparation and initial behavioral characterization of PDE10A knockout mice (Siuciak et al., ICOSR 2003; McCarthy et al., SFN, 2004). These studies have also assessed the effects of PAP in both wild-type (WT) and homozygouse knockout (KO) mice to verify mechanism of action. PAP, like haloperidol, clozapine, risperidone and ziprasidone, dose-dependently inhibited conditioned avoidance responding and antagonized both PCP- and d-amphetamine-induced hyperactivity. PAP did not produce catalepsy, but did potentiate the catalepsy produced by a low dose of haloperidol. In the conditioned avoidance test, WT and KO mice responded similarly to haloperidol and clozapine, however, the response to PAP was negligible in the KO mice, suggesting that inhibition of PDE10A mediates its actions in this model. Both male and female KO mice showed decreased baseline locomotor activity compared to WT mice. The response of both WT and KO mice to the locomotor stimulating effects of both PCP and methamphetamine (MET) were examined. WT mice showed a dose-dependent hyperlocomotor response to PCP, however, the PDE10A KO mice showed a blunted response to PCP compared to the WT mice. In contrast, both WT and KO mice showed similar levels of MET-stimulated locomotor activity. These data suggest that PDE10A plays a modulatory role on rodent locomotor behaviors and deletion of the PDE10A gene effects reponses to PCP. The present results demonstrate that papaverine has a pharmacologic profile in behavioral models that is similar to that of the atypical antipsychotics clozapine, ziprasidone and risperidone, but different from haloperidol. Thus, PDE10A inhibitors have the potential to be a novel approach in the treatment of psychotic symptoms in patients with schizophrenia.

UNDERSTANDING THE EARLY-ONSET OF ANTIPSYCHOTIC ACTION: AN ANIMAL AND COMPUTATIONAL MODEL

A. J. Smith,* M. Li, S. Kapur
Psychology, McMaster University, Solihull, United Kingdom

Introduction: All known antipsychotic drugs (APDs) block the dopamine D2-receptor. Although stable dopamine receptor blockade is achieved within the first few days of treatment, it has traditionally been thought that antipsychotic action shows a delayed onset of 2-3 weeks. Recently, this "delayed onset" hypothesis has been challenged by the "early onset" hypothesis, which suggests that the action of APDs can be observed immediately following drug treat-

ment, with asymptotic benefit being reached after 4-6 weeks. At present there are no animal models to study this temporal course. Since conditioned avoidance (CA) disruption provides an established animal model of antipsychotic action, we undertook an experimental and computational study to examine the temporal course of APD-induced avoidance disruption. Methods: Twenty four male Sprague-Dawley rats were first subjected to 11 sessions of two-way CA training. They were then tested under increasing doses of haloperidol (0.03, 0.05, 0.07mg/kg, ip) with a vehicle 'retraining' session inserted between each dose. This protocol allows us to examine within session and across session changes in CA, and to understand the temporal properties of dopamine blockade within the context of a computational model. Results: Two key observations were: 1) an immediate change in avoidance responding at the beginning of each new session; 2) an additional progressive change in responding that decreased towards a dose-dependent asymptote during each drug session, and that increased back towards baseline during drug-free sessions. The computational model simulates these findings by proposing dual roles for dopamine in both learning new associations and performing on the basis of old associations. Conclusion: Empirical observations and our computational model suggest that dopamine blockade impacts both the performance and learning of an avoidance response. We suggest that these two modes of dopaminergic action can account for both the immediate and subsequent components of antipsychotic action. The computational model also paves the way for an investigation into the functional role of dopamine in the onset of psychosis itself.

A MODEL OF EFFECTS OF KETAMINE, A NMDA GLUTAMATERGIC ANTAGONIST, ON EXECUTIVE CONTROL IN MONKEYS

G. Stoet,* L. H. Snyder
Anatomy & Neurobiology, Washington University in St. Louis, St. Louis, MO, USA

Executive control is the mental capacity to plan, coordinate, and regulate how we respond to stimuli. The capacity to switch between different tasks is an important index of executive control commonly used in psychiatric tests. We studied an animal model of executive control. Monkeys performed trials of two visual discrimination tasks, which were randomly interleaved. On each trial, the monkey was presented a task cue, which informed him to perform either a color or a shape discrimination on the following stimulus. The animal responded with a left or right button press to the subsequent stimulus. We measured response time as a function of whether a trial followed the same task (repeat trial) or a different task (switch trial), and whether stimuli required a low or a high level of selective attention. Monkeys are not slower on switch trials, unless the intertrial interval (ITI) is extremely short. This is different from humans, who reliably show switch costs. Some human studies have reported that ketamine administration lengthens switch times. Although our data show a dose-related increase in reaction time, we found no specific impairment on the ability to switch between tasks. There are a number of differences between task-switching studies that report increased task-switching costs and ours. The animals in our study were highly trained before we measured the effect of ketamine on behavior. Another difference is methodological. Many of the human studies required subjects to use short-term memory to detect the occurrence and type of task switch (e.g., Wisconsin Card Sorting Task, WCST), while we directly instructed the task to be performed on each trial. Thus it is possible that the effect of ketamine on switch times in human studies was mediated by an effect on short-term memory and not on executive control per se. In conclusion, the capacity to switch between tasks is unaffected by ketamine in monkeys. Factors other than executive control might contribute to task switching problems in humans tested using WCST or a related paradigm. Finally, our results suggest that ketamine may be of limited use for understanding executive disorders in animal models. Supported by Conte Center Grant MH 71616.

DIFFERENTIAL EFFECTS OF CLOZAPINE AND HALOPERIDOL ON MAPK ACTIVATION IN CORTICAL NEURONS

S. Sundram,* A. Pereira, G. Fink
Mental Health Research Institute of Victoria, Melbourne, VIC, Australia

Differentiating the molecular bases for the actions of the atypical antipsychotic clozapine and the typical drug haloperidol may allow understanding of the different side effect and clinical profiles of the two drugs which may in turn open avenues for new improved therapeutics for psychotic disorders. One promising lead is the neuronal mitogen activated protein kinase (MAPK) pathway. This intracellular pathway mediates many behavioural, cognitive and neural processes implicated in the pathology of schizophrenia(1). Furthermore, acute administration of clozapine decreased and haloperidol increased phosphorylation of the MAPK enzymes, ERK 1 and 2 in the dorsal striatum of the rat(2) suggesting this pathway may be implicated in mediating extrapyramidal side effects seen with haloperidol but absent with clozapine. We investigated whether these contrasting effects of clozapine and haloperidol on ERK 1 and 2 phosphorylation were also evident in cortical neurons possibly mediating the different antipsychotic effects of these two drugs. Using a primary murine mixed cortical culture system, haloperidol and clozapine (10^{-4}M) were incubated for 10 or 60 minutes. Activation of ERK 1 and 2 (pERK1 and 2) was measured with protein immunoelectrophoresis using phospho specific antibodies and results standardised against non-drug control wells and total ERK 1 and 2 levels. Both clozapine (9±6% of control) and haloperidol (43±11%) significantly ($p<0.01$; 0.02) decreased pERK1 at 10 minutes, however, only clozapine increased pERK1 levels by 2.5 fold at 60 minutes. Neither clozapine nor haloperidol altered significantly pERK2 levels at 10 minutes but clozapine increased levels by 3.3 fold at 60 minutes, an effect not observed with haloperidol. Therefore as in the striatum, clozapine and haloperidol exert differential effects in cortical neurons on a signalling pathway critical to cognitive functioning(3) suggesting a novel avenue through which clozapine might exert its beneficial effects on cognitive function in schizophrenia. 1. Kyosseva (2004) *Int. Rev. Neuorbiol*. 59 2. Pozzi et al. (2003) *J. Neurochem*. 86 3. Thomas and Huganir (2004) *Nat. Rev. Neuroscience* 5.

ELECTROPHYSIOLOGICAL PROPERTIES OF HIPPOCAMPAL AND PREFRONTAL CORTICAL AMPA RECEPTORS FOLLOWING SUBCORTICAL DOPAMINERGIC HYPERACTIVITY—RELEVANCE TO SCHIZOPHRENIA

V. Suppiramaniam,* T. Vaithianathan, N. Rajakumar
Pharmacal Sciences, Auburn University, Auburn, AL, USA

Synaptic dysfunction is now considered as the central problem in schizophrenia. In addition to the abnormal number, affinity and density of synapses, altered channel properties may play important role

in mediating abnormal neuronal function seen in schizophrenia. We studied single channel properties of AMPA receptors in isolated synaptosomes in combination with whole cell patch clamp recordings on slices from the prefrontal cortex, or the hippocampus from animals that showed chronic subcortical dopaminergic hyperactivity following neurodevelopmental lesions. The single channel recordings of synaptosomes have indicated that the open probability of AMPA is decreased by 70% in the prefrontal cortex and 55% in the hippocampus in animals with subcortical dopaminergic hyperactivity. After addition of CX516 (ampakine), the open probability was partially restored and is now decreased only by 45% and 35%. The whole cell patch clamp experiments showed a considerable reduction in both amplitude and frequency of AMPA-EPSCs in the prefrontal cortex and the hippocampus in animals with subcortical dopaminergic hyperactivity. Results indicate that decreased cortical and hippocampal AMPA receptor function may occur secondary to subcortical dopaminergic hyperactivity, and this may partly contribute to cognitive impairment seen in schizophrenic patients. Supported by the Ontario Mental Health Foundation.

COMBINED ALPHA2- AND D2 RECEPTOR BLOCKAGE ENHANCES CORTICAL GLUTAMATERGIC TRANSMISSION AND REVERSES COGNITIVE IMPAIRMENT INDUCED BY MK-801 IN THE RAT

T. H. Svensson,* M. M. Marcus, K. E. Jardemark, M. L. Wadenberg, P. Hertel
Physiology and Pharmacology, Karolinska Instititutet, Stockholm, Sweden

Clozapine (CLOZ) shows superior efficacy compared with conventional antipsychotic drugs (APDs), particularly on cognitive and negative symptoms, in spite of lower D2 receptor (D2R) occupancy in brain. In contrast to most APDs, CLOZ has a high affinity for alpha2 adrenoceptors (alpha2Rs), and adjunctive treatment with the alpha2R antagonist idazoxan (IDA) enhances the efficacy of typical D2 antagonists in treatment-resistant schizophrenia. Adding IDA also enhances the antipsychotic-like effect of low doses of the selective D2/3 antagonist raclopride (RAC) in the rat. CLOZ, but not typical APDs, as well as the combination of RAC and IDA, also produces a marked increase in dopamine (DA) release in the medial prefrontal cortex (mPFC), which is significant because of the role of prefrontal DA in cognitive functioning. In addition, CLOZ potentiates N-Methyl-D-Aspartate (NMDA) receptors in the mPFC via a DA-mediated activation of D1 receptors (D1Rs) . Thus, facilitation of both DA- and glutamate-mediated transmission in the PFC may contribute to the superior efficacy of CLOZ. Using intracellular recording we studied the effects of RAC, IDA and a combination of RAC and IDA, as well as CLOZ, on electrically evoked excitatory postsynaptic potentials and currents in pyramidal cells of the rat mPFC. Neither RAC nor IDA alone caused any significant potentiation. In contrast, the combination of RAC and IDA completely mimicked the potentiation by CLOZ. This effect was abolished by previous monoamine depletion, showing that it is mediated via presynaptic alpha2Rs, as well as blocked by a selective D1R antagonist (SCH 23390) confirming the mediation by D1Rs. Using the 8-arm radial maze we also studied the effects of CLOZ, a low dose of RAC, IDA, and the combination of IDA and RAC, on the impairment of cognitive function in the rat induced by the NMDA receptor antagonist MK-801. Both CLOZ and a combination of RAC and IDA completely restored cognitive functioning, whereas neither RAC nor IDA alone had any significant effect. Thus, adding alpha2R blockage to a D2R antagonist not only augments dopaminergic, but also glutamatergic neurotransmission in the PFC, and concomitantly improves cognitive dysfunction, in complete analogy with the effects of CLOZ. These results indicate that presynaptic alpha2R blockage has a major role in the superior effect of CLOZ on cognitive and negative symptoms in schizophrenia.

CHRONIC EXPOSURE TO TYPICAL OR ATYPICAL ANTIPSYCHOTICS IN RODENTS: TEMPORAL EFFECTS ON CENTRAL ALPHA 7 NICOTINIC ACETYLCHOLINE RECEPTORS

A. V. Terry,* D. Gearhart, S. Mahadik, S. Warsi, L. Davis
College of Pharmacy, University of Georgia, Augusta, GA, USA

Several studies suggest that cholinergic deficits in the brains of schizophrenic patients may contribute to the cognitive dysfunction. For example, reduced numbers of alpha 7 nicotinic acetylcholine receptors (nAChRs) in the hippocampus have been hypothesized to contribute to the alterations in auditory gating and the impairments of sustained attention often observed in schizophrenia. However, while both typical and atypical neuroleptics are routinely used in the therapeutics of schizophrenia, little is known about their effects on the cholinergic system when they are administered for an extended period of time (which is quite often the case). In the present study in rats, the residual effects of prior exposure to representative typical and atypical neuroleptics on the densities of alpha 7 nAChRs in the brain were investigated. Rats were exposed to haloperidol (HAL, 2.0 mg/kg/day), chlorpromazine (CPZ 10.0 mg/kg/day) or the atypical neuroleptics, risperidone (RISP, 12.5 mg/kg/day) or olanzapine (OLZ, 10.0 mg/kg/day) in drinking water for periods of 90 or 180 days. The test subjects were subsequently given a washout period (i.e., returned to normal drinking water) for two weeks and then sacrificed. Quantitative receptor autoradiography was subsequently performed using 16 micron saggittal slices of whole brain incubated with [125I]-alpha-bungarotoxin to measure alpha 7 nAChR densities. The results indicated only a few minor changes in receptor densities in the brains of animals that received either class of neuroleptic for 90 days. However, prior exposure to both classes of neuroleptics for 180 days resulted in moderate, but significant decreases in binding densities in a number of brain regions (including cortex and hippocampus). The effect was particularly notable with risperidone in which decreases were noted in 25 out of the 36 brain regions that were analyzed. These data indicate that certain (commonly used) typical and atypical neuroleptics are associated with time dependent and persistent negative effects on important biological substrates of memory such as the alpha 7 nicotinic receptor. Supported By: NIMH (MH 066233).

EFFECT OF ANTIPSYCHOTIC MEDICATIONS ON THE X-RAY IDENTIFICATION OF THE ORDER AND STRUCTURE OF MODEL MEMBRANES

C. Tessier,* P. Nuss, F. Ferreri, M. Ferreri, C. Wolf
Inserm U538, Paris VI University, Paris, France

The aim of our study is to explore the modifications induced by several antipsychotics compounds on the organisation and order of a membrane model mimmicking a synapse membrane. Previous works have demonstrated the high intercalation potency of chlorpromazine

in model membranes mimicking cell membranes, in particular synapses membranes. This may suggest that, independently to their receptor binding properties, antipsychotic medications may exert part of their therapeutical properties via changes induced in the order and structure of the membranes. One can anticipate that, due to their different 3-D structure and polarity, the antipsychotic compounds may interfere specifically and differently on model membranes. We prepared samples of a ternary mixture of phospholipids (PL) [phosphatidylcholine, sphyngomyeline and cholesterol] in which a pure powder (0,5% and 1%) of antipsychotic medication was including during their preparation. In order to get less interference with water still remaining in these model membranes, a various degree of deshydratation was obtained by adding PVP into the samples. X-ray diffraction methods, when applied to PL model membranes, allows the calculation of the repetitive distance of the PL polar head between a single bilayer structure and all the piled bilayers. Intercalation processes may thus be determined by the measurement of the d-spacing between 2 polar heads; the organisation of the PL inside of the membrane can also be approximate by the analysis of the diffractogram shape. Several antipsychotic compounds have been studied at 0,5% and 1% concentration. The samples were studied at 2 temperatures levels (25C and 37C) and with a various deshydratation state (0 to 60% concentration of PVP). The studied antipsychotic compound were: haloperidol, chlorpromazine, risperidone and 9-OH risperidone, olanzapine, aripiprazol and quetiapine. The measures were assessed at Daresbury synchrotron (Daresbury, UK) and Spring 8 (Japan). Two major parameters were used in order to establish differences in the diffractogram patterns within the different antipsychotics: repetitive distance between polar heads (d-spacing) and measure of the mid-bilayer signal intensity. Significant differences could be seen on these two parameters suggesting for each antipsychotic studied, a unique intercalating profile, in particular a location of the antispychotics more frequently between the fatty acid chains than between the polar heads.

OLANZAPINE AND FLUOXETINE EFFECTS ON HIPPOCAMPAL PREGNENOLONE AND PERIPHERAL DEOXYCORTICOSTERONE: RELEVANCE TO THERAPEUTIC EFFICACY

W. T. Trost,* R. Khisti, L. J. Shampine, J. A. Lieberman, G. Parke, A. L. Morrow, C. E. Marx
Duke University Medical Center and Durham VA, Durham, NC, USA

Olanzapine and clozapine elevate the GABAergic neuroactive steroid allopregnanolone (ALLO) to physiologically relevant concentrations in rodent cerebral cortex (Marx et al). Fluoxetine also elevates ALLO (Uzunov et al). Pregnenolone (PREG) is a potential precursor to all steroids, and PREG and its sulfated derivative demonstrate pronounced effects on learning and memory in rodents (Flood et al, Akwa et al, Vallee et al). Deoxycorticosterone (DOC) is a precursor to THDOC (tetrahydrodeoxycorticosterone), a neuroactive steroid with actions at GABAA receptors comparable to ALLO. We therefore investigated neuroactive steroid alterations following olanzapine, fluoxetine, and the combination of both agents on hippocampal and peripheral neuroactive steroids. Male rats (n=8-10 per condition) were injected IP with vehicle, olanzapine, fluoxetine, or the combination of both agents in high-dose (0, 10, 20, or 10/20 mg/kg, respectively) and low-dose (0, 5, 10, or 5/10 mg/kg, respectively) experiments. The neuroactive steroids PREG and ALLO were determined by gas chromatography/mass spectrometry, preceded by HPLC. DOC levels were determined by radioimmunoassay. Hippocampal PREG levels were significantly elevated following olanzapine, fluoxetine, or the combination of these agents in both the high-dose (ANOVA $p=0.0065$, post-hoc Dunnett $p< 0.05$ for all 3 groups) and low-dose (ANOVA $p<0.0001$, post-hoc $p<0.01$ for all 3 groups) experiments. Hippocampal ALLO levels were also elevated in all three groups. Serum DOC levels were significantly elevated following olanzapine, fluoxetine, or the combination in the high- and low-dose experiments. PREG levels were positively correlated with DOC and ALLO levels in both the high-dose ($r=0.83$, $r=0.73$, respectively) and low-dose experiments ($r=0.87$, $r=0.45$, respectively). PREG increases robustly in rodent hippocampus following acute administration of olanzapine, fluoxetine, or the combination of these agents. Since PREG and its sulfate enhance learning and cognitive performance in rodents, increases in PREG may potentially contribute to effects on cognition following olanzapine or effects on concentration in patients with depression following fluoxetine. Since PREG alterations have been linked to depression in humans (George et al), olanzapine- and fluoxetine-induced alterations in this neuroactive steroid may contribute to the antidepressant actions of these compounds and represent a novel treatment strategy.

STIMULATION OF THE ENTORHINAL CORTEX POTENTLY INHIBITS PREFRONTAL CORTICAL PYRAMIDAL NEURON ACTIVITY

O. Valenti,* A. A. Grace
Neuroscience, Psychiatry, and Psychology, University of Pittsburgh, Pittsburgh, PA, USA

The prefrontal cortex (PFC) in both rat and primate plays an important role in cognitive processes such as behavioral flexibility and set shifting; factors known to exhibit deficits in schizophrenia patients. Moreover, recent studies suggest that pathophysiology within the PFC may underlie the prodromal deficits observed in schizophrenia and ultimately be a trigger for the development or psychosis later in life. Our previous findings showed that disconnection of the hippocampal-PFC circuit selectively disrupts retrieval of information during delayed responding. Anatomical studies in rats indicate that the entorhinal cortex (EC) projects extensively to the superior layers of PFC and such widespread cortical projections of the EC arise only from a restricted group of cells in the ventral bank of the rhinal fissure, close to or at the border between the entorhinal and perirhinal cortices. The majority of these projections are glutamatergic, but may also inhibit PFC output neurons via synaptic excitation of GABAergic interneurons. We have employed single unit extracellular recordings to characterize the physiological role of EC activation on the spontaneous activity of mPFC pyramidal cells in anesthetized male Sprague-Dawley rats. In our experiments a local, single-pulse stimulation of 0.5 or 1 mA of amplitude, 250 msec of duration and 0.5 Hz of frequency was delivered to the EC. In ~ 50% of the prelimbic and infralimbic PFC neurons examined, EC activation induced a powerful inhibition (latency of ~37 msec), followed by a rebound excitation. Furthermore, 12% of the cells that failed to respond at low stimulation currents presented a similar response pattern when stimulated at higher current intensities. In contrast, approximately 15% of the recorded pyramidal neurons exhibited a short latency excitation (~25 msec) followed by a rebound inhibition following EC stimulation. Therefore the EC produces primarily an inhibitory response within the PFC. Moreover, this potent inhibition may mask a direct excitatory response from this region.

SPATIAL MEMORY IMPAIRMENTS ASSOCIATED WITH PERINATAL ASPHYXIA: AN ANIMAL MODEL FOR SCHIZOPHRENIA

T. Wakuda,* K. Suzuki, Y. Iwata, T. Watanabe, N. Takei, K. Sato, N. Mori
Department of Psychiatry, Hamamatsu University School of Medicine, Hamamatsu, Japan

Epidemiological studies suggest that obstetric complications, especially in the perinatal period, increase the risk of schizophrenia. In particular, hypoxic brain insults at birth are postulated to be a plausible cause. We have previously reported that an animal model of perinatal asphyxia may serve as a model for schizophrenia, showing that asphyxia-exposed and grow-up rats incurred hyperlocomotion after receiving methamphetamine, indicative of a long-lasting abnormality in the dopaminergic (DA) system of the brain. (Suzuki et al. *Schizopr Res*. 53: 241-2, 2002). We further investigated behavioral traits in this asphyxia model, in particular cognitive functions. We assessed performance of spatial working memories and reference memories in asphyxia-exposed rats using an eight-arm radial maze. Male Sprague-Dawley fetuses were exposed to asphyxia, which was done by immersing a fetus-containing uterus horn in water bath at 37°C for 15 min before Cesarean section (A group, n=9). Fetuses delivered from the other uterus horn of the same mother rats without asphyxia were used as Cesarean sectioned controls (C group, n=8), and rats bone spontaneously were used as vaginally delivered controls (V group, n=6). At the age of nine months, rats underwent 10 sessions for training in a four-arm-baited eight-arm radial maze task to achieve a baseline performance. After the training sessions, the number of entries into the never-baited arm was counted as a reference memory error (RME), and the number of re-entries into the arms, where the baits had already been eaten, was regarded as a working memory error (WME). The number of RME and WME for five consecutive sessions was compared between the three groups. The A group rats (2.33±0.15) showed a significantly increased RME compared to the V group rats (3.64±0.34)(p=0.02); however, there was no significant difference in WME among the three groups. These results further support the notion that animal asphyxia models serve as a model for schizophrenia since the disorder has been reported to have memory impairments as demonstrated in our rat models.

PERINATAL ASPHYXIA DISRUPTS PREPULSE INHIBITION OF ACOUSTIC STARTLE REFLEX IN ADULT RATS

T. Watanabe,* K. Suzuki, Y. Iwata, T. Wakuda, N. Takei, K. Sato, N. Mori
Department of Psychiatry, Hamamatsu University School of Medicine, Hamamatsu, Japan

Epidemiological studies indicate that asphyxia at birth increases the risk of schizophrenia in adulthood. We have previously reported that an animal model of perinatal asphyxia may serve as a model for schizophrenia, showing that asphyxia-exposed and grown-up rats incurred hyperlocomotion after receiving methamphetamine, indicative of a long-lasting abnormality in the dopaminergic (DA) system of the brain.Auditory gating deficits measured by prepulse inhibition (PPI) of acoustic startle reflex (ASR) have been demonstrated in patients with schizophrenia and proposed to be a biological marker for schizophrenia.We thus investigated behavioral traits in this asphyxia model, in particular the sensori-motor system. Sprague-Dawley rat fetuses were exposed to asphyxia from one uterus horn as an asphyxia group (A group, n=11), and fetuses delivered from another uterus horn of the same mother rats without asphyxia were used as the Cesarean sectioned group (C group, n=11). Fetuses borne spontaneously were used as the vaginally delivered control group (V group, n=10). At the age of 9 months, startle challenge was performed during the light phase. Two startle chambers (SR-LAB, San Diego Instruments, San Diego, CA) were placed in a sound-attenuated room, and the scale-responses sensitivities were calibrated using an SR-LAB startle calibrating system. After a 1-min acclimation period in the chamber to 70 dB background noise, rats were exposed to two stimulus types presented in a pseudorandom order: a 120dB 40ms noise burst (P) or P preceded 100ms earlier by 80dB 20ms noise burst (pP), with a variable intertrial interval (average 15sec) for 16 trials (6 prepulse trials and 10 pulse alone trials). The startle amplitude for stimulus was defined as the average value of trials measured in arbitrary units. The percentage PPI was defined as 100-[(startle amplitude on pP trials/startle amplitude on P trials)x100]. The A group showed a significant PPI deficit compared with the V group (p=0.039), although there was no difference in PPI between the A and C groups (p=0.17). The finding of impaired sensori-motor gating in hypoxia-exposed rats further supports the notion that asphyxia animal models may serve as a model for our understanding of schizophrenia in humans.

TRANSCRIPTIONAL PROFILING OF POST-NATAL CORTICAL DEVELOPMENT

A. H. Wong,* M. O. Semeralul, P. C. Boutros, O. Likhodi, H. H. Van Tol
Psychiatry, University of Toronto, Toronto, ON, Canada

Background: There is substantial evidence of both gross and histological pathology involving the prefrontal cortex (PFC) in schizophrenia. Corticogenesis and neuronal migration occur in utero, but significant remodeling of the cortex continues into adolescence. Post-natal changes in the large-scale patterns of cortical gene expression remain poorly understood. Disturbances of later developmental events may be more relevant to neuropsychiatric disorders like schizophrenia and autism that have an onset in childhood or adolescence. Objectives: (1) To use expression microarrays to describe both the higher-order organization of gene transcription and the expression of specific functional gene clusters relevant to cortical development and differentiation. (2) To identify novel members of known functional gene groups through analysis of co-regulated expression trajectories. Methods: Total RNA samples were prepared from PFC of male C57BL/6 mice at postnatal weeks 2 to 10 inclusive. Target cRNA (n=4) was then synthesized and hybridized to high density Affymetrix MOE430A mouse expression arrays containing 22,690 distinct genes and expressed sequence tags (ESTs). Following GCRMA preprocessing, gene-wise linear models were fitted. The model-based p-values were then moderated with empirical Bayes and false-discovery rate corrections. Independent validation of selected candidate genes will follow using quantitative RT-PCR for RNA and Western blot analysis of protein expression. Functional cluster analysis as well as promoter sequence and transcription-factor binding site analysis will be presented. Results: We found substantial numbers of differentially-expressed genes between developmental stages. Hierarchical cluster analysis indicates that the vast majority of significant gene-expression changes occur between weeks 2 and 5. There appears to be a critical developmental window between 4 and 5

weeks after birth, but that the overall pattern involves a gradual change. Among the differentially expressed genes are MARCKS-like protein and neuronatin, which are known to be involved in neurodevelopment. Discussion: Our data provide an overall map of developmental changes in cortical gene expression in the postnatal period. Ongoing pathway and ontology analysis may identify genes not previously implicated in this period of neurodevelopment, and may introduce novel candidate genes involved in mediating the onset of childhood and adolescent neuropsychiatric disorders.

QUETIAPINE REVERSES THE SUPPRESSION OF HIPPOCAMPAL NEUROGENESIS CAUSED BY REPEATED RESTRAINT STRESS

H. Xu,* C. Luo, X. M. Li
Department of Psychiatry, University of Saskatchewan, Saskatoon, SK, Canada

Hippocampal neurogenesis has been extensively studied and associated with the pathophysiology and pharmacotherapy of psychiatric disorders. In the present study we used an established repeated restraint stress (RS) animal model to compare the post-stress time-courses of neurogenesis in subgranular zone (SGZ) of the dentate gyrus of quetiapine- and vehicle-treated rats. This drug has been shown to protect PC12 cells against the cytotoxic effects of various treatments including serum withdrawal and addition of MPP+ or amyloid beta peptide. Also it was shown to attenuate chronic stress-induced decrease of brain-derived neurotrophic factor levels in rat hippocampus. We wondered if this drug could reverse the suppression of hippocampal neurogenesis by stress. The levels of hippocampal neurogenesis were measured as the numbers of bromodeoxyuridine (BrdU)-labeled and phosphorylated cAMP response element-binding protein (pCREB)-positive cells in SGZ by using immunohistochemical methods. After repeated RS, the numbers of BrdU-labeled and pCREB-positive cells in SGZ were significantly decreased as compared to non-stress controls. Post-stress administration of quetiapine for one or three weeks reversed the stress-induced decreases in the numbers of BrdU-labeled and pCREB-positive cells in SGZ to the non-stress levels whereas the indices remained at lower levels in the vehicle-treated rats. This reversal effect of quetiapine on the stress-induced decrease in hippocampal neurogenesis provides a new insight into the possible mechanisms of actions of the drug on patients with schizophrenia and depression.

DOES HOMER1A INDUCTION REFLECT DOPAMINE DIFFERENTIAL MODULATION BY ANTIPSYCHOTICS? COMPARISON TO DOPAMINE TRANSPORTER BLOCKADE

A. de Bartolomeis,* A. Ambesi-Impiombato, F. Panariello, C. Tommasetti, G. Muscettola
Neuroscience and Behavioral Sciences, Laboratory of Molecular Psychiatry Univ. of Naples Federico II, Naples, Italy

Dopamine-glutamate interaction is thought to play a relevant role in the pathophysiology of psychosis. Several lines of evidence suggest a potential impact of antipsychotics on the glutamatergic system. We have previously demonstrated that typical and atypical antipsychotics may modulate differentially the gene expression of Homer 1 a key postsynaptic density protein in glutamate metabotropic receptors regulation (de Bartolomeis et al., 2002; de Bartolomeis and Iasevoli, 2003). Here we explored the putative differential expression of Homer 1a and Ania 3, a gene related to Homer family, in cortical and subcortical regions of Sprague-Dawley male rats brain after haloperidol (1.0 mg/kg), or quetiapine (15 and 30 mg/kg) or GBR12909 (30 mg/kg) or vehicle i.p. treatment. Quetiapine was chosen based on its in vivo demonstrated fast dissociation from dopamine D2 receptors. Molecular imaging was performed by means of quantitative in situ hybridization on 12 microns coronal section. A significant increase of Homer 1a mRNA was detected in the caudate putamen of haloperidol treated rats compared to saline and to both 15mg and 30 mg quetiapine treated rats (ANOVA: p=0.0131). Dopamine transporter blockade by GBR 12909 showed a trend to an increased induction of Homer 1a specifically in the dorsolateral caudate putamen. Homer1a is an inducible early gene belonging to a family of proteins including also constitutive forms (Homer1b/c, 2 and 3) that can multimerize and interact with mGlur1/5 on the surface of the membrane and with several intracellular molecules such as IP3R and RyR, key molecules in the regulation of intracellular calcium. Homer 1a cannot multimerize (due the absence of C-C coil domain) and its induction can disrupt the interactions of the constitutive forms and may represent a molecular mechanism to prevent an excess of intracellular calcium elevation. The putative relationship between calcium elevation and dopamine receptor blockade needs to be clarified. The lack or weak induction of Homer 1a gene expression in rat caudate-putamen after acute administration of the atypical antipsychotic agent quetiapine as opposed to treatment with the typical agent haloperidol is consistent with the hypothesis that Homer 1a expression increase could be related to D2 receptor affinity or receptor dissociation and mirror at molecular level the onset of extrapyramidal movements. The study was partially supported by an unrestricted grant from Astra Zeneca Italy.

11. Psychology, Neuro-

THE RELATIONSHIP BETWEEN NEUROCOGNITION AND FUNCTIONAL MEASURES IN SCHIZOPHRENIA

D. Abi-Saab,* J. Fiszdon, E. Perry, M. Usman, N. Rajhans, M. Bell, J. Krystal, D. C. D'Souza
Psychiatry, Yale School of Medicine, New Haven, CT, USA

Background: Social skills, medication management abilities, and daily living skills are impaired in schizophrenia. Green (2000) concluded that functional outcome measures are related to overall neurocognitive functioning and mostly associated with deficits in memory and attention. The purpose of this report is to highlight the predictive value of cognitive measures on various functional measures. Methods: The relationship between functional outcome measures and neurocognitive functioning was studied in patients with schizophrenia (N=18; Age: 45.8 ± 8.6) as part of an on-going study investigating the combination of pharmacotherapy and cognitive training. Patients performed a battery of neuropsychological tests and functional measures at baseline. Neuropsychological measures tested the domains of memory, attention, and executive functioning and included tests such as the WAIS-III, the Hopkins Verbal Learning Test, and the Wisconsin Card Sorting Test (WCST). Functional assessment measures included the Medication Management Ability Assessment (MMAA), Social Skills Performance Assessment (SSPA), and the UCSD Performance-Based Skills Assessment (UPSA). Significant pearson correlations were entered in separate stepwise regression analyses for each functional measure. Results: Performance skills in the areas of planning, comprehension, and communication as measured by the UPSA were significantly correlated with measures of intellectual, executive, and memory functioning ($r \geq 0.5$; $p \leq .05$), with the WCST perseverative errors accounting for 75 % of the variance. In addition, patients who were employed at study entry performed significantly better on the UPSA as compared to patients who were not (53.00 ±11.2 vs. 43.7 ±6.7). Social skills performance significantly correlated with measures of attention (33 % of the variance) and memory, whereas medication management ability correlated with only cued memory recall (39% of the variance). Finally, amongst the functional measures, only the MMAA and the UPSA were positively correlated. Discussion: Functional outcome measures are not unitary and can be differentially affected by cognitive functioning. Social skills depend on both attention and memory and are not related to the other measures. Functional capacity in planning, comprehension, and communication is related to executive functioning, memory, and overall intellectual ability whereas the ability to manage medications depends on cued memory recall.

EMOTIONAL WORKING MEMORY IN SCHIZOPHRENIA

A. Aleman,* M. Van 't Wout, R. S. Kahn
Dept Psychiatry, Univ Medical Center, Utrecht, Utrecht, Netherlands

It has recently been shown that emotional saliency can impede working memory performance in healthy people. Based on models of abnormal fronto-limbic circuits in schizophrenia on the one hand, and of abnormal saliency processing on the other hand, we hypothesized that this emotional interference effect would be exaggerated inschizophrenia. We tested this prediction by asking schizophrenia patients and healthy subjects to perform two working memory tasks, one with emotional stimuli (fearful and angry faces) and one with neutral stimuli (numbers). Participants were not only required to hold information on line in working memory, but also to compare this information to other information presented on a computer screen. The results confirmed a general effect of emotional saliency on reduction of working memory performance across groups, F=10.9, p=0.003. However, there was also a significant interaction between group and emotional saliency, F=5.9, p=0.025. The increase in errors on the working memory task relative to the neutral working memory task was considerably larger in patients than in healthy subjects. We conclude that emotional factors disproportionally affect working memory in schizophrenia. Our findings suggest that abnormalities in the processing of emotional saliency might account, in part, for working memory impairments in schizophrenia.

PROGRESSION OF NEUROLOGICAL SOFT SIGNS DURING ADOLESCENCE IN HEALTHY POPULATION AND IN PATIENTS WITH FIRST EPISODE PSYCHOSIS

C. Arango,* A. Zabala, D. Moreno, O. Robles, M. T. Burdalo, O. Medina, M. Parellada, J. Bobes
Dto. de Psiquiatria. Unidad de Adolescentes, Hospital Gregorio Maranion, Madrid, Spain

The purpose of this study is to determine the decrease of NSS during adolescence and to compare this evolutionary process in two groups of adolescents with first episode psychosis: a) schizophrenia and b) non schizophrenia. The structured Neurological Evaluation Scale (NES) was administered to 24 adolescents with first episode psychosis (schizophrenia:9, non schizophrenia:15). Total and scale scores were compared to those obtained from 39 healthy controls and correlated with age. Adolescents with first-episode psychosis had a higher prevalence of NSS than healthy controls, being higher the prevalence in schizophrenia patients than in non schizophrenia; 100% of schizophrenia patients displayed one or more NSS versus 93% of the non schizophrenia patients and 64% of healthy controls. From the total sample of each group, the 89% of the schizophrenia patients displayed two or more NSS versus 73% of the non schizophrenia patients and 28% of the healthy controls. The number of NSS correlated inversely with age in the healthy control group (r=-.45, p<0.01), and also the total and scale scores of the NES (with exception of -others- scale). No correlation was found for the schizophrenia group. For the non schizophrenia group, only a significant negative correlation in the sequencing of complex motor acts subscale were found (r=-.63, p=0.012). It can be conclude that the decrease of NSS during adolescence in healthy population but not in psychosis may be an indicator of an alteration of brain processes that take place during development. We did not find a clear pattern of NSS differencing schizophrenia from other psychosis, although the Sequencing of Complex Motor Acts may be more preserved in other psychosis than schizophrenia.

CORTICAL/STRIATAL DYSFUNCTION IN SCHIZOPHRENIA: SPECIFIC IMPAIRMENT IN THE DORSOLATERAL PREFRONTAL CORTEX/CAUDATE CIRCUIT

R. Asarnow,* K. Foerde, B. Knowltown, F. Sabb, S. Bookheimer, R. Bilder, K. Neuchterlein, D. Guthrie, R. Poldrack
Psychiatry, UCLA, Los Angeles, CA, USA

Parallel cortical/striatal circuits involving the frontal lobes have been defined based on anatomical evidence (Alexander, DeLong & Strick,

1986) that are functionally discrete. Disruptions of specific circuits can lead to distinct neuropsychiatric syndromes (Mega & Cummings, 1994). We tested the hypothesis that there is a dysfunction in a specific cortical/striatal circuit in patients with schizophrenia Performance on the Probability Classification Test (PCT; Knowlton et al., 1996) was used to assess the function of the dorsolateral prefrontal cortex/caudate (cognitive habit learning system) circuit. Performance on the Serial Reaction Time task (SRT; Nissen & Bullemer, 1997) was used to assess the function of the motor cortex/putamen (motor learning circuit). Schizophrenia patients and controls were trained for three hours on both the PCT and SRT. On 33% of the trials, participants performed the primary task (PCT or SRT) while performing a secondary task (tone counting). Fifteen recent onset schizophrenia patients who met DSM-IV criteria for schizophrenia were studied. All patients were on maintenance doses of Risperdal. Fifteen normal controls were matched for gender, age, education and handedness. Both at the beginning and at the end of practice there were no differences in the SRT performance of patients with schizophrenia and controls. Both schizophrenia patients and controls learned the underlying sequence and benefited from it equivalently across practice on the SRT task. Furthermore, the effect of the secondary task on SRT performance was equivalent between the schizophrenia patients and control groups. In contrast, the normal controls showed a significantly faster rate of learning on the PCT, particularly within the first hour of practice, compared to schizophrenia patients. The performance of schizophrenia patients improved at a consistent, slow rate across three hours of practice, and was still vulnerable to the secondary task after three hours of training. These results suggest that there may be a disruption in a specific cortical/striatal circuit: the dorsolateral prefrontal cortex/caudate circuit in patients with schizophrenia. Limitations of this study are the inability to exclude the possibility that this differential performance deficit is due to: a) potential differential effects of anti-psychotic medication on specific cortical/striatal circuits; and b) differences in the psychometric properties of the PCT and SRT tasks.

IMPROVEMENT IN VERBAL WORKING MEMORY (WM) IN A CLINICALLY STABLE SAMPLE WITH SCHIZOPHRENIA

E. C. Atbasoglu,* H. Devrimci Ozguven, M. C. Saka, S. Olmez
Psychiatry, Ankara University School of Medicine, Ankara, Turkey

We report the 1-year course of verbal WM in a recent-onset, clinically stable schizophrenia sample with the hypothesis that WM, proposed to underlie the clinical symptoms, would remain unchanged in the absence of an exacerbation (1). Twenty-eight patients were assessed at baseline and at the end of the 1-year follow-up, during which they remained stable on typical (n=5) or atypical (n=23) antipsychotics. Symptoms were rated with the SANS and SAPS. Two composite mesaures derived from a factor analysis were used to assess verbal WM and learning. z scores were calculated by using data from healthy controls, similar in education and gender distribution. Controls were older and had better premorbid cognition. Performance across groups was compared with MANCOVA (covariates: age and WAIS Vocabulary), performance at two time points by repeated measures ANOVA. Bonferoni correction was applied and effect sizes (ES) estimated. Relevant characteristics, cognitive performances and statistical comparisons are in the Table. Patients performed worse than controls on both cognitive measures. At follow-up, verbal learning remained stable, whereas verbal WM improved with a large ES. These results challenge the view that WM is a core feature that remains stable or deteriorates over the course of schizophrenia (1). A favorable clinical course may be accompanied by improvement in WM. Since this study focused on verbal WM, findings are not generalizable to all WM functions. Response to treatment of the phonological loop and the visuospatial sketch-pad (2) might be different in the presence of a favorable clinical course. Future studies should explore the course of verbal WM in heterogenous samples and by varying the difficulty level of the tasks. 1. Goldman-Rakic PS (1994) Working memory dysfunction in schizophrenia. *J Neuropsychiatr Clin Neurosci*, 6:348-357 2. Baddeley AD (1992) Working memory. *Science*, 255:556-559 Supported by the Psychiatric Association of Turkey.

DECREASED REGIONAL GREY MATTER VOLUME AND COGNITION IN FIRST-EPISODE SCHIZOPHRENIA

M. Bagary,* S. B. Hutton, M. R. Symms, G. J. Barker, S. H. Mutsata, T. R. Barnes, E. A. Joyce, M. A. Ron
Neuroinflammation, Institute of Neurology, London, United Kingdom

Introduction: Abnormalities in multiple cognitive domains are well described in schizophrenia, but the neural correlates of these abnormalities are less well known. We have examined the relationship between grey matter volume and measures of fronto-striatal cognitive function in first-episode schizophrenia using high-resolution volumetric imaging. Methods: 26 (16 male, 3 left handed) first-episode schizophrenia subjects with mean age 27.3 years were recruited. The Cambridge Neuropsychological Test Automated Battery (CANTAB) sub-tests sensitive to fronto-striatal dysfunction (spatial working memory, search strategy and set-shifting) were selected for this analysis. Subjects underwent T1-weighted imaging. Correlations were made between neuropsychological tests and regional grey matter volume (GMV) using statistical parametric mapping covariate analysis corrected for age, gender and handedness. Results: Subjects with a poor spatial working memory had decreased GMV in the left precuneus. Subjects with a poor search strategy had decreased GMV in the right prefrontal cortex. Subjects with more ID/ED total errors had reduced grey matter volume in the anterior cingulate gyrus bilaterally. Conclusions: Our study suggests

abnormalities in specific neuronal networks may be involved in the cognitive phenotype of schizophrenia.

COGNITIVE FUNCTION IN FIRST EPISODE PSYCHOSIS: A COMPARISON BASED ON PRELIMINARY DIAGNOSIS

S. L. Barrett,* C. Mulholland, S. J. Cooper, T. M. Rushe
School of Psychology, University of Ulster Jordanstown, Newtownabbey, Co. Antrim, United Kingdom

The investigation of neurocognitive deficits in schizophrenia[1] and the affective psychoses[2], as well as in high-risk groups[3], suggests that cognitive dysfunction is not only an important determinant of outcome, but also an intrinsic risk factor for psychosis that is of a neurodevelopmental origin. One aim of the Northern Ireland First Episode Psychosis Project (NIFEPS) is to examine the incidence and nature of deficits in patients with psychosis at illness onset, to determine (i) the stability of these deficits over time, and (ii) the functional correlates of persistent deficits at follow up. A preliminary analysis of the data collected to date was conducted to compare the cognitive functioning at illness onset of 48 first episode patients with schizophrenia (SCZ; Age = 30.3 ± 12; M/F = 37/11), and 38 patients with a preliminary diagnosis of an affective psychosis (AP; Age = 36.8 ± 9.4; M/F = 20/14), to that of 15 controls (CON; Age = 36 ± 10.8; M/F = 9/6). The neuropsychological test battery included tests of: executive function; verbal/visuospatial attention and working memory; visuospatial construction and long-term memory; verbal learning; phonological processing; motor dominance and callosal function. It was hypothesised that first episode SCZ patients would have more pronounced cognitive deficits than AP patients, but both patient groups would show deficits relative to CON. Data were analysed using one-way ANOVA. The results showed that the SCZ group had a significantly lower IQ than both AP and CON groups. They also demonstrated clear deficits in executive function, unlike AP patients. Verbal working memory and learning were impaired in both patient groups but visuospatial attention and long-term memory deficits were present only in SCZ patients. Phonological deficits, whilst present in both groups, were more pronounced in SCZ patients. First episode SCZ patients also showed some evidence of increased right hemispheric dominance and callosal dysfunction. It was concluded that patients experiencing a first episode of SCZ demonstrate a global deficit that affects multiple cognitive domains, whereas AP patients display more selective deficits in verbal working memory, learning and phonological processing. 1 Green MF. et al. (1999) *Schizophrenia Bulletin*, 25(2), pp 309-19. 2 Bearden CE. et al. (2001) *Bipolar Disorders*, 3(3), pp 106-50. 3 Byrne M. et al. (1999) *Psychological Medicine*, 29, pp 1161-73. Funded by The R & D Office (NI).

STANDARDISATION AND CROSS-VALIDATION STUDY OF COGTEST AN AUTOMATED NEUROCOGNITIVE BATTERY FOR USE IN CLINICAL TRIALS OF SCHIZOPHRENIA

P. Barua,* R. Bilder, A. Small, T. Sharma
Clinical Neuroscience Research Centre, Dartford, United Kingdom

Paper and pencil tests are increasing being replaced by computerized batteries for cognitive testing in clinical trials. We sought to standardize and crossvalidate Cogtest, an automated neurocognitive battery with electronic data capturing ability. 200 cognitively healthy individuals took part in two studies, one aimed at assessing concurrent validity with respect to paper and pencil measures and another to establish norms for individual Cogtest endpoints that comprise a Neurocognitive Global Score (NGS) for use in clinical trials. The overall design of the first study (N=75) involved parallel, counterbalanced administration of both the Cogtest computerised test battery and a battery of paper and pencil (P&P) tests (selected to approximate the testing done in current clinical trials). There were two test sessions, and both sets of instruments were presented in counterbalanced order at both sessions, with testing at 0 and 4 weeks (+/ 3 days) controlling for time of day. Four alternate forms of the Cogtest battery were counterbalanced so that each subject experienced two different forms. The 75 subjects were stratified by age over 4 decades from age 20 to 60. Age 20 subjects, equally distributed across age group and sex. The second study (N=120) involved two baseline sessions and one follow up session, similar counterbalancing of alternate forms, and 20 participants (10 men and 10 women) in each of 6 age bands from age 13 to 69. The first study revealed sex differences with men generally faster and more accurate on spatial processing but women more accurate in face recognition memory, paralleling prior research. Correlations of Cogtest measures with analogous P&P tests revealed correlations in the range of r=.3 to r=.7. The second study revealed a classic curvilinear age effect on NGS and individual domains with lower scores in the 13 to 19 year age group, highest scores in the 20 to 29 year group, and then monotonically decreasing scores through the 6th decade. Both studies revealed that testretest stability over up to 4 weeks was in keeping with published results for the paperpencil tests, with typical testretest reliability coefficients in the range of 0.4 to 0.9. This study shows that the Cogtest computerized testing battery has similar psychometric properties to paper and pencil tests that have been used in clinical trials and offer the added advantage of computerization, millisecond accuracy electronic data capture and audit trail.

COGNITIVE PHENOMICS FOR NEUROPSYCHIATRIC THERAPEUTICS

R. M. Bilder
Psychiatry & Biobehavioral Sciences, UCLA, Los Angeles, CA, USA

We recently established an exploratory Center for Cognitive Phenomics (CCP) at UCLA under the aegis of the NIH Roadmap Initiative. This new center aims to accelerate identification and efficient measurement of cognitive phenotypes across syndromes and across species to advance interdisciplinary research on neuropsychiatric therapeutics. Cognitive abnormalities have been identified in all major neuropsychiatric disorders, offer quantitative phenotypes for genomic studies and clinical trials, and provide strong bridging relations to neural systems models. The CCP aims to iteratively refine cognitive phenotypes in interdisciplinary research using neurobehavioral, neuroimaging, and neuropsychopharmacological approaches to provide translational validation of physiological endophenotypes, and thereby overcome bottlenecks in the discovery of treatments for neuropsychiatric syndromes that are caused by the use of traditional behavioral "symptom" phenotypes, which are heterogeneous and overlapping, and difficult to translate to basic research. The CCP is coordinating activities of a large group of experts at UCLA and elsewhere to: (1) generate cross-disorder and cross-species catalogs of phenotypes; (2) develop a phenotype selection algorithm to identify the most promising candidates for genomics and interventions research; (3) design a phenomics database for empirical data representation, data mining, and hypothesis testing;

and (4) support proof-of-concept pilot projects. This presentation focuses on the first 3 of these aims, showing the current status of the phenotype catalog, the draft criteria for a phenotype selection mechanism, and the informatics architecture and ontologies for cognitive phenomics developed so far. Specific emphasis will be placed on the relevance of these aims to research on neural systems abnormalities in schizophrenia, cognitive and neuroimaging markers of these abnormalities, and how these may help guide therapeutic discovery. Supported by NIH Grant P20-RR20750.

CONFIGURAL NOT SCALAR INVARIANCE OF THE UNIVERSITY OF PENNSYLVANIA SMELL IDENTIFICATION TEST THROUGH THE COURSE OF PSYCHOSIS FROM HIGH RISK TO CHRONIC SCHIZOPHRENIA AND IN TEMPORAL LOBE EPILEPSY

W. Brewer,* P. Reed, S. Wood, S. Bowden, C. Pantelis, P. D. McGorry
ORYGEN Research Centre, Melbourne, VIC, Australia

We have previously demonstrated Odor Identification Deficits (OIS) in patients deemed to be at high risk for psychosis who later develop schizophrenia (Brewer et al; *Am J Psychiatry*, 2003). As the ability to detect individual odors may implicate specific genes, we investigated item performance on the 40-item University of Pennsylvania Smell Identification Test (UPSIT) in a sample of 320 participants from populations of temporal lobe epilepsy patients, people deemed at high risk for psychosis, first episode psychosis patients and in people with chronic schizophrenia compared with healthy controls. Configural invariance of the UPSIT was established by exploratory factor analysis across psychotic versus non-psychotic populations. Whereas prior studies have examined mean differences in UPSIT score using ANCOVA, this study used a MIMIC CFA model to establish that items of the UPSIT measured a single latent trait, -olfactory ability, which increased with education, decreased with age, was higher for females than males and higher for healthy controls compared with members of the clinical groups. Increased psychomotor poverty decreased latent olfactory ability in people with first episode psychosis and chronic schizophrenia. Fifteen of the UPSIT′s forty items were found to exhibit differential item functioning, or item bias resulting in poorer performance by people with chronic schizophrenia relative to the healthy controls. Differences in item performance across groups were a function of person ability, item difficulty, discriminability and item bias. Item difficulty was related to familiarity but not pleasantness ratings in a subsample of thirty healthy controls. It was concluded the UPSIT had diagnostic utility as a premorbid marker for psychosis however conclusions with respect to localisation of compromise may be limited due to its insensitivity to component processes.

GOAL-ORIENTED PERCEPTION ANALYSIS IN SCHIZOPHRENIA SPECTRUM PATIENTS

G. Buoiano,* M. Betti
AUSL 2, Centro di Salute Mentale, Fornaci di Barga, LU, Italy

Background: Goal-Oriented Perception Task (GOPT) is a test elaborated in order to assess whether subjects are able to implement a perception analysis that implies gestalt and actors' goals understanding as well as constructing correct grammatical structures. In the former sense it is similar to classical Theory of Mind tasks (ToM). Materials and methods: GOPT consists of two sides: 1)perceptual-orienteering; 2)grammatical. GOPT perceptual-orienteering side encompasses 4 parameters, the grammatical side 15. We administered GOPT to ten schizophrenia spectrum outpatients. As group of control we tested ten healthy subjects. Results: The schizophrenics performed significantly worse than controls in both sides of GOPT: grammar $t = 4.49$ two-tailed $p = 0.0015$, $SD = 8.530$. Perceptual-orienteering: $t = 6.04$ two-tailed $p = 0.0002$, $SD = 4.71$. We found a positive correlation between Positive Formal Thought Disorders (PFTD: SAPS evaluation) patients and global GOPT performances in both perceptual and grammatical side: perceptual side Pearson's $r = 0.97$, two-tailed $p<0.0001$. Grammatical side Pearson's $r = 0,86$ two-tailed $p = 0.0014$. We did not find correlation between Negative FTD (NFTD, SANS evaluation) and global GOPT performances. Positive correlations exist between PFTD severity and three GOPT perceptual-side parameters: 1)errors concerning the thematic figure right analysis: Pearson's $r = 0.72$, 2-tailed $p = 0.0183$; 2)missing of thematic figure description with particulars: Pearson's $r = 0.70$, 2-tailed $p = 0.0229$; 3)fragmented description of the thematic figure Pearson's $r = 0.67$, 2-tailed $p = 0.0340$. We found positive correlation between NFTD severity and missing of thematic figure description with particulars: Pearson's $r = 0.63$, 2-tailed $p = 0.0486$. Conclusions: GOPT grammatical side results show that syntax is not properly parsed. In the perceptual side, the positive correlations between PFTD and three parameters and NFTD and a single parameter show that it is mainly the gestalt interpretation deficit that affect the patients' analysis of perception. Schizophrenics' failure in ToM tests has been reported in literature as well as the link between FTD and inability of performing in ToM tasks. Our study confirms these findings. Data confirm that these perceptual-analysis mechanisms are more ill-functioning in FTD patients and are reported as damaged mainly in presence of alterations affecting left dorsolateral prefrontal cortex and IFG.

NEUROPSYCHOLOGICAL DEFICITS AT AGE 13 AND LATER SCHIZOPHRENIFORM DISORDER: A LONGITUDINAL BIRTH COHORT STUDY

M. Cannon,* T. E. Moffitt, A. Caspi, H. L. Harrington, R. M. Murray, R. Poulton
Department of Psychiatry, Royal College of Surgeons in Ireland, Dublin, Ireland

There is compelling evidence that individuals with schizophrenia exhibit generalised impairment on a wide range of neuropsychological tasks even at the time of the first episode. In order to investigate the earliest cognitive deficits in schizophrenia it is important to get information on specific neuropsychological functioning already in childhood or adolescence many years prior to the onset of psychosis. The Dunedin Multidisciplinary Health and Development Study is an unselected prospective birth cohort of 1037 individuals born in Dunedin, New Zealand between April 1 1972 and March 31, 1973. Study members have participated in ten assessments between ages 3 and 26 including a comprehensive neuropsychological test battery at age 13. Of the 850 cohort members who participated in the study at age 13, complete neuropsychological assessment data is available on 710 subjects. Psychiatric diagnostic interviews conducted at age 26 revealed that 23 of these individuals fulfilled diagnostic criteria for schizophreniform disorder, 10 for a manic episode and 196 for depressive or anxiety disorder. Study members with a subsequent diagnosis of schizophreniform disorder performed significantly

worse than the other groups at age 13 on the Trails B test, Trails B-A, and the Grooved Pegboard test (right hand). These deficits survived correction for multiple testing. Deficits in Verbal Fluency and the Arithmetic and Coding subtypes of the Weschler Intelligence Scale for Children- Revised did not survive correction for multiple testing. No significant deficits were noted in Study Members who later developed a manic episode. Study members who later developed a non-psychotic depressive illness exhibited significant deficits in Trails A and B but the effects were smaller than for schizophreniform disorder. These results indicate that neuropsychological deficits are already evident at age 13 in individuals who later develop schizophreniform disorder. However unlike first episode or chronic patients this is not a generalised deficit. Deficits primarily involve motor and attentional abilities with less impairment in executive functioning and verbal and spatial working memory than seen in patients with established disorder. These findings underscore the importance of viewing cognitive impairments in schizophrenia within a developmental context. This work was supported by NARSAD and Wellcome Trust (UK).

NEUROPSYCHOLOGICAL FUNCTIONING IN DEFICIT VS. NONDEFICIT SCHIZOPHRENIA

N. G. Cascella,* L. R. Kingery, S. M. Meyer, G. Pearlson, D. J. Schretlen
Psychiatry, Johns Hopkins University, Baltimore, MD, USA

The extent to which patients with deficit and nondeficit schizophrenia differ on neuropsychological testing has received limited empirical attention so far. The aim of this study was to compare the extent and pattern of neuropsychological impairments in deficit vs. nondeficit schizophrenia. Twenty-one patients with deficit schizophrenia, diagnosed according to the SDS criteria, (mean age = 35 SD 12) and 31 patients with nondeficit schizophrenia (mean age = 42 SD 12) were compared with healthy control groups (deficit control group n=45, nondeficit control group n=41) matched on demographic (i.e., age, gender, education, race) and premorbid IQ. All patients were administered the SANS and SAPS. The neuropsychological test battery included 19 tests grouped into seven domains, including psychomotor speed, executive functioning, attention, word fluency, verbal memory, visual memory, and recognition memory. Because of differences in age, education, and estimated premorbid IQ between deficit and nondeficit schizophrenics, test scores for each patient were standardized to those of their own controls to create a Z score of each test score. Deficit patients differed significantly on SANS total score but not on SAPS total from the non deficit patients. Univariate ANOVAs revealed that deficit schizophrenics differed significantly from their control group across all domains. Nondeficit schizophrenics were less impaired overall, and were not significantly different from their control group on the domains of word fluency and recognition memory. When the pattern of cognitive deficits were rank-ordered according to severity, a nearly significant ($r = .75$, $p = .052$) correlation emerged, suggesting that the two schizophrenic groups showed very similar patterns of overall cognitive impairments across the seven domains. These results seem to suggest that patients with deficit schizophrenia are "more of the same" in terms of neuropsychological functioning when compared to non deficit patients with the exception of more impairment on verbal fluency generally associated with frontal lobe function and on memory recognition associated with temporal lobe neuropsychological abnormality.

NEUROCOGNITIVE AND CLINICAL PREDICTORS FOR VOCATIONAL OUTCOME FOLLOWING FIRST EPISODE SCHIZOPHRENIA: A 3 YEAR PROSPECTIVE STUDY

E. Y. Chen,* D. K. Tam, E. L. Dunn, M. Y. Miao, W. S. Yeung, C. K. Wong, W. F. Chan, W. N. Tang
Psychiatry, University of Hong Kong, Hong Kong, China

Objective: We aim to identify early clinical and cognitive features that may predict vocational outcomes after first episode schizophrenia in Hong Kong. In addition, we investigated associated effects of unemployment on the symptomatic outcome of the illness at three years. Method: We studied the employment history of 93 patients with first-episode schizophrenia, schizoaffective and schizophreniform disorders who was longitudinally followed up over three years. Pre-morbid factors, as well as clinical and cognitive variables which are present at the first episode were studied in relation to subsequent vocational outcomes. The relationship between employment status and clinical outcome at three years was also explored. Results: The median number of months of full time employment is 8 out of 36 months. Forty-one percent of the patients did not return to full-time employment at all. Patient with poor vocational outcome (less than 8 months of full time employment) had more impaired scores on the premorbid adjustment scale ($t = 2.889$, $p = .005$) as well as more impaired work functioning at the time of presentation ($t = 3.671$, $p < 0.001$). They also performed worse in Logical memory ($t = -2.072$, $p = .04$), visual reproduction ($t = -2.624$, $p = .01$), as well as in both perseverative errors ($t = 2.685$, $p = .009$)and cateogory completion in the Wisconsin Card Sorting Test ($t = -2.655$, $p = .009$). A binary logistic regression model suggest that poor vocational outcome is predicted by poor pre-morbid occupational functioning, Premorbid adjustment, and executive function impairment after the first episode. Compared with others, patient with poor vocational outcome showed a decline in negative symptoms over the three year period. Conclusion: Vocational outcome is unfavorable after first-episode psychosis. Early predictors for poor outcome may identify at-risk patients for timely intervention. Unemployment is associated with an increase in negative symptoms.

COMPARISON OF REMEDIATION TECHNIQUES ON THE WISCONSIN CARD SORTING TEST (WCST) IN SCHIZOPHRENIA

J. Choi,* R. Niziolek, T. Herlands, J. Ferrand, M. Kurtz
Psychiatry, Yale University School of Medicine, New Haven, CT, USA

We compared two promising remediation techniques, didactic instructions versus self-monitoring, for improving performance on the Wisconsin Card Sorting Test (WCST) in schizophrenia. Relatively little is known whether improvements can generalize to other executive measures with enduring benefits. We hypothesized that (a) participants treated with either remediation method would show significantly improved performance on the WCST, (b) improved performance on the WCST would generalize to performance on non-trained executive tests, (c) self-monitoring instruction would promote greater acquisition of executive strategies than didactic instruction as demonstrated by greater generalization to non-trained executive tests, and (d) benefits from both remediation techniques would be maintained over a 1-month period. Patients were randomly assigned to one of three conditions: Condition A consisted of didactic training which incorporated a detailed account of the changing sorting principles throughout the test (Bellack et al., 1996; Gold-

berg et al., 1986); Condition B consisted of a self-monitoring strategy that was simply based on having the participants verbalize their strategies out loud after each card sort (Perry et al., 2001; Stratta et al., 1994); Condition C was a non-trained control group that received the same battery as the two training groups at identical time intervals. Preliminary results from the first 14 participants to complete protocol to date showed that participants receiving either remediation method obtained more categories on the WCST during training and post-testing, but only the didactic group made fewer errors (total and perseverative) during training and post-testing than the control group. As predicted, benefits from both remediation methods were maintained over a 1-month period (see table). The significance of these results for development and implementation of executive remediation methods in schizophrenia will be discussed. Funded by a Hartford Hospital New Investigator Grant awarded to Dr. Jimmy Choi (with Dr. Matthew Kurtz as senior investigator).

Number of Categories Achieved on WCST (T-Scores)

*** p < .05**

IMPAIRMENTS IN COGNITION ACROSS THE SPECTRUM OF PSYCHIATRIC DISORDERS: EVIDENCE FROM A SWEDISH CONSCRIPT COHORT

A. David,* S. Zammit, G. Lewis, C. Dalman, I. Lundberg, P. Allebeck
Section of Cognitive Neuropsychiatry, Institute of Psychiatry, London, United Kingdom

Cognitive deficits are now considered to be part of the schizophrenia syndrome. We used data from a Swedish conscript cohort to explore the association between cognition and psychiatric illness in two new ways. First, we sought to examine the effect of schizophrenia at the time of initial diagnosis, upon general and specific cognitive functions assessed contemporaneously; second, we examined the association between cognition and diagnosis across the whole range of psychiatric disorders from psychosis through affective to personality and substance abuse disorders. The cohort comprises of approximately 50,000 18 year-old male conscripts from 1967/8. All underwent a detailed assessment including a battery of cognitive tests (standardized in to 9 bands) and self-report questionnaires covering social demographics, upbringing and current psychopathology. Those indicating current psychological difficulties were further assessed by a clinical psychologist and where appropriate, a psychiatric diagnosis was made according to ICD-8 criteria. At the time of conscription, 34 men were diagnosed as suffering from a psychotic disorder, 650 with depression, 2031 with a neurosis other than depression (includes anxiety disorders), 195 had alcoholism, and 331 had drug dependence. After adjustment for confounders, the odds ratio (OR) for having a psychotic disorder at 18 years-old (including schizophrenia, affective and non-affective psychoses) was 1.29 (95% CI 1.09-1.52) for every drop in cognitive function from the highest band. This is of the same order of magnitude as the OR for lower IQ and schizophrenia developing after conscription. The risk for other psychiatric disorders was also raised: depression: 1.06 (1.02-1.52); other neuroses: 1.14 (1.12-1.17); personality disorder: 1.26 (1.22-1.30), and was highest for alcoholism: 1.49 (1.38-1.62). There is therefore a general association between lower intellectual functioning and psychiatric disorder which is presumably a combination of premorbid and illness-related deficits (including neurotoxic effects of drugs). The likelihood is that any psychiatric disturbance can affect cognition, by a variety of mechanisms. The level of expectation placed on patients to follow or comply with complex therapies should take this into account.

THE NEUROPSYCHOLOGICAL CORRELATES OF POSITIVE, NEGATIVE, AND DISORGANISATION SYNDROMES IN SCHIZOPHRENIA: A META-ANALYSIS

C. Dibben,* C. Rice, P. J. McKenna, K. Laws
Psychiatry, Fulbourn Hospital, Cambridge, United Kingdom

The purpose of this meta-analysis was to examine the validity of claim that negative and disorganisation symptoms in schizophrenia are associated with the deficit in executive function found in the disorder. We meta-analysed data from studies reporting correlations between positive, negative or disorganisation symptoms and any measure of executive function. The pooled r for 73 studies of the executive correlates of negative symptoms was –0.21, in the 'medium' range. That for 27 studies examining the correlates of disorganisation was –0.22, also in the medium range. The pooled r for positive symptoms, however, was close to zero. For both negative symptoms and disorganisation the magnitude of the correlation increased with length of illness. Negative symptoms and disorganisation showed significantly different patterns of correlation among the different executive tests. Impairment on the Stroop Test was more than twice as highly correlated with disorganisation than with negative symptoms, and this was also the case for the WCST. The reverse pattern was seen for verbal fluency. Meta-analysis therefore supports the existence of significant correlations between executive impairment and both negative and disorganisation symptoms in schizophrenia. The claim that the the two syndromes are associated with different types of executive impairment also receives support. The association with chronicity could indicate that executive impairment is preferentially associated with persistent as opposed to relapsing and remitting symptoms, as proposed by Liddle.

A COMPARISON OF COGNITIVE STRUCTURE IN SCHIZOPHRENIA AND HEALTHY CONTROL GROUPS USING CONFIRMATORY FACTOR ANALYSIS

D. Dickinson,* J. D. Ragland, M. E. Calkins, J. M. Gold, R. C. Gur
Psychiatry, University of Maryland Medical School, Baltimore, MD, USA

Current analyses address two unresolved issues about cognition in schizophrenia: (1) whether cognitive variables sort into the same domains in this illness as in healthy populations and (2) how these domains associate with one another. Confirmatory factor analyses were conducted on 19 standard neuropsychological variables from a sample of people with schizophrenia and related disorders (n = 146) and healthy controls (n = 157). The variables were selected to tap 6 cognitive domains: verbal, visuospatial, verbal memory, visual memory, processing speed, and complex attention/executive. We separately compared the fit of a series of models to data

from the schizophrenia and control groups: (a) a baseline model with all variables loading on a single factor (no separate cognitive domains); (b) a 6-factor model (variables divided into the six cognitive domains); and (c) a hierarchical model (variables loading on 6 first order factors and these all loading on a single second order factor). Each of the models fit data from schizophrenia patients similarly to data from healthy controls. For both groups the 6-factor and hierarchical models fit the data adequately (e.g., for the 6-factor model: schizophrenia group CFI = .9528, NNFI = .9393, RMSEA = .0695; control group CFI = .9506, NNFI = .9365, RMSEA = .0532), whereas the single factor model did not. Cross model contrasts and comparisons suggest that neuropsychological variables sort reliably into a number of cognitive domains, and that they sort consistently for schizophrenia and healthy groups. However, results for the 6-factor and hierarchical models also indicate that the cognitive domains are themselves closely related. In the 6-factor model, the factors were free to correlate and all showed moderate to high bivariate relationships (average predicted correlations: .78 in schizophrenia and .57 for controls). Not surprisingly, constraining the factors to be fully independent entirely undercuts model fit for both groups (chi-square difference = 594, df 15, for schizophrenia group and 284, df 15, for controls; $p < .001$ for both). Results for the hierarchical model suggest further that the correlations among the factors are attributable to a single, higher order cognitive ability factor. Evidence of a hierarchical, "three stratum" organization of cognitive abilities is consistent with prior analyses in healthy populations (Carroll, 1993, 1997), but has not been shown previously in schizophrenia.

THE BRUDERHOLZ STUDY: A PROSPECTIVE PILOT STUDY OF AT-RISK PATIENTS IN NORTH WESTERN SWITZERLAND

D. N. Dvorsky,* A. E. Simon, D. Umbricht
Specialised Outpatient Clinic for the Assessment and Intervention in Early Psychosis, Bruderholz, Switzerland

Recent research in early psychosis has focussed on defining at-risk states (Yung & McGorry 1996, McGlashan et al. 2001, Cornblatt et al. 1998) and on prospective studies of at-risk individuals (Klosterkoetter et al. 2001). In a semi-urban catchment area in North Western Switzerland (pop. = 300'000), a specialised, low-threshold outpatient clinic with a mobile service was established. Referred patients undergo prospective clinical assessment at 3-monthly bases (SCID DSM-IV, SPI-A, SIPS, PANSS, SUMD) and comprehensive neuropsychological assessment at 1-yearly bases. According to their clinical features, they are included into one of the following study groups: First Episode Group (FE), At-Risk Group (AR), Patient Controls (Pco). Between-group comparisons of base-line characteristics showed higher SIPS +/- scores in the FE group. SPI-A dimensions for disturbances of cognition and body perception differed significantly between AR and Pco groups. WCST (PE) and Category Fluency showed significant between-group differences. Our study suggests that it is possible to distinguish AR patients from FE patients and patients with other psychiatric pathologies in terms of clinical and neuropsychological sub-dimensions. In particular, at-risk patients show higher levels of basic symptoms compared to patients with other psychiatric pathologies. The study also includes a comparison between the three groups concerning negative symptoms in the sense of the CASIS-model by Barbara Cornblatt (Cornblatt et al. 2003). The poster will contain two-year data of the study.

SELF-REPORTED DATA ON COGNITIVE AND EVERYDAY FUNCTIONING IN PERSONS WITH PSYCHOSIS: WHAT IS BEING MEASURED?

T. Ehmann,* R. Goldman, G. W. MacEwan, Y. Xu, J. Yager
Fraser South Early Psychosis Intervention Program, White Rock, BC, Canada

This study sought to examine the correlates of self-reported data on cognitive and social function in persons with psychosis. We examined the reliability and validity of a self-report scale designed to assess subjective judgments of functioning. The Patient Perception of Functioning Scale (PPFS) is a simple six-item scale that calls for ratings of both community functioning and cognition. Method: Sixty-eight subjects with psychotic disorders were recruited to complete the PPFS on two occasions and to complete a battery of neurocognitive tests. Objective ratings of overall illness severity (Clinical Global Impression), illness severity (GAF) and functioning (SOFAS and Role Functioning Scale) were also obtained. Results: The internal consistency and test-retest correlation coefficients revealed that the PPFS possesses good reliability characteristics. The PPFS did not show relationships to demographic, historical or illness related variables such as diagnosis or length of illness. The PPFS showed significant associations with a limited number of dimensions of community functioning. However, no significant associations were found with neurocognitive measures or clinical status. Conclusions: In populations with psychotic disorders, self-reported ratings of community function and cognition may converge less with objective cognitive measures than with objective ratings of everyday functioning. Several factors inherent to self-report methodology may have contributed to the poor convergent validity results. Theoretical underpinnings and operationalization of the underlying constructs of some neuropsychological instruments may not closely match how patients conceptualize those constructs.

WHAT INCREASES ACCURACY OF PREDICTION FROM CHILDHOOD ASSESSMENTS TO ADULT SCHIZOPHRENIA?

N. Erlenmeyer-Kimling,* S. A. Roberts, D. Rock, S. L. Ott, I. I. Gottesman
Medical Genetics, NYS Psychiatric Institute, New York, NY, USA

Studies of children or adolescents at genetic risk to schizophrenia have sought to identify deficits in neurobehavioral or other endophenotypic traits that predict to adult schizophrenia and schizophrenia-related psychoses (SRP). Several traits have been found, consistently, across numerous studies from different countries, as well as from various locations in the United States, to show greater performance deficiencies in individuals at risk to schizophrenia than in those at risk to other adult psychiatric disorders or normal comparison subjects. Nevertheless, because of false high positive rates (and high population base rates), and sometimes significant, false negative rates, predictions to SRP from earlier examinations of neurobehavioral measures have been largely uninformative for use in developing clinical follow-up or intervention programs or in gene search efforts. Prediction from childhood to adult SRP has been evaluated in the New York High-Risk Project (NYHRP), a prospective study following 326 offspring of schizophrenic, affectively ill and psychiatrically normal parents over a 32 year span from initial assessment at age 9 through the peak SRP onset period. We reported (Erlenmeyer-Kimling et al., Am J Psychiatry 2000; 157:1416-1422) that deficits in attention, verbal working memory and gross neuromotor

skills tested at age 9, each showed high sensitivity of prediction but also relatively high false positive rates. Assuming deficits in all 3 endophenotypes to be rare in the general population, we analyzed them as a composite pattern. This composite yielded a 50% sensitivity of prediction among those from the schizophrenic parent group who themselves received diagnoses of SRP in adulthood by the end of the peak onset period, with a false positive rate of 10% occurring only in the SRP-risk group, but not in the children of affectively ill or normal comparison parents may indicate that there will be a few, later onset manifestations of SRP. We are now analyzing other measures from the evaluation at age 9 years: distractibility, neurological soft signs, performance variability, social isolation and others, that may reveal heterogeneity of patterns expressed within the overall genetic liability to SRP. We have already seen that inclusion of some of these measures further increases the accuracy of prediction, raising sensitivity and lowering false positive rates to a better level of prediction.

FRONTAL LOBE FUNCTIONING IN THOSE BORN PRE-TERM

A. Fern,* M. Walshe, M. Allin, E. Giouroukou, S. Frearson, C. Nosarti, L. Rifkin, R. Murray
Institute of Psychiatry, London, United Kingdom

Individuals born very preterm (33 weeks gestation) are at risk of neonatal brain injury, which may affect the frontal lobes. We assessed frontal lobe functioning using the Hayling Sentence Completion Test (HSCT) and the Verbal Fluency Test (VFT) in 91 young adults born very preterm (age 18-22), and 50 age-matched individuals born at term. The HSCT is a test of response inhibition that requires completion of a sentence with a related or an unrelated word. The VFT tests response initiation, and requires the generation of a number of words per minute in three different categories. Between group differences were analysed using one-way Analysis Of Variance (ANOVA). The preterm group scored significantly lower on the HSCT than the full-term control group ($F= 9.44$, d.f.(1,136), $p= 0.003$), and also produced significantly more type A errors (defined as failure to inhibit the most salient responses) ($F= 12.44$, d.f.(1,136), $p= 0.001$). On the VFT, the preterm group produced significantly fewer words in total than those born full-term ($F= 6.61$, d.f.(1,132), $p= 0.011$). The preterm group performed significantly worse in two of the three categories of the VFT: letters ($F= 6.85$, d.f.(1,132), $p= 0.01$); and animals ($F= 6.07$, d.f.(1,132), $p= 0.015$). Young adults born very preterm show deficits on frontal lobe tasks that test both initiation and inhibition of verbal responses. Similar deficits are reported in schizophrenia. Such frontal lobe deficits may underlie the increased risk of psychosis in individuals born preterm. This Research is supported by The Wellcome Trust.

RELATIONS AMONG SUICIDAL BEHAVIORS, DEPRESSION, ALCOHOLISM, AND COGNITIVE DYSFUNCTION IN INDIVIDUALS WITH SCHIZOPHRENIA

G. Goldstein,* G. L. Haas
Research (151R), VA Pittsburgh HCS, Pittsburgh, PA, USA

Background/Aims: Elevated rates of suicidal behaviors have been associated with schizophrenia, mood disorder, cognitive dysfunction and alcoholism. The purpose of this study was that of ascertaining the relationships among these concomitant risk factors and suicidal behavior in patients with DSM-IV Schizophrenia or Schizoaffective Disorder. Methods: The sample consisted of 93 participants with Schizophrenia or Schizoaffective Disorder, some of whom had comorbid alcohol abuse or dependence. All subjects received a series of cognitive tests assessing abstract reasoning and problem solving. Clinical records were reviewed and classified for presence/absence of suicidal behaviors, and subclassified for presence/absence of suicidal ideation and/or suicidal attempts. To evaluate the influence of mood syndromes, cases were divided into participants with Schizoaffective Disorder or Schizophrenia. The influence of cognitive dysfunction on suicidal behavior was evaluated by comparing all participants with suicidal behaviors with those without such behaviors using discriminant function analysis. Results: No difference was found across these two suicidal behavior groups on measures of cognitive dysfunction. However, there was an association between frequency of suicidal ideation and attempts and diagnosis, with the Schizoaffective Disorder participants having a substantially higher frequency of these behaviors than did participants with Schizophrenia. A comparison between participants with and without a history of alcohol use disorders did not reveal a significant difference in suicidal behaviors across the two groups. It was concluded that the syndromes characteristic of Schizoaffective Disorder may contribute to the substantially increased risk of suicidal behaviors found in Schizoaffective Disorder as compared to Schizophrenia. In contrast, indicators of cognitive dysfunction and/or a history of alcohol use disorder did not contribute substantially to risk for suicidal behavior.

SELF ESTEEM IS AN IMPORTANT PREDICTOR OF IMPROVEMENTS IN REAL WORLD FUNCTIONING IN SCHIZOPHRENIA

K. E. Greenwood,* T. Wykes
PO79 Psychology, Institute of Psychiatry, London, United Kingdom

Cognitive remediation therapy (CRT) assumes that the cognitive variables that are targeted in therapy are the most important predictors of real world function. However, CRT has been shown to affect symptoms and social function and these factors may also be important. This study investigated whether cognitive and/or symptom factors were significant in predicting improvements in real world function. A referred sample of 42 participants with DSM-IV schizophrenia (half of whom had received CRT) was administered: (i) a direct real world assessment of community function in the form of a supermarket shopping test (ii) 5 tests of cognition function to encompass memory, working memory and executive function. (ii) symptom measures (positive and negative symptoms and self esteem) at baseline and at 6 months follow-up. Change in two community functions measures (accuracy and efficiency) were correlated with baseline levels and measures of change in cognitive functions and symptoms. Lower baseline accuracy ($r = -.66$, $p <0.001$), self-esteem ($r = -.44$, $p = 0.004$) and working memory ($r = -.26$, $p = 0.094$) each correlated with improvements in accuracy in community function. Lower baseline efficiency ($r= -.769$, $p<0.001$), greater negative symptoms ($r = -.41$ $p = 0.007$) and poorer executive function ($r = .36$, $p = 0.019$) were correlated with improved efficiency in community function. There were no correlations between change in community function and change in any measures. CRT status (CRT therapy or waiting list control), age, premorbid IQ and significant cognition and symptom measures from correlation analyses were entered into regression analyses. Baseline self esteem ($t = -2.3$, $p=0.031$) and accuracy ($t = -5.4$ $p <0.001$) were the only significant independent predictors of change in accuracy of community function. Age ($t =$

2.2, p = 0.034) and baseline efficiency (t = -7.0, p <0.001) were the only significant independent predictors of change in efficiency (time taken). There were no independent cognitive predictors of change in community function. Higher initial self esteem is an important predictor of greater subsequent improvement over time in community function. CRT has been found to improve self esteem and this improvement is associated with improved cognition (Wykes et al. 2005). Targeting self-esteem early in CRT may lead also to more tangible improvements in real world function.

SCHOLASTIC HISTORY AND PREMORBID ADJUSTMENT OF INDIVIDUALS WITH FIRST-EPISODE PSYCHOSIS

S. Y. Griffiths,* A. E. Thornton, W. G. Honer
Psychology, Simon Fraser University, Burnaby, BC, Canada

The current study 1) describes the methodology used to quantify the scholastic records of a subset of participants enrolled in a large, catchment-area first episode psychosis program and 2) provides preliminary results linking school record information to the Premorbid Adjustment Scale (PAS, Cannon-Spoor et al., 1982), which was rated from semi-structured maternal interviews. The study included eighteen participants from our first episode psychosis program. All teacher comments from the primary and secondary school records were extracted and categorized into seven general content domains (e.g., social behavior, academic progress). Inter-rater agreements were high for both the extraction of teacher comments from the records (91%) and categorization (86%) of these comments into content domains (x = 294 comments per file). For illustrative purposes, the proportions of all comments in the social and academic domains, as well as the proportions of negative comments in these two domains were calculated relative to overall volume of comments. In subsequent analyses, these proportions were correlated with participant scores on PAS-rated domains of sociability and withdrawal, peer relationships, school performance, and adjustment to school. Findings indicated that higher PAS-rated peer relationship problems were associated with proportionally fewer teacher comments regarding social behaviour in school records (r = -.65, p < .01). Additionally, more PAS-rated sociability and withdrawal problems were associated with a higher proportion of comments in the school records concerning academic progress (r = .54, p < .05). The proportion of negative teacher comments concerning social and academic functioning was not significantly related to any PAS ratings. In addition, information derived from school records was unrelated to PAS-rated scholastic performance and adaptation to school. The methodologies derived from this project and the preliminary findings presented suggest that school records offer an opportunity to sample data from the premorbid and prodromal period in individuals who go on to develop psychosis. Indeed, such methods may provide an important complement to retrospective sources of information about adjustment during this period.

SPECIFICITY OF NEURO-COGNITIVE IMPAIRMENTS IN ADOLESCENT-ONSET SCHIZOPHRENIA PATIENTS AND NON-PSYCHOTIC SIBLINGS: COMPARISON WITH ADHD

M. Groom,* T. Calton, C. Hollis, G. Jackson, P. Liddle
Division of Psychiatry, University of Nottingham, Nottingham, United Kingdom

Neuro-cognitive impairments are prevalent in schizophrenia. A number of these impairments are present at illness onset, during illness remission, and are not completely abolished by treatment with antipsychotic medication despite symptom improvement. The first degree relatives of individuals with schizophrenia also show evidence of neuro-cognitive impairment. Schizophreniform disorders and functional psychoses are more prevalent in this group than in the general population suggesting they carry some genetic loading for the disorder. The presence of neuro-cognitive impairments in healthy relatives of people with schizophrenia may be related to the underlying genetic vulnerability for the illness. As such, these impairments may be reliable endophenotypes for the schizophrenia genotype, bridging the gap between diagnosis and genes. The identification of valid, reliable risk markers may assist in the development of early detection and intervention strategies to prevent the onset of illness in those at risk. The Study Of Nottinghamshire youth At Risk (SONAR) aims to identify neuro-cognitive markers of schizophrenia. Recruitment of young people with adolescent-onset schizophrenia, their first degree siblings (High Risk group), a healthy control group and a developmental control group of adolescents with ADHD is ongoing. All participants are aged 14 to 21. Inclusion of a developmental control group will determine the specificity of any neuro-cognitive deficits identified in the schizophrenia and High Risk (HR) groups. All groups are currently being assessed in the following areas of cognitive function: IQ, Executive Function, verbal learning and memory, vigilance and sustained attention, information processing. Preliminary results are available for the current sample. The adolescent-onset schizophrenia group show consistent and significant impairment on all measures. The HR group typically yield a mean score between that of the schizophrenia and healthy groups but there is heterogeneity in this group with outliers at both ends of the performance continuum. The ADHD group also show impairment in a number of areas. Analysis of the final data-set will provide clarification of the pattern of impairment specific to the schizophrenia genotype.

FRONTO-TEMPORAL FUNCTION MAY DISTINGUISH BIPOLAR DISORDER FROM SCHIZOPHRENIA

M. Haldane,* V. Kumari, S. Frangou
Section of Neurobiology of Psychosis, Institute of Psychiatry, London, United Kingdom

Objectives: There is evidence for differential neural alterations within the prefrontal cortex (PFC) in Bipolar Disorder I (BDI) and schizophrenia that may translate into different cognitive deficits. Our objective was to compare the cognitive profile of stable BDI and schizophrenia patients using neuropsychological tasks which utilize frontal systems but differ in terms of the exact neural circuits and cognitive processes involved. Methods: We studied 43 patients with BDI, 54 with schizophrenia and 46 matched healthy participants. All participants completed (1) the Wisconsin Card Sort test (WCST) which is known to recruit the dorsal and ventral PFC (2) the verbal fluency task (VFT) which engages frontal-temporal regions, and (3) the Stroop Colour Word Test (SWCT) which depends on the integrity of the cingulo-frontal network. A series of multivariate analyses examined differences between the cognitive profiles of BD and schizophrenia patients relative to that of healthy participants controlling for general intellectual ability and gender. Results: BDI patients showed minimal verbal fluency impairment while schizophrenia patients demonstrated marked deficits on this task relative to the control and BDI groups. The two patient groups had comparable performance on the WCST. In the SWCT, schizophrenia patients showed impairment in both congruent and incongruent conditions

while BD patients had deficits only in the latter. Conclusions Absence of significant verbal fluency abnormalities and by inference dysfunction in the associated fronto-temporal circuitry may distinguish BDI from schizophrenia. Both disorders may show impairment in tasks involving cingulo-frontal networks with evidence of greater cingulate dysfunction in schizophrenia.

THE VIRTUAL MORRIS WATER TASK IDENTIFIES A HIPPOCAMPAL BEHAVIORAL DEFICIT IN SCHIZOPHRENIA

F. M. Hanlon,* M. P. Weisend, D. A. Hamilton, A. P. Jones, R. J. Thoma, M. X. Huang, K. Martin, R. A. Yeo, G. A. Miller, J. M. Canive
Psychiatry, University of New Mexico, Albuquerque, NM, USA

Traditional neuropsychological tests of visual and verbal memory have been used to describe memory deficits in schizophrenia, which are similar to deficits found after hippocampal damage in humans. However, these tests of memory cannot be used in nonhuman animal research. Nonhuman animal research is imperative not only for the discovery of medications that will improve cognitive deficits found in schizophrenia but also for the discovery of the etiology of schizophrenia. To help bridge the gap between human and non-human animal research on hippocampal function in schizophrenia, this study sought to characterize the pattern of hippocampal dysfunction exhibited by patients using a task, the Morris water task (MWT), that on theoretical and empirical grounds, based on human and non-human animal studies, relies on the hippocampus. In the version developed to test humans, the virtual Morris water task (VMWT), subjects navigate a computer-generated environment to escape from the "water" by locating either a hidden or a visible platform using the arrow keys on a keyboard. Twenty-two schizophrenia patients and 22 controls performed two versions of the VMWT: a hidden-platform version that is hippocampal-dependent, relying on relational mnemonic and allocentric navigational abilities, and a visible-platform version that is not dependent on hippocampus, relying on simple mnemonic and cued-navigational abilities. Schizophrenia patients traveled further and took longer to find the hidden platform over training blocks and spent less time in the correct quadrant during a probe trial (with the platform removed). However, the groups did not differ in distance traveled to locate the visible platform or on percent time spent in the quadrant containing the visible platform, measures which are not hippocampal-dependent. Results showed an allocentric spatial navigation impairment, with sparing of cued navigation, in schizophrenia. These findings identify a hippocampal behavioral deficit in schizophrenia and, importantly, support the use of the MWT in developing and testing animal models of schizophrenia, as direct comparisons of hippocampal function in human clinical research and non-human animal research can be performed. This research was supported by an NIMH (R01 MH65304) grant to JMC.

RELATION OF NEUROBEHAVIORAL SIGNS, MINOR PHYSICAL ANOMALIES, AND SCHIZOTYPY IN HIGH-RISK ADOLESCENTS

S. Hans,* J. Marcus, J. G. Auerbach
School of Social Service Administration, University of Chicago, Chicago, IL, USA

Although individuals at genetic risk for schizophrenia show increased numbers of neurobehavioral signs and schizotypal personality features, little is known about whether these signs co-occur in vulnerable individuals. The data derive from the adolescent follow up of the Jerusalem Infant Development Study. The sample includes Israeli adolescents (average age 17) who have a schizophrenic parent (n=41), a parent with other mental disorder (n=39), or parents with no mental disorder (n=36). Schizotypal symptoms were assessed using the Semi-Structured Kiddie Interview for Personality Syndromes (K-SKIPS). Minor physical anomalies were assessed by physical examination and a variety of neurobehavioral measures were administered including neurological examination of motor soft signs, Trailmaking Test, Continuous Performance Test, Span of Apprehension Test, and Wisconsin Card Sort Task. Young people at risk for schizophrenia were more likely to have schizotypal symptoms than others in the sample. Neurobehavioral signs were correlated with schizotypal symptoms. Associations were strongest between motor dyscoordination and social withdrawal. K-means 2-group cluster analyses identified a cluster of individuals who had elevated schizotypy scores, physical anomalies, trailmaking times, and motor dyscoordination scores. That deviant cluster included an overrepresentation of male offspring of schizophrenia patients. Similar analyses computed without minor physical anomalies did not differentiate the offspring of schizophrenic parents from others. The combination of adolescent schizotypy, neurobehavioral signs, and anomalies may be markers to vulnerability to schizophrenia. Further of longitudinal study of this sample will be needed to determine whether this pattern of behavior is related to eventual onset of schizophrenia. The presence of minor physical anomalies within the high-risk cluster suggests an early neurodevelopmental origin to the clustering of schizotypy and neurobehavioral signs. Findings are consistent with a view that the developmental course of schizophrenia may be different for males and females.

PREDICTION OF REAL-WORLD FUNCTIONAL SKILLS IN SCHIZOPHRENIA: PERFORMANCE-BASED ASSESSMENTS AND NEUROPSYCHOLOGICAL PERFORMANCE

P. D. Harvey,* C. R. Bowie, T. L. Patterson, R. K. Heaton
Psychiatry, Mt. Sinai School of Medicine, New York, NY, USA

Functional impairments in schizophrenia are a major source of disability and a target for pharmacological treatment, through cognitive enhancement. The nature of the relationship between real-world functional skills and performance-based functional skills assessment is not clear and it is further unclear as to which of these measures would be most related to Neuropsychological (NP) performance. Baseline data from a longitudinal study of the course of NP and functional status of older (age 50-85) schizophrenia patients (N=91) were examined. A composite score was created from a battery of NP tests. Symptoms were rated with the PANSS. Functional status was examined with a performance-based measure (UPSA) as well as ratings from real-world caretakers (SLOF). The UPSA assesses the ability to plan activities, manage finances, communicate, and use public transportation. The SLOF consists of caretaker ratings of physical functioning, personal care skills, interpersonal relationships, social acceptability, activities, and work skills. The two functional variables

were highly correlated with each other (r = .63 p<.01) and the NP composite score was somewhat more highly correlated with performance-based functional skills (r = .66, p<.01) than with real world functioning (r = .54, p <.01). When the relationship between the SLOF and NP performance was examined for direct vs indirect (mediated by UPSA performance) influences, it was found that the entire relationship between NP performance and real-world functional status was mediated by UPSA scores, which accounted for 40% of the variance in the SLOF. It was found that PANSS general symptoms predicted an additional 7% of the variance in SLOF scores above and beyond UPSA performance. Similar to previous research, NP performance was a significant correlate of real-world functional skills performance, but this relationship did not account for any unique variance when performance-based measures of functional skills were considered. These data suggest that performance-based measures of functional skills may be suitable outcome measures for clinical interventions aimed at functional outcome in schizophrenia. These findings are remarkably consistent with recent studies of patients with HIV, where NP performance was correlated with proxy measures of functional skills, but where those proxy functional skills measures and severity of depression accounted for the majority of the reliable variance in real-world outcome.

FINDING VERBAL MEMORY-BASED SUBTYPES AND ENDOPHENOTYPES FOR SCHIZOPHRENIA: TRAITS, STATES OR BOTH?

W. Heinrichs,* S. McDermid Vaz
Psychology, York University, Toronto, ON, Canada

The possibility that biobehavioral endophenotypes underpin broad illness categories like schizophrenia has spurred a search for objective indicators of these putative vulnerabilities and disease-promoting diatheses (Gottesman & Gould, 2003). Measures of verbal memory acquisition (VMA) show promise because VMA deficits correlate with neural systems implicated in schizophrenia, show evidence of heritability, occur in a large proportion of patients and predict aspects of medication response and functional outcome. Recent VMA-based approaches include a cortical-subcortical-normative typology derived from dementia patients (Turetsky et al., 2002) as well as an impaired-unimpaired dichotomy based on psychometric criteria (McDermid Vaz & Heinrichs, 2002). Both approaches have shown preliminary evidence of clinical and biological validity, but only on a cross-sectional basis. It is not known whether VMA-based typologies represent enduring or transitory disease features. The issue is complicated further by the enrollment of patients medicated with second-generation antipsychotic drugs, which may enhance cognition and restrict VMA variance. The purpose of our study was to examine the stability of the reported typologies and to propose refinements in their definitions. We retrospectively analyzed California Verbal Learning Test data from 102 DSM-III-R schizophrenia patients treated with conventional neuroleptic medication prior to the widespread introduction of novel antipsychotic drugs in the mid 1990s. Fifty-five of these patients were followed up three years later. Employing the clustering method described by Turetsky et al. (2002), we partially replicated their cortical-subcortical-normative subtypes. However, three-year stability was modest (kappa = .57; p < .001). Analysis of the McDermid Vaz and Heinrichs (2002) dichotomy, which defined VMA impairment as cumulative word list learning at least two standard deviations below normative values, also showed modest stability (kappa = .50; p < .001). Internal analysis of the data suggest the existence of three VMA patterns in the schizophrenia population: a stable or trait-like impairment, a transitory or state-like impairment associated with progression and regression, and a stable or trait-like normal performance. Trait-like VMA impairment, with an estimated prevalence of 40% in the patient population, may represent the next step in the search for cognitive endophenotypes of schizophrenia.

LONGITUDINAL NEUROPSYCHOLOGICAL FINDINGS OF FIRST EPISODE SCHIZOPHRENIA AFTER TEN YEARS OF ILLNESS

A. Hoff,* L. E. DeLisi, A. Maurizio
Department of Psychiatry, New York University, New York, NY, USA

With an increasing emphasis on neurocognitive impairment as a target in the treatment of schizophrenia, there is a greater necessity to understand the degree of such dysfunction prior to, at the time of onset, and over the course of illness. There have now been a number of longitudinal studies of neuropsychological function, but most evaluate patients at two time points after the onset of illness, at relatively short follow-up intervals, and most frequently without a control group to assess normal change in cognitive functioning over time. These limitations are understandable in light of the difficulty in maintaining subjects, particularly controls, in long-term follow-up studies. Nevertheless, careful systematic longitudinal studies of first episode patients at regular intervals are essential in being able to accurately determine the developmental and potentially progressive aspects of this illness. A careful review of this literature over the past 15 years yields only three studies with controls, two studies with a follow-up period of at least 5 years, and one study with a 4 to 5 year follow-up and a control group (Hoff et al.,1999). We have continued to follow this cohort of first episode patients (n=21) and controls (n=8) over 10 years measuring symptoms, neuropsychological functions, and MRI variables of brain hemisphere and lateral ventricular volume. Analyses of covariance, with baseline performance as covariate, examined differences in change from years 1 to 10 between patients and controls. Compared with controls, patients improved less in verbal intellectual functioning, delayed visual recall, and cognitive inhibition and deteriorated more than controls on a measure of verbal learning. Correlations computed between neuropsychological difference scores and difference scores of symptom ratings and MRI variables yielded few statistically significant results. Compared to data from the 4 to 5 year follow-up study (Hoff et al., 1999), these data suggest relatively greater deterioration, or relative lack of improvement, in patients compared to controls on measures of cognitive function over 10 years of illness. These data have implications for early treatment intervention as a means of reducing cognitive deterioration associated with the course of schizophrenic illness.
Hoff AL, Sakuma M, Wieneke M et al.: Longitudinal neuropsychological follow-up study of patients with first-episode schizophrenia. *Am J Psychiatry* 1999; 156:1336-1441.

NEUROCOGNITIVE PROFILES OF PRODROMAL PSYCHOSIS

S. A. Hunt,* U. Schall, S. A. Halpin, C. J. Beckmann, V. Carr
Centre for Mental Health Studies, Newcastle, NSW, Australia

Researchers have been trying for some time to accurately identify young people who are at risk of developing schizophrenia. One method of doing this, is to examine early cognitive and social func-

tioning in young people deemed to be at increased risk of developing psychosis (e.g. with a family history of schizophrenia and/or bipolar disorder, significant decline in role functioning, brief episode or acute psychotic symptoms), as research has linked cognitive impairment with later transition to schizophrenia. In the study presented here, 340 fourteen to thirty year-olds at high risk of psychosis, were prospectively assessed at a community early psychosis clinic in Newcastle, Australia. At first referral to the service a range of data was collected including neurological soft signs, executive function, attention, auditory and visual memory, and illicit drug use history. A representative subset of 113 subjects, were then followed up one to three years after their initial assessments, and completed the Diagnostic Interview for Psychosis (DIP). The results showed that young people with first episode psychosis differ from those deemed to be at high risk in the severity of impaired verbal recall and semantic clustering (California Verbal Learning Test), impaired logical and verbal memory (WMS), impaired delayed visual recall memory (Rey Complex Figure) as well as fewer categories completed due to increased total errors (perseverative and non-perseverative errors) in the Wisconsin Card Sort Test. Stroop and Verbal Fluency performance however, did not differ between groups. The contribution of illicit drug use and family history of severe mental illness to the recorded cognitive impairment was minimal. These findings suggest that pronounced neurocognitive deficits in these domains in combination with prodromal psychotic symptoms indicate a higher probability of transition to schizophrenia.

LONGITUDINAL STUDIES OF INDIVIDUALS AT HIGH-RISK FOR SCHIZOPHRENIA: WHY THEY WERE NECESSARY, WHAT THEY DISCOVERED, AND WHAT REMAINS TO BE DONE

L. J. Ingraham,* J. Auerbach, L. Erlenmeyer-Kimling, B. Fish, S. Hans, J. Marcus, T. McNeil, A. Mirsky, E. Schubert

Program in Professional Psychology, George Washington University, Washington, DC, USA

Identification of the earliest manifestations of schizophrenia spectrum disorders (SZSD) has long been a goal of investigators seeking clues to pathophysiology and opportunities for prevention and early intervention. A related goal has been to examine the role of environmental factors from conception through adulthood on outcome. Retrospective analyses of early development and events may be influenced by the effect of knowledge of present illness influencing recall, or the limitations of archival material collected for other reasons. Prospective longitudinal studies (beginning as early as the second trimester) of infants and children at risk for SZSD capitalize on the approximately 10% risk for schizophrenia in the offspring of a parent with schizophrenia. Prospective studies allow unbiased sampling of the early developmental course across multiple domains of individuals who later develop SZSD. The 2 earlier studies used normal or community comparison groups. Later studies also included mentally ill comparison groups. A major limitation of these studies is that they are very labor-intensive over a long period, so that the total number of subjects is limited. We propose to compensate for this major limitation by pooling the data from 5 such studies which have now followed their subjects until adult diagnoses can be made. Two require additional assessment in later adulthood to follow subjects through a significant portion of their lifetime risk for SZSD. All 5 studies have successfully identified neurobehavioral differences between at-risk and control subjects. In combination, samples from the New York Infant High-Risk Study (Fish), the Swedish High-Risk Study (McNeil, Schubert), the Jerusalem Infant Development Study (Hans, Marcus, Auerbach), the NIMH Israeli Kibbutz Study (Ingraham, Mirsky) and the New York High-Risk Project (Erlenmeyer-Kimling) allow for a comparison between 271 children at high risk for schizophrenia and 412 control children, with index children having a mean age at most recent follow-up of 28.3 years.

NEUROCOGNITIVE DETERMINANTS OF FUNCTIONAL RECOVERY: A LONGITUDINAL EXAMINATION IN 250 RECENTLY DISCHARGED PATIENTS WITH SCHIZOPHRENIA

J. Jaeger,* P. Czobor, S. M. Berns, A. M. Donovan-Lepore, B. Creech, R. Basile-Sculz, S. Farella-Busch, S. Davis-Conway, C. Gomes

Center for Neuropsychiatric Outcome and Rehabilitation Research, Zucker Hillside Hospital-NSLIJHS, Glen Oaks, NY, USA

Neurocognitive (NC) deficits may play a major role in functional disability in schizophrenia (SZ). Thus, clarifying the relationship between NC performance & functional course is critical for better targeting of pharmacologic, cognitive & psychosocial interventions. While the presence of such a relationship has been repeatedly suggested in the literature, a number of issues remain. Most studies have insufficient power to 1) handle the numerous, often intercorrelated measures generated by a full NC battery, 2) examine which (if any) cognitive domains independently explain functional improvement (FI), or 3) clarify the role of positive & negative symptoms in the NC-disability relationship. We studied these relationships in 250 recurrent SZ sufferers over a period ranging 18-24 months post-hospital discharge. Functioning was rated monthly using the MSIF, an anchored scale developed & validated in SZ (Jaeger et al, 2003a). A comprehensive NC battery and the PANSS were administered at baseline (within 6 months post-discharge) and again 6 & 18 months hence. Independent variables (IV's) included 11 NC measures, selected and aggregated according to published methods (Jaeger et al,2003b). Covariates were PANSS positive & negative subscales (POS/NEG). *Predictive* models examined both *probability* & *speed* (in days) of significant FI, defined as a 2-point global MSIF improvement, achieved by 61 subjects (24.4%). Logistic regression showed that among the 13 IV's & covariates obtained at baseline, only the Attention Factor (ATTN) (also tapping processing speed) independently predicted subsequent FI (Odds Ratio(OR)=2.16;p=.027). Since later NC testing might better reflect enduring deficits, this analysis was repeated using 6 month data. Six month ATTN (OR 5.47;p=.0002) & Finger Tapping (OR 1.65;p=.026) each independently predicted FI for the remaining follow up period. Again, POS/NEG ratings were not predictive. Cox Proportional Hazard procedure was used to examine factors associated with speed of FI. Time to FI was regressed on the NC factors & POS/NEG in a single model. Only ATTN independently predicted time to recovery (Hazard Ratio=2.205;p=.003). *Associative* models using HLM yielded similar findings, although here NEG rating was also associated with disability over time. Findings suggest a reliable & relatively selective relationship between NC measures of Attention/Processing Speed and both FI and overall functioning over an 18-24 month period post-discharge.

METACOGNITION AMIDST NARRATIVES OF SELF AND ILLNESS IN SCHIZOPHRENIA: ASSOCIATIONS WITH SYMPTOMS AND NEUROCOGNITIVE FUNCTION

J. K. Johannesen,* P. H. Lysaker
Psychology, Indiana University-Purdue University Indianapolis, Indianapolis, IN, USA

Objective: There is evidence that poor performance on laboratory tasks of metacognition relates to neurocognitive impairment in schizophrenia, primarily in domains of verbal and visual memory, and executive function. We sought to replicate these results in a study of metacognition within personal narratives of self and illness. *Methods:* Narratives were collected from 61 male outpatients, meeting diagnostic criteria for schizophrenia, and rated using the Metacognition Assessment Scale. Partial correlations controlling for age and education were conducted with concurrent assessment of PANSS symptom ratings and neurocognitive function in domains of verbal and visual memory, processing speed, executive function and vocabulary. *Results:* Better understanding of one's own mind was linked with less emotional withdrawal and better verbal and visual memory, processing speed, and vocabulary. These neurocognitive scores were entered into a stepwise multiple regression as predictors of understanding of one's mind [$F(4,56) = 4.73$, $p < .01$], in which both vocabulary (partial $R^2 = .15$) and digit symbol (partial $R^2 = .10$) scores uniquely contributed, and accounted for a quarter of the variance cumulatively (Total $R^2 = .25$). Greater understanding of other's mind was linked with less emotional withdrawal and better verbal memory. Greater metacognition in the context of purposeful problem solving was associated with less emotional withdrawal and paranoia, and better verbal memory. *Conclusions:* Naturally occurring deficits in metacognition within the narratives of persons with schizophrenia are linked with symptoms that are particularly detrimental to social behavior, as well as neurocognitive functioning in domains relevant to interpersonal communication.

NEUROCOGNITIVE PREDICTORS OF OUTCOME 5 YEARS AFTER A FIRST EPISODE OF SCHIZOPHRENIA: THE WEST LONDON STUDY

E. Joyce,* S. B. Hutton, C. Foster, S. H. Mutsatsa, I. Harrison, T. R. Barnes
Dept Psychological Medicine, Imperial College, London, United Kingdom

Neurocognitive impairment is considered a core feature of schizophrenia. Cross-sectional studies of established schizophrenia have found that neurocognitive function is more related to social function than residual symptoms. In a prospective first episode study, we examined the predictive value of neurocognitive function at first presentation to psychiatric services with regard to outcome five years later, and also the associations between neurocognitive function, symptoms and social function at the 5-year assessment. 68 patients with DSM IV schizophrenia were assessed at first episode and a mean of 58 months later (median 60, range 33-106) on clinical and neurocognitive measures (IQ, recognition memory, spatial span, spatial working memory, planning, attentional set shifting) and the Birchwood Social Function Scale. At initial assessment of this patient cohort, there was evidence of a significant fall in mean IQ compared to pre-morbid estimates (NART). Further, compared to age and IQ matched normal volunteers, they showed impairments on all memory and executive functions. At 5-year follow-up, there was no change in mean IQ. Executive functions had tended to improve modestly or show no change. The only measure showing deterioration was pattern recognition memory. Duration of untreated psychosis significantly predicted residual symptoms at 5 years (negative symptoms: r=0.3; p=0.03) although there were trends for age of onset (r=-0.22; p=0.07) and pre-morbid IQ (r=-0.22; p=0.09). Of all measures, only pre-morbid IQ predicted social function at 5 years (r=0.28, p=0.028). At the 5-year assessment, negative symptoms and current IQ independently predicted social function. The subgroup of patients who were in gainful full-time employment or who were full-time students demonstrated significantly fewer symptoms and had a higher mean IQ than a group who were unemployed. Individual measures of memory or executive function assessed either at first episode or 5 years later were not associated with outcome. In this study, poor premorbid IQ was a predictor of social function at 5 years. A decline in IQ around the time of onset was found in a proportion of this sample and at 5-year follow-up, current IQ was strongly related to the ability to undertake gainful employment or full-time studies. Because it captures a range of intellectual functions, IQ may be a better indicator of outcome than individual measures of memory or executive function. Funded by The Wellcome Trust.

A DIFFERENTIAL IMPACT OF ATYPICAL ANTIPSYCHOTICS ON NEUROCOGNITIVE FUNCTIONING IN VIOLENT FORENSIC SCHIZOPHRENIA PATIENTS

S. Kertzman,* I. Reznik, L. Luthorovich, H. Grinspan, M. Birger, N. Shlapnicov, M. Kotler
Beer-Yakov Mental Health Center, Beer-Yakov, Israel

Recent research data point on probable efficacy of atypical antipsychotics (AA) in improving neurocognitive functioning (NCF) and on their anti-aggressive benefits. The objective of this study was to detect the changes of NCF under treatment with various AA among violent schizophrenia (Sch) patients. Male violent forensic Sch inpatients were treated with: olanzapine (OLZ) (n=14), clozapine (CLZ) (n=11), risperidone (RIS) (n=9) for 12 weeks. The mean age of the whole study group was 36.26 (11.38) years, without significant between-groups differences. An assessment tools were subtests derived from computerized neuro-cognitive battery (CogScan, Anima-Scan Ltd): Finger Tapping Test (FTT), Inspection Time (IT), Simple Reaction Time (SRT), Digit Running Time-Accuracy Trade-off, Stroop test (ST). Statistics: univariate analyses of variance for between-groups differences. No significant between-groups differences were found in all tests before the treatment. Following treatment, significant differences were found in SRT (ms) ($F[1,30]=3.87$, $p<.05$): RIS group showed better performance comparing to the other groups (RIS: 274.3(71.88), CLZ: 332.7 (71.9), OLZ: 366.9 (97.1), time-accuracy trade-off, only accuracy ($F[2,29]=4.14$, $p<.05$) with RIS group being more accurate comparing to the CLZ group and equivalent to OLZ group (RIS: 92.9 (5.2), CLZ: 86.5 (6.3), OLZ: 92.3 (5.0). On ST, marginally significant differences were found only in OLZ group: neutral ($F[1,24]=3.34$,$p=.08$), 1598.7 (452.3) vs 1216.6 (519.1), congruent ($F[1,24]=2.23$, $p=.15$), 1350.3 (408.3) vs 1091.0 (475.4), non-congruent ($F[1,24]=3.37$, $p=.07$), 1636.9(580.0) vs 1236.4(530.8). No significant between-groups differences were found on FTT and IT. Differential changes in NCF following treatment with various AA among violent Sch patients were shown.

RIS did not change input and output stages of information processing but it improves simple psychomotor reactions, measured by SRT. Under RIS, in situations of information overload, improvement was found in accuracy of performance which could be expained, at least partialy, by lower sedation effect of RIS. The improvement in selective attention, measured by ST, was found in OLZ group, which may be relevant to the explanation of the antiaggresive effect of OLZ as independent from general antipsychotic activity. This antiagressive effect may be a result of improvement of inhibition ability, which is a function of better information selection.

IMPAIRED EARLY-STAGE VISUAL MOTION PROCESSING IN SCHIZOPHRENIA

D. Kim,* G. R. Wylie, R. Pasternak, P. D. Butler, D. C. Javitt
Cognitive Neuroscience and Schizophrenia, Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, USA

Patients with schizophrenia show impairments in discriminating the velocity of moving gratings, a finding that has been interpreted as showing selective impairment in functioning of dorsal-stream visual areas such as V5 (MT). However, lower level disturbances in visual processing have also been reported in schizophrenia. These findings reflect dysfunction of the magnocellular visual system and/or early visual sensory regions (e.g., V1). We investigated information processing at low vs. high levels of the visual system by comparing integrity of incoherent vs. coherent motion processing. When all the elements in a display move in a similar direction (coherent motion), MT is more active than when the elements move randomly (incoherent motion). Here, velocity thresholds for motion detection were determined separately for incoherent and coherent motion, and levels were compared between groups. Further, coherent motion sensitivity was tested explicitly at incoherent motion threshold. First, velocity discrimination thresholds were measured for schizophrenia patients (n=14) and age-matched normal control subjects (n=16) for both coherent and incoherent motion. Then, the incoherent motion threshold was used as the threshold for a coherent motion discrimination task in which accuracy was the primary dependent measure. Subjects viewed two moving targets sequentially (1000 ms duration, 500ms between displays) that differed in velocity and reported if the velocities were same or different. A three-down, one-up staircase procedure was used (resulting in an accuracy rate of 79.4%). Patients and controls differed in both incoherent ($t=-3.1$, $p=0.005$) and coherent ($t=-3.5$, $p=0.002$) motion thresholds. When both incoherent and coherent measures were entered into an ANOVA, there was a group effect ($F(1,28)=13.2$, $p=0.001$) but no significant group x task interaction ($F<1$). Further, when coherent motion performance was measured at individually determined incoherent motion thresholds, accuracy levels for patients (81%) were similar to controls (78.3%) with no significant between-group difference ($t=0.9$, $p=0.4$). These results demonstrate deficits in both incoherent and coherent motion detection, suggesting deficits in early as well as stages of motion processing. The lack of between-group difference in coherent motion tested at individually determined incoherent motion thresholds suggests that deficits in early processing may significantly drive subsequent higher order deficits.

NEURAL CORRELATES OF IMPAIRED SYNTAX PRODUCTION IN SCHIZOPHRENIA

T. T. Kircher,* T. Oh, M. Brammer, P. K. McGuire
Dept. of Psychiatry, RWTH University of Aachen, Aachen, Germany

Background: The production of grammatically complex sentences is impaired in schizophrenia. It has been proposed, that impaired syntax processing reflects a risk for the disorder. Aims: We examined the neural correlates of syntax production in patients with schizophrenia using functional Magnetic Resonance Imaging (fMRI). Method: Blood oxygenation level dependent (BOLD) contrast was measured with fMRI while 6 patients with schizophrenia and 6 healthy control subjects spoke about 7 Rorschach inkblots for 3 min each. Subjects produced varying amounts of syntactically simple and complex sentences during each run. In a within subject design, the number of simple and complex sentences was correlated separately with the BOLD contrast in the 2 runs from each participant that showed the highest variance in sentence complexity. Results: In control subjects, the number of complex sentences produced was correlated with activation in the posterior portion of the middle temporal gyrus bilaterally (BA 21, 39). In patients this correlation was evident in the left posterior middle temporal gyrus but not the right. Conclusions: An association between the production of syntactically complex sentences and engagement of the posterior temporal cortex is consistent with data from functional imaging studies in healthy volunteers. The absence of activation in the right posterior temporal cortex in patients with schizophrenia might contribute to the articulation of grammatically more simple speech in people with this disorder.

ASSOCIATION OF SYMPTOMS AND EXECUTIVE FUNCTION IN SCHIZOPHRENIA AND BIPOLAR DISORDER

E. Kravariti,* T. Dixon, C. Frith, R. Murray, P. McGuire
Psychiatry, Institute of Psychiatry, London, United Kingdom

We aimed to investigate the extent to which cognitive impairment in psychosis is related to the particular disorder or the pattern of symptoms. Executive function tasks of verbal fluency, response inhibition, sentence completion and strategic thinking were administered to two groups of schizophrenia patients with predominant symptoms of disorganisation (n=15) and psychomotor poverty (n=15), respectively, two groups of bipolar I disorder patients with predominant symptoms of mania (n=15) and depression (n=15), respectively, and 30 healthy controls. We predicted that the pattern of symptoms ('excess' [disorganisation/mania] or 'deficiency' [negative symptoms/depression]) would be more related to executive ability than the underlying disorder. The patient groups showed partially overlapping executive dysfunctions relative to the control group. There were no significant differences between groups with 'excess' symptoms (schizophrenia patients with thought disorder and bipolar patients with mania), or between groups with 'deficiency' symptoms (schizophrenia patients with negative symptoms and bipolar patients with depression). In contrast, differences were noted between groups with the same diagnosis: Schizophrenia patients with disorganisation were less accurate in semantic verbal fluency than those with negative symptoms; and bipolar patients with mania tended to be faster, but less accurate, in sentence completion than those with depression. A statistical comparison of the associations of 'diagnosis' and the 'excess-deficiency' dimension with executive function revealed a trend for a greater association of the latter with two measures of performance accuracy. Executive dysfunction in patients with

psychotic disorders may be more related to their symptom profile than their diagnosis. Dr Kravariti is supported by a research grant from the Psychiatry Research Trust.

NEUROCOGNITION AND RECOVERY FROM PSYCHOSIS DURING AN INITIAL MONTH OF TREATMENT

Z. Kupper,* W. Tschacher
University Hospital of Social and Community Psychiatry, University of Bern, Bern, Switzerland

In cross-sectional studies neurocognition and symptom ratings in schizophrenia patients have been frequently found to be independent. Although significant associations between neurocognition and symptoms have been reported by other studies, these results fail to converge. A longitudinal approach may be helpful in clarifying the relationships between symptoms and neurocognition. In the "Schizophrenia Process Study" performed at the University of Bern, Switzerland, symptom courses of 43 schizophrenia spectrum patients were observed. A 10-item scale for daily symptom assessment was applied (Today's Evaluation of Psychopathology, TEP). The rating scale was composed of four factors: psychoticity, excitement, affective symptoms and negative symptoms. Daily ratings of psychopathology were performed during the 30 initial days of community based inpatient treatment. Individual courses were analyzed by time series regression yielding mean values of symptoms, slopes of symptom changes and estimates of symptom fluctuations for each patient. A comprehensive neurocognitive assessment was used to test for associations between the longitudinal symptom patterns and neurocognition. Results revealed specific relationships between neurocognition and the longitudinal symptom patterns. As an example, a specific problem with verbal memory, intrusion errors during recall, was associated with no recovery or worsening of psychoticity during this initial one-month period of treatment. The result held still true if residualized change of psychoticity was considered. Furthermore, recall intrusions were also positively related to symptom fluctuations. Comparing the relative predictive value in the four symptom domains, neurocognitive factors were associated most strongly with psychoticity and least with affective symptoms. A longitudinal "fine grained" approach to the evolution of symptoms may be helpful, if not necessary, to uncover common factors underlying neurocognition and symptoms.

NEUROCOGNITIVE REMEDIATION FOR PATIENTS WITH SCHIZOPHRENIA: HOW SPECIFIC IS THE INTERVENTION AND ITS EFFECTS?

M. M. Kurtz,* J. C. Seltzer, D. S. Shagan, B. E. Wexler
Schizophrenia Rehabilitation Program, Institute of Living, Hartford, CT, USA

A growing body of research suggests that neurocognitive deficits in patients with schizophrenia can be ameliorated with behavioral training procedures (e.g., Twamley et al., 2003). Conclusions from these studies, however, have been limited by control groups that were not matched with behavioral interventions on crucial dimensions including interaction with a clinician, exposure to a computer and non-specific cognitive challenge. To address these issues, we evaluated the effects of a comprehensive, standardized set of computer-assisted cognitive exercises targeted at improving attention, memory, and problem-solving through repeated practice, on a variety of neuropsychological outcome measures. Patients were randomly assigned to one of two groups: group 1 was a cognitive remediation group that consisted of 100 hours of training on cognitive exercises administered over a 12-month period. Group 2 was a computer-skills training control group that consisted of a series of lessons in basic computer literacy matched with the remediation group for hours on a computer and clinician contact. To date, 38 patients with schizophrenia have enrolled and 20 have completed their training. A series of dependent sample t-tests on pre- vs. post-training scores (Table 1) for completed patients revealed significant improvement on measures of working memory (WAIS-III, WMI) after cognitive remediation, but not after computer-skills training. Significant improvement was evident in both groups on a measure of verbal learning (CVLT-II) and a trend toward improvement in both groups was evident on a measure of executive-function (BCT). No effects of either condition were evident on a measure of speeded motor sequencing (Grooved Pegboard). The significance of these findings for the development and implementation of interventions for cognitive deficits in schizophrenia will be discussed.

Table 1. Pre- and post-training scores on neuropsychological outcome measures.

Note: WAIS-III WMI=Wechsler Adult Intelligence Scale-III, Working Memory Index; CVLT-II=California Verbal Learning Test-II; BCT=Booklet Category Test. *=p<.05.

DURATION OF UNTREATED PSYCHOSIS AND NEUROPSYCHOLOGICAL FUNCTION IN THE AESOP FIRST-ONSET PSYCHOSIS STUDY

J. M. Lappin,* K. D. Morgan, P. Dazzan, C. Morgan, P. Fearon, G. Hutchison, R. M. Mallett, J. Leff, P. B. Jones, R. M. Murray
Division of Psychological Medicine, Institute of Psychiatry, London, United Kingdom

Introduction: This study aimed to investigate the relationship between duration of untreated psychosis (DUP) and neurocognitive function in patients with first-episode psychosis. Method: Subjects were recruited as part of a large epidemiological study (AESOP). Duration of psychotic symptoms and of other symptoms of behavioural change was estimated from structured interviews. A comprehensive neuropsychological test battery that assessed general intellectual function, executive function and working and short-term memory was administered to 98 patients (n=38.9% female; mean age 27.2 +/- SD 0.82 years) shortly following commencement of treatment for their first episode of psychosis. Subjects were divided into long and short DUP according to the median value (56 days) of DUP. Performance in neuropsychological tests was compared between long DUP and short DUP patient groups. In addition, correlational analysis investigated whether there was a significant relationship between length of DUP and neuropsychological performance. Results: There were no significant differences in

neurocognitive performance between long DUP and short DUP groups on any of the test battery items. Correlational analyses identified no significant association between length of DUP and measures of neurocognitive function. However, there was a trend for a negative correlation for visual memory (p=0.068) and verbal memory (p=0.079). Conclusion: These data suggest that there is only a weak association between duration of untreated psychosis and neurocognitive function at time of first treatment for psychosis. Thus, DUP is unlikely to explain why patients with first-episode schizophrenia have widespread deficits in cognitive functioning.

PRELIMINARY DATA ON NEUROPSYCHOLOGICAL FUNCTIONING REVEAL CLOSE TO NORMAL PERFORMANCES IN A SAMPLE OF FIRST-EPISODE PSYCHOSIS PATIENTS

A. Lefebvre,* C. Lehoux, K. Letourneau, J. Bourbeau, A. Barrette, C. Vallieres, L. Laplante, R. Bouchard, R. Ouellet, M. Cayer, C. Emond, C. Merette, M. Roy
F-4500, Centre de Recherche Universite Laval Robert-Giffard, Beauport, QC, Canada

Schizophrenia patients display various neuropsychological impairments with many performances being one to two standard deviations below the norms (Heinrichs & Zakzanis, 1998). This conclusion is drawn, however, from chronic schizophrenia populations treated with first-generation antipsychotics. Modern studies conducted with first-episode psychosis patients have found mixed results (Addington, Brooks & Addington, 2003). We investigated the neuropsychological functioning of first-episode patients treated in an optimal context. In a study aimed at investigating the relationship between neurocognition and outcome, we assessed 35 DSM-IV first-episode psychotic disorder patients and 15 controls (investigated functions: vigilance, working memory, verbal memory, nonverbal memory, language, visuo-spatial perception, visuo-spatial organization, executive functioning, motor dexterity, and estimated IQ). Preliminary results revealed nearly normal performances for 7 out of 10 neuropsychological constructs. Only verbal fluency, nonverbal memory and motor dexterity performances were found to be one standard deviation below the norms. In an optimal treatment context, first-episode psychosis patients may exhibit near to normal neuropsychological performances. Duration of untreated psychosis and subtle differences in treatment may explain the different results. Catherine Lehoux and Andree-Anne Lefebvre are funded by student awards (FCAR: Fonds pour la Formation de Chercheurs et Aide a la Recherche; FRSQ: Fonds pour la Recherche en Sante du Quebec). Marc-Andre Roy is funded by a clinical scientist award from the FRSQ and by a Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression.

NONVERBAL FUNCTIONS ARE CORRELATED TO SOCIAL FUNCTIONING IN FIRST-EPISODE PSYCHOSIS

C. Lehoux,* A. A. Lefebvre, K. Letourneau, J. Bourbeau, L. Gauvin, S. Poirier, J. Everett, R. Ouellet, C. Emond, M. Cayer, C. Merette, M. A. Roy
Centre de Recherche Universite Laval Robert-Giffard, Beauport, QC, Canada

Most of the studies investigating the relationship between neuropsychological performances and social functioning have been conducted with chronic schizophrenia patients treated with first-generation antipsychotics. Moreover, most of these studies have focussed on verbal functions thus neglecting nonverbal functions such as visuo-spatial perception and visuo-spatial organization. The goal of this study is to investigate the relationship between a comprehensive neuropsychological battery and social functioning in first-episode psychosis patients treated with atypical antipsychotics in an optimal context. To date, 35 DSM-IV first-episode psychotic disorder patients (schizophrenia, schizophreniform disorder, schizoaffective disorder and delusional disorder) and 15 community controls have been assessed. The neuropsychological battery examined vigilance, working memory, verbal memory, nonverbal memory, language, visuo-spatial perception, visuo-spatial organization, executive functioning, and motor dexterity functions and also provided an estimated IQ. Social functioning was assessed through the Strauss and Carpenter Outcome Scale. Our preliminary results revealed that visuo-spatial perception, visuo-spatial organization and nonverbal memory are associated with social functioning, with correlations ranging from 0.37 to 0.61. These results suggest that nonverbal impairments might be a crucial determinant of social functioning in first-episode patients. Catherine Lehoux and Andree-Anne Lefebvre are funded by student awards (FCAR: Fonds pour la Formation de Chercheurs et Aide a la Recherche; FRSQ: Fonds pour la Recherche en Sante du Quebec). Marc-Andre Roy is funded by a clinical scientist award from the FRSQ and by a Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression.

IMPLICIT MOTOR LEARNING AND SET-SHIFTING DEFICITS IN FIRST EPISODE SCHIZOPHRENIA

T. Lencz,* E. Turkel, D. G. Robinson, A. K. Malhotra, P. R. Szeszko, M. Woerner, J. M. Kane, R. M. Bilder
Dept. of Psychiatry Research, The Zucker Hillside Hospital, Lake Success, NY, USA

Background: Deficits in cognitive set-shifting are among the most well-replicated neurocognitive abnormalities associated with schizophrenia. However, most such tests are dependent on higher-order cognitive processes that can be confounded by multiple deficits in domains such as attention, working memory, and motoric response. Consequently, we developed a task that assesses implicit motor set acquisition (learning) and set-shifting where conscious awareness does not subserve task performance; such functions are likely mediated by dopaminergic fronto-striatal circuits that may be compromised in schizophrenia. Methods: The task is a computerized measure of reaction time (RT) in which the subject responds by pressing a right or left hand key corresponding to the side of the screen that the stimulus appears. There are two fixed stimulus sequences used, each consisting of repeated triads: Right-Right-Left (RRL), and Left-Left-Right (LLR). After a baseline condition of randomly appearing stimuli, there are 6 blocks of 24 sequenced trials, alternating between RRL and LLR blocks. Key dependent measures are shift-cost (increase in RT between blocks, when the pattern shifts) and learning (decrease in RT within a block). Seventy-six patients in the first episode of schizophrenia were tested at pre-treatment baseline, along with 67 healthy volunteers. Results: 1) Factor analysis revealed that learning and set-shifting scores loaded together (convergent validity), and these were dissociable from baseline RT and traditional neuropsychological measures (discriminant validity). 2) Implicit learning was significantly impaired in patients, even controlling for differences in baseline RT. 3) In patients, learning was

significantly correlated with left anterior cingulate gyrus volume, as measured from high-resolution structural MRI. 4) In patients, preliminary data suggest that learning and shift-cost scores are significantly predicted by genotype of the catechol-O-methyltransferase (COMT) Val158Met polymorphism, with met/met patients having significantly greater learning effects, but also shift costs, relative to patients with either one or two copies of the val allele. Conclusions: Implicit motor set-acquisition and set-shifting can be experimentally isolated using a relatively simple paradigm. Deficits in patients with first episode schizophrenia may provide a window on fronto-striatal functioning, mediated by structural anatomic and genomic variability.

GRIP STRENGTH IS CORRELATED TO SOCIAL FUNCTIONING IN SCHIZOPHRENIA

K. Letourneau,* J. Everett, C. Lehoux, C. Emond, L. Laplante, R. H. Bouchard, M. Michel, C. Merette, M. A. Roy
Centre de Recherche Universite Laval Robert-Giffard, Quebec, QC, Canada

It is now well known that cognitive deficits in schizophrenia are related to daily functioning of patients. In 2003, Lehoux et al. found that fine motor dexterity as measured by the Purdue Pegboard Test is among the strongest predictors of social functioning in a sample of schizophrenic patients. The main goal of the present study is to determine which specific component of the Purdue Pegboard test better explain this relationship. The protocol was designed to assess motor speed (Finger Tapping Test), visual-motor coordination (Color Trail Test), tactile perception (two-point discrimination test), grip strength (Dynamometer), anxiety (Covi Anxiety Scale) and extrapyramidal symptoms (Extrapyramidal Symptoms Rating Scale). The type of medication was also used as a covariate in the analyses. Social functioning (dependant variable) was assessed by the Social and Occupational Functional Assessment Scale (American Psychiatric Association, 1995). Univariate regressions show that grip strength (r = .69), fine motor dexterity (r = .65), parkinsonism (r = .63) and visual-motor coordination (r = .46) are significantly correlated to social functioning. Multivariate analyses revealed that grip strength and parkinsonism are the only remaining predictors of social functioning. Even if these analyses should be interpreted cautiously due to the small size of the sample, some possible explanations can be formulated. Indeed, our results are consistent with the cognitive dysmetria theory (Andreasen, Paradiso, & OLeary, 1998) suggesting that similar neural circuits are involved in motor skills and in daily living activities coordination.

CONFABULATION IN SCHIZOPHRENIA—A SYMPTOM-RELATED NEUROPSYCHOLOGICAL ABNORMALITY

E. Lorente-Rovira,* E. Pomarol-Clotet, G. E. Berrios, P. J. McKenna
Psychiatry, University of Cambridge, Cambridge, United Kingdom

This work replicates and extends Nathaniel-James and Frith's (1996) study which documented the occurrence of a form of confabulation in schizophrenia. Twenty-seven RDC chronic schizophrenic patients and 13 matched normal controls were given a story recall task designed to elicit confabulations. We also measured performance on a range of memory and executive tests. The patient sample included 11 with moderate or severe formal thought disorder; 19 were relatively intellectually intact (WAIS-R IQ ≧85) and 8 showed general intellectual impairment. Confabulation was present in 22 (81.48%)patients versus 5 (38.46%) controls (χ=5.57, P=0.02), with 15 (55.55%) patients showing multiple instances of the phenomenon (range 2-21/five stories). Patients with thought disorder showed more confabulation than those without (mean 4.59 vs 1.39 confabulations/five stories; t=2.04, P=0.05). However, there was no difference in the amount of confabulation produced by patients with and without general intellectual impairment (mean 3.31 vs 3.18 confabulations/five stories; t=1.33, P=0.19). Confabulation was associated with impairment on some of the memory tests but not with impairment on any measure of executive function. The findings suggest that confabulation in schizophrenia is closely related to the symptom of formal thought disorder. It may also be a function of memory impairment, but in contrast to Nathaniel-James and Frith (1996) findings, there was little to suggest that it is associated with executive impairment.

RBANS NEUROPSYCHOLOGICAL PROFILES WITHIN SCHIZOPHRENIA SAMPLES RECRUITED FROM NON-TREATMENT SETTINGS

C. M. Loughland,* T. J. Lewin, V. J. Carr, A. W. Harris
Neuroscience Institute of Schizophrenia and Allied Disorders (NISAD), Sydney, NSW, Australia

Previous research has demonstrated that schizophrenia samples derived from different sources vary markedly (eg, illness onset, relationships and supports, current functioning, illness course) (Loughland et al., 2004, *Psychiatry Research* 125: 117-127). This paper extends this research by comparing the neuropsychological performance of volunteers from the NISAD Schizophrenia Research Register with recently published RBANS data. The Register sample comprised 287 volunteers (149 M, 138 F) with a confirmed ICD-10 diagnosis of schizophrenia or schizoaffective disorder who had completed the RBANS (Repeatable Battery for Neuropsychological Status). Their neuropsychological functioning was compared with normative data from the original RBANS standardisation sample (Randolph, 1998) and with recently published US data from a sample of 575 predominantly outpatient-recruited patients (391 M, 184 F) who met DSM-IV criteria for schizophrenia or schizoaffective disorder (Wilk et al., 2004, Schizophrenia Research 70: 175-186). Expressed as standardised (effect-size) differences, the Register sample was least like the standardisation sample (Mean=100, SD=15 per scale) on the Immediate (-1.09) and Delayed Memory (-1.04) tasks, but reasonably similar on the Language (-0.29), Attention (-0.25) and Visuospatial-Constructional (-0.24) tasks. The Register sample's overall RBANS score (Mean=88.48, SD=16.34) was approximately three-quarters of an SD (-0.77) below the normative sample. By contrast, RBANS scores for the US health service-recruited schizophrenia patients were substantially below the normative sample: Immediate (-1.88) and Delayed Memory (-1.74); Attention (-1.79); Visuospatial-Constructional (-1.42); Language (-1.03); with an overall RBANS score (Mean=70.54, SD=14.80) almost two SD units (-1.96) below the normative sample. Within the Register sample, volunteers with relatively low levels of current functioning (GAF =< 50) had comparable Immediate and Delayed Memory profiles to the US sample (Wilk et al., 2004). These findings reinforce the notion that a severity/functioning gradient exists across various schizophrenia recruitment sources, which has important implications for

the generalizability of findings and for research design. These data also suggest that memory impairments may be a core feature of schizophrenia.

SEMANTIC AND PHONETIC FLUENCY IN SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS: THE AESOP FIRST-ONSET STUDY

A. B. Martinez Sanchez,* K. D. Morgan, P. Dazzan, C. Morgan, P. Fearon, T. Lloyd, R. Mallet, G. Harrison, P. Jones, J. Lefft, R. M. Murray
Division of Psychological Medicine, Institute of Psychiatry, London, United Kingdom

Previous investigations have demonstrated that verbal fluency is impaired in schizophrenia.However, few studies of psychosis have compared patterns of semantic fluency (SF) and phonetic fluency (PF)) across different diagnostic groups. The aim of this investigation was to examine verbal fluency in first-onset psychosis, both in patients with schizophrenia and those with other psychotic disorders. An epidemiologically based sample of 160 first-onset psychosis patients (mean age=30.9, male=90, ICD10 diagnosis: schizophrenia & schizoaffective disorder=61, bipolar disorder=40, depressive psychosis=24, other psychosis=35) and 186 healthy controls (mean age=30.7, males=82) was recruited from South East London, Nottingham and Bristol.For semantic fluency the subjects were asked to generate words from three categories (animals, body parts and fruits) and for phonetic fluency from three initial letters (F, A, S). All subjects had an estimated premorbid IQ (NART) of >84. ANCOVA (controlling for estimates of pre-morbid IQ) was used to examine differences in verbal fluency between the healthy controls and the different patient groups. There were no significant differences between the groups in terms of total errors, total repetitions and PF. Significant differences between the groups were found for TVF ($F=5.68$, $p<.001$), SF ($F=10.56$, $p<.001$) and the difference between PF and SF scores ($F=6.79$, $p<.001$). Post-Hoc analysis revealed that the controls performed significantly better than all the patient groups on TVF and SF, and showed a significantly greater difference between PF and SF scores. The mean difference between the total scores on SF minus PF was 12.6 (52%) in the patients and 17.4 (65%) in controls. There were no significant differences on any measure of verbal fluency between the different patient groups. These data indicate that impaired verbal fluency is characteristic of all psychotic disorders. The finding of greater deficits in semantic fluency suggests that the impaired performance of the patients is more closely related to a disorganization in the storage of semantic information rather than a more generalized failure to retrieve verbal information.

DIFFERENTIAL DYSFUNCTIONS IN MENTAL AT-RISK STATES COMPARED TO VULNERABILITY STATES OF SCHIZOPHRENIA

W. Maier,* I. Frommann, J. Berning, F. Buhtz, E. Plitzko, M. Wagner
Dept. of Psychiatry, University Bonn, Bonn, Germany

Background: Neuropsychological and -physiological deviations were found to precede the onset of schizophrenia; they were particularly also observed among first-degree relatives of patients. There is emerging evidence of comparable neuropsychological deficits in patients with prodromal syndromes (mental states at risk). However, direct comparison between unsymptomatic relatives and subjects with mental at-risk states are lacking up to now. Furthermore, their predictive power for psychosis is not yet clarified. Methods: We recruited (a) relatives of patients with schizophrenia subdivided by the degree of familial loading (“more” vs “less” likely carriers) (n=80), and (b) subjects with so-called prodromal symptoms subdivided by being close to psychotic symptoms (n=60), as well as (c) unsymptomatic controls (n=80). We compare a battery of broad neuropsychological tests as well as mismatch negativity and P300 waves between the comparison groups. Results: Substantial similarities were observed between mental at-risk states and unsymptomatic vulnerability states. Most noteworthy dissimilarities between both groups: Impairment in working memory and mismatch negativity were most pronounced among unsymptomatic subjects with high familial loading, whereas executive dysfunctions characterized mainly subjects with prodromal symptoms. Conclusion: Mental at-risk states and genetically transmitted vulnerability to schizophrenia display differential neuropsychological and -physiological dysfunctions.

EXECUTIVE FUNCTIONS IN FIRST-EPISODE PSYCHOSIS: A CASE-CONTROL STUDY

S. M. Malta,* S. M. Brucki, A. C. Chaves
Department of Psychiatry, Federal University of Sao Paulo, Sao Paulo, Brazil

Objective: to assess executive functions in first-episode psychotic patients and evaluate the relationship between executive performance and socio- occupational functioning. Methods: thirty first episode psychotic outpatients, followed at the First Episode Psychotic Program of the Federal University of Sao Paulo, Brazil, were compared with 30 healthy volunteers, paired by gender, age, schooling and socio-economic status. Both groups were submitted to a battery of tests to assess executive functions: Digit Span, Wisconsin Card Sorting Test, Verbal Fluency (letters and categories), Trail Making Test and Hanoi Tower and a test for intellectual level, Raven Progressive Matrices. The socio-occupational functioning was evaluated by the Social and Occupational Functioning Assessment Scale (SOFAS). Results: the first-episode psychotic patients presented significant poorer performance in executive, intellectual and social-occupational functioning, when compared to the healthy control group. Patients presented deficits in mental flexibility, in their ability to formulate abstractions and create concepts, in their capacity to inhibit a response used previously with success, in changing their response with environmental feedback, in working memory, in planning and sequencing complex problem resolutions, and they needed a longer period of time to carry out the tasks than the control group. The Wisconsin Card Sorting Test showed correlation to the SOFAS in twelve of the sixteen evaluated variables, these correlations have varied between $r = 0{,}457$, $p<0{,}001$ and $r = -0{,}656$, $p<0{,}001$. Conclusions: First-episode psychotic patients presented lower performance in executive, social and occupational functions when compared to the healthy control group. The results suggest that the poorer executive function, the lower the socio-occupational performance of first-episode psychotic patients.

ASSOCIATIVE HYPERACTIVITY, VERBAL REPETITION, AND CONTEXT MEMORY IN SCHIZOPHRENIA

T. C. Manschreck,* B. A. Maher, N. L. Khan, S. F. Candela
Psychiatry, Harvard University School of Medicine, Boston, MA, USA

Recent research on associational processes in schizophrenia has focused on the concept of neural activation in associational networks

with the findings suggesting hyperactivity of associational networks. We have recently concluded studies on the hyperactivity of association in utterances: schizophrenia subjects produce higher total associations using a computer-based measure that identifies the frequency with which an associated word occurs within a specified distance to any other index word (using a dictionary of association norms to a large number of index words). In this investigation, we extended these findings in an effort to define the extent to which repetition in schizophrenic speech, also a measure of the associational character of utterances, is related to semantic priming and measures of context memory. We studied a well-defined schizophrenia sample and compared that to a sample of normal controls. The findings indicate that, in patients who show positive semantic priming at the controlled inter-stimulus interval of 1250 msec., there are strong relationships to perseveration and repetitions in speech utterance and magnitude of facilitation. Different patterns are found among patients who show negative facilitation.

VERBAL ASSOCIATIVE LEARNING IN EARLY PSYCHOSIS: DIFFERENTIAL ABILITY BY SUBDIAGNOSIS

C. Markulev,* S. J. Wood, T. M. Proffitt, L. C. Simpson, M. A. McConchie, M. J. Kerr, G. R. Savage, M. M. Saling, P. D. McGorry, G. E. Berger, C. Pantelis
ORYGEN Research Centre, University of Melbourne, Parkville, VIC, Australia

Aim: To examine the performance of first episode psychosis diagnostic subgroups on a test of verbal associative learning. Background: Verbal learning and memory impairments have been frequently described in patients with schizophrenia, and may be a result of hippocampal pathology. Recently we have shown that first episode psychosis patients with a non-schizophrenia diagnosis do not have reduced hippocampal volumes, but the impact of this condition on verbal associative learning remains to be shown. Methodology: Twenty-five first episode patients with schizophrenia or schizophreniform disorder (SZ) and 25 with another psychotic disorder (excluding mania; PSYCH) were compared with 39 healthy controls (CTRL) using the Melbourne Relational Learning test (MelRel). This test incorporates four learning trials of 8 hard word pairs (four concrete and four abstract). Results: SZ patients were significantly impaired relative to controls across all four learning trials for both concrete and abstract pairs ($F_{2,86}=3.96$, $p=0.023$). While the two patient groups did not significantly differ, the PSYCH group out-performed the SZ group by an equivalent amount to CTRL (PSYCH vs SZ d=-0.43: CTRL vs SZ d=-0.54). There were no significant Group X Trial, Group X Pair Type or Group X Trial X Pair Type interactions. Recall after interference did not differ between the groups. Conclusion: These data indicate that there is a significant impairment of verbal associative learning in first episode schizophrenia and schizophreniform disorder, but not in other psychoses. While this broadly supports our hippocampal volume findings, the effects of global function remain to be examined.

COGNITIVE PROFILES OF PATIENTS WITH SCHIZOPHRENIA AND BIPOLAR DISORDER: A META-ANALYSIS

K. Martin,* T. Girard, B. Christensen
Centre for Addiction and Mental Health, Toronto, ON, Canada

Schizophrenia (SCZ) and Bipolar Disorder (BD) are among the leading psychiatric causes of disability, including impairments of cognition. However, in contrast to the abundance of empirical data published on cognitive functioning in SCZ, far fewer studies have investigated the cognitive deficits experienced by individuals suffering from BD. Existing studies suggest that the presence of cognitive impairment is a core and enduring symptom of BD, yet the nature and extent of this deficit are poorly understood. Additionally, it remains to be determined if the cognitive symptoms experienced in BD and SCZ are qualitatively or quantitatively different. Moreover, many consider BD (or at least affective psychoses) to lie along the continuum between SCZ and healthy functioning. In this regard, comparisons of the cognitive profiles of these two patient groups may provide insight into this issue. Thus, the current study undertook a quantitative review, using meta-analytic methods, to characterize cognitive profiles associated with BD, in relation to those associated with SCZ and normative functioning. Individual scores on neuropsychological tasks obtained from 63 original studies were grouped into conventional cognitive domains (immediate verbal memory, delayed verbal memory, non-verbal memory, global cognition, visuo-spatial ability, motor ability, language function, executive function, attention, and inhibition) and compared across groups. Results indicate that both SCZ and BD are characterized by significant cognitive impairment across all cognitive domains relative to healthy control groups; however, the SCZ groups scored consistently worse than those with BD. Effect sizes varied across cognitive domains such that immediate verbal memory was most discriminating, whereas fine-motor ability and inhibition were least able to differentiate between groups. Overall however, the cognitive profiles that emerged suggest that the difference between groups is one of magnitude rather than quality. Further analyses of BD groups revealed only improved global cognition among those in remission. In conclusion, results support continuum-based perspectives of these mental illnesses. These findings are informative towards understanding the aetiologies and underpinnings of psychiatric afflictions, but suggest limited clinical utility of neuropsychological measures for differential diagnosis.

IMPLICIT RULE-BASED SEQUENCE LEARNING IN SCHIZOPHRENIA

C. L. Marvel,* D. S. O'Leary, G. T. Goldsberry, T. W. Jewett, N. C. Andreasen
Psychiatry, University of Iowa Hospitals and Clinics, Iowa City, IA, USA

Recent evidence suggests that implicit learning of sequences is impaired in schizophrenia. This is in stark contrast to numerous schizophrenia studies showing normal implicit processing for non-sequential information, including general motor learning. This study explored the possibility that limitations for normal implicit learning may be bound by the sequential nature of the information that is learned. Sequence learning and motor learning were assessed using a rule-based version of the spatial serial reaction time task (SRT). The unique feature of this SRT task design was that sequence (or pattern) trials were embedded with random trials, which prevented declarative knowledge of the sequence and provided a measure of implicit learning as it developed across blocks. A 2(group) by 2(trial type) by 9(block) design was used. Schizophrenia patients (n=27) and healthy controls (n=25) pressed keys that corresponded to visual stimuli shown in 4 spatial locations on a computer screen. Stimulus locations were determined by a complex set of rules. However, every 4th location was determined randomly by the computer. Post-experimental testing confirmed that none of the participants was able to generate, recognize, or articulate the nature of the sequence that

had been presented throughout testing. Implicit sequence learning, nonetheless, was measured by the difference in reaction time (RT) between rule-consistent pattern trials and random trials across blocks. Motor learning was measured by the steady decrease in RT across blocks. Patients had overall slower RTs relative to controls but did not differ in their rate of motor learning. There was a group by trial type interaction, $p < .01$, indicating that controls exhibited a greater difference in RT between pattern and random trials than did the patients. Trial type effects for controls emerged in Block 5 and continued to develop through Block 9. The patients, however, failed to show RT differences between the two trial types. These results suggest that there are limits to normal implicit processing in schizophrenia. Moreover, implicit learning impairments may be specific to sequential information. An inability to develop sensitivity to regularly occurring events on an implicit level may underlie an array of cognitive and motor deficits in schizophrenia, such as interpreting social cues and executing complex movements.

ARE SCHIZOPHRENIC SUBJECTS ABLE TO LIE?

M. Mazza,* I. Frangou, V. Gaspari, R. Roncone, M. Casacchia
Psichiatric Department, L'Aquila, Italy

The ability to "mentalize," that is to understand and manipulate other people's behaviour in terms of their mental states, is a major ingredient in successful social interactions. People affected by schizophrenia show deficits in social interactions (Mazza, 2003); such a deficit may stem from an alteration in the representation of mental states. The aim of our study is to examine the ability to understand deception to use tactical strategy in schizophrenic subjects. Our study involved 143 people affected by schizophrenia (DSM IV) and 123 matched healthy controls, evaluated with clinical and neuropsychological instruments: BPRS version 4.0 (Morosini, 1994); PANSS; Raven's Progressive Matrices Scale (1938); first order Theory of Mind (ToM) stories; second order false-belief ToM stories and second order deception ToM stories (Mazza, 2001); Mach IV scale, (Christie and Geis, 1970) assessing Machiavellian intelligence. The results show dissociation in people with schizophrenia for social cognition tasks as regarding to positive vs negative symptoms dichotomy. Negatives are impaired in all the tasks, but they have good performances in understanding tactical strategy. Conversely positives show good performances in understanding deception respect to other false belief tasks but are incapable to use "strategic social thinking" and contextualising tactical strategy. References Mazza M., De Risio A., Surian L., Roncone R., Casacchia M. Selective impairments of Theory of mind in people with schizophrenia. *Schizophrenia Research*, 47,2,(3): 299-308,2001. Mazza, A. De Risio; C. Tozzini; R. Roncone, M. Casacchia: Machiavellianism and theory of mind in people affected by schizophrenia. *Brain and Cognition*, 2003, 42(1)536-540.

NEUROCOGNITIVE FUNCTION IN FIRST EPISODE PSYCHOSIS: RELATIONSHIP WITH DEPRESSIVE SYMPTOMS

R. McCaul,* S. L. Barrett, R. Anderson, T. M. Rushe, S. J. Cooper, C. Mulholland
Division of Psychiatry and Neurosciences, Queens University Belfast, Belfast, Co. Antrim, United Kingdom

Both cognitive function and depressive symptoms have been identified as important predictors of outcome in patients with schizophrenia[1,2]. Depressive symptoms are also known to cause/worsen cognitive deficits in patients with unipolar depression[3,4], and bipolar disorder[5]. The Northern Ireland First Episode Psychosis Study (NIFEPS) aims to investigate the relationship between depression and cognitive dysfunction in first episode psychosis, and to determine the relative contribution these factors make to long-term outcome. A preliminary correlational analysis was conducted on data collected from patients at illness onset ($n = 100$; age = 33.4 ± 12; M/F = 70/30), who completed the self-report Beck Depression Inventory (BDI) and Hopelessness Scale (BHS) and underwent a comprehensive neuropsychological test battery. Cognitive functions examined were: executive function; verbal/visuospatial attention and working memory; visuospatial construction and long-term memory; verbal learning; phonological processing; motor dominance and callosal function. As WASI IQ significantly correlated with the BDI ($r = -0.17$, $p \leq 0.05$) and BHS ($r = -0.19$, $p \leq 0.05$), this factor was controlled for using partial correlations. No significant relationships were found between the BHS and measures of cognition using this procedure. However, the BDI significantly correlated with digit span backward ($r = -0.2$, $p \leq 0.05$), spatial span backward ($r = -0.21$, $p \leq 0.05$) and verbal fluency ($r = -0.19$, $p \leq 0.05$). The results suggest that depressive symptoms have a negative impact on global cognitive function. Furthermore, a specific association between higher ratings of depressive symptoms and working memory deficits was identified, but the causal significance of these relationships needs to be established. 1 Green M.F. & Neuchterlein K.H. (1999) *Schizophrenia Bulletin*, 25, pp.309-19. 2 Carpenter W.T. Jr et al. (1988) *American Journal of Psychiatry*, 145, pp. 578-83. 3 Antikainen R. et al. (2001) *European Archives of Psychiatry and Clinical Neuroscience*, 251, pp. 6-11. 4 Butters M. et al. (2000) *American Journal of Psychiatry*, 157, pp. 1949-54. 5 Sweeney J.A. et al. (2000) *Biological Psychiatry*, 48(7), pp.674-84. Funded by The R & D Office (NI).

DOES THE COGNITIVE ESTIMATION TEST MEASURE EXECUTIVE FUNCTIONING IN SCHIZOPHRENIA AND BIPOLAR DISORDER?

S. M. Meyer,* N. Cascella, L. R. Kingery, G. D. Pearlson, D. J. Schretlen
Department of Psychiatry, Johns Hopkins University, School of Medicine, Baltimore, MD, USA

Patients with schizophrenia exhibit widespread cognitive deficits, including impairments of abstraction and executive functioning. Bipolar patients also show cognitive impairments, but their deficits are less severe than those seen in schizophrenia. The Cognitive Estimation Test (CET) consists of 10 factual questions to which most persons do not know the correct answer (e.g., "How heavy is a full-grown elephant?"). Thus, the CET requires both reasoning and self-monitoring of response plausibility. It has been proposed as a measure of frontal-executive functioning. This study aimed to compare CET performance among patients with schizophrenia and bipolar disorder, and to examine its correlation with performance on other cognitive tests and symptom ratings. Twenty-seven patients with schizophrenia, 20 with bipolar disorder, and 136 normal controls (NC) were administered the CET and other cognitive tests of frontal-executive abilities, premorbid IQ, psychomotor speed, and memory. Positive and negative symptoms were rated using the SAPS and SANS. Univariate ANOVAs revealed that patients with schizophrenia performed worse than NCs on the CET. Bipolar patients produced scores that were intermediate between those of the schizophrenic and normal groups, but did not differ significantly from either

group. Using Spearman's rho, CET performance correlated significantly but weakly with measures of executive and non-executive functioning, and most strongly with IQ among NCs. Among patients with schizophrenia, CET performance correlated most strongly with the Wisconsin Card Sorting Test, and moderately with IQ. Among bipolar patients, CET performance did not correlate significantly with any cognitive measure. Finally, CET scores correlated significantly with the SANS attention subscale, but only in patients with schizophrenia. CET performance differentiated only patients with schizophrenia from normal controls. In these patients, CET performance correlated most strongly with a test of executive functioning (WCST). CET performance did not correlate with any cognitive measure in bipolar patients, and it correlated significantly, but weakly, with other cognitive measures in NCs. These results suggest that schizophrenia reveals or "unmasks" a relationship between executive functioning and self-monitoring of response plausibility that is not apparent in patients with bipolar disorder or normal controls.

ODOR IDENTIFICATION AND FACIAL EMOTION RECOGNITION IN PATIENTS WITH SCHIZOPHRENIA

P. J. Moberg,* C. G. Kohler, F. Barrett, D. R. Roalf, C. Brensinger, R. E. Gur, B. I. Turetsky
Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

Purpose: Olfactory deficits in patients with schizophrenia, including odor identification, detection threshold sensitivity, discrimination and memory, have been described. Deficits in emotional perception and processing have also been reported. While anatomical connections testify to the relationship between olfaction and emotion, there has been little investigation of the relationship between olfactory and emotional processing. This study examined the relationship between odor identification/threshold sensitivity and facial emotion recognition in schizophrenia patients. Methods: Nineteen schizophrenia patients (13 men, 6 women) and 14 healthy controls (8 men, 6 women) underwent unirhinal assessment of odor identification ability (University of Pennsylvania Smell Identification Test; UPSIT) and odor detection threshold sensitivity to phenyl ethyl alcohol (PEA). Each subject also completed standardized testing of their recognition of four universal facial emotions as well as neutral facial expressions (Penn Emotion Recognition Task—40; ER—40). Results: The two groups did not differ in UPSIT performance and PEA detection thresholds, but differed in their ability to identify emotional facial expressions. In patients, a significant association between overall emotion recognition on the ER—40 and right-nostril UPSIT performance was observed (r=0.46, p=0.049). This relationship appeared to be primarily mediated by the ability to accurately identify sad facial emotions (r=0.53, p=0.018). No significant correlations were observed between UPSIT performance and ER—40 scores in healthy controls. Conclusion: These data support a relationship between odor identification abilities and the recognition of facial emotion in schizophrenia patients. Specifically, the finding of a relationship with right nostril UPSIT performance to facial emotion recognition is consistent with the literature showing an advantage for the right-hemisphere in the processing of both olfactory and emotional stimuli. There is also evidence suggesting that the amygdala plays a role in mediating both emotional and olfactory processing. Recent studies have shown that subjects with unilateral right amygdala damage showed impairment in their ability to identify sad facial expressions. Overall our findings indicate that olfactory and emotional processing utilize similar neural substrates, specifically in the limbic system.

A BRIEF INTERVENTION CAN IMPROVE DECISIONAL CAPACITY IN SCHIZOPHRENIA

D. J. Moser,* R. L. Reese, C. T. Hey, M. L. Benjamin, S. K. Schultz, F. W. Fleming, S. Arndt, N. C. Andreasen
Psychiatry, University of Iowa, Iowa City, IA, USA

Although a small percentage of people with schizophrenia lack the ability to provide informed consent for research, many of these individuals can benefit significantly from interventions designed to improve this capacity. Typically, however, these procedures are rather prolonged, sometimes taking place over several days. The current study was conducted to determine whether a very brief intervention could yield beneficial effects on decisional capacity. Thirty individuals with schizophrenia and 30 healthy controls were asked to pretend they were considering taking part in a research study and were then presented with consent information for a hypothetical medication trial. Decisional capacity was then assessed with the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR). Those with schizophrenia then received a brief intervention, consisting of a PowerPoint slideshow reiterating the key elements of the hypothetical study, followed by discussion of all MacCAT-CR items on which s/he earned less than the maximum score. Decisional capacity was then re-assessed. A neuropsychological battery and psychiatric rating scales were also administered. At baseline, the schizophrenia group earned significantly lower scores than controls on two aspects of decisional capacity [Understanding: t (58) = -2.68, p = .009; Appreciation: t (58) = -2.45, p = .017]. At follow-up, the schizophrenia group had improved significantly on Understanding [t (29) = -2.85; p = .008] and were no longer significantly different from controls on any of the four dimensions of decisional capacity. These effects were evident, despite the fact that the schizophrenia group performed quite well at baseline, causing a ceiling effect that left little room for improvement. When analyses were limited to the 11 participants with baseline Understanding scores below 23 (out of 26 possible points), results were again significant, showing a moderate-to-large improvement (effect size: Cohen's d = .62). Participants with schizophrenia earned significantly lower scores than controls across multiple neuropsychological domains. These findings indicate that a brief and basic intervention can improve decisional capacity in individuals with schizophrenia, despite the fact that the illness typically causes significant cognitive dysfunction. The use of such interventions will enable a larger number of people with schizophrenia to make informed decisions regarding research participation.

AWARENESS OF ILLNESS AND EXECUTIVE FUNCTION IN SCHIZOPHRENIA

A. Mysore,* R. Bhaker, K. H. Lee, R. W. Parks, P. B. Birkett, P. W. Woodruff
Sheffield Care Trust, Sheffield, United Kingdom

Introduction: Lack of insight has been one of the major predictors of non-compliance in schizophrenia. Our aim was to investigate the relationship of insight with neuropsychological executive functioning and symptom profiles. Method: Forty-one patients with DSM-IV schizophrenia took part (mean age 36.8, SD = 10.4). Insight was assessed using David's (1990) Schedule for Assessing Insight (SAI). SAI is composed of three dimensions, namely, patient's treatment compliance, awareness of illness, and capacity to re-label psychotic experiences as abnormal. The Wisconsin Card Sorting Test was used as a measure of Executive function while the symptoms were assessed using the Scales for the Assessment of Negative Symptoms

and the Scales for the Assessment of Positive Symptoms. Results: Impaired WCST performance was significantly correlated to decreased insight in schizophrenia. Among sub-scales of SAI, awareness of illness had highly significant correlation with WCST performance scores. On the other hand, treatment compliance was not related to WCST performance. We then divided patients into two groups based upon the score on the awareness of illness sub-scale (those scoring below and above 4). Those who scored more than 4 on the sub-scale (N= 19) scored significantly more on the WCST (total correct response: p = .02; categories completed: p = .01; perseverative errors: p = .07) than those who scored low on the sub-scale (N = 22). Those with high score on the subscale also had significantly low scores on Disorganisation and Reality distortion symptoms. Conclusion: These findings suggest that degree of awareness of illness as opposed to treatment compliance is related to executive function. This adds to a growing body of evidence linking illness insight and executive function and for a dissociation between (psychological) awareness of illness and (behavioral) treatment compliance.

AWARENESS OF ILLNESS IN SCHIZOPHRENIA

K. Nael,* A. Kennedy, A. Wood, A. Tapp
MIRECC, VA PSHCS, American Lake Division, Tacoma, WA, USA

Poor insight, or awareness of illness, in schizophrenia has been linked to reduced treatment adherence and poorer outcome. Hence, interventions that enhance insight are a key to treatment. Amador et al (1) proposed insight as multi-dimensional encompassing global understanding of having an illness, recognizing its symptoms and correctly attributing them to the illness. We assessed insight in 22 stable chronic outpatients diagnosed with schizophrenia or schizoaffective disorder. We utilized two instruments to assess insight: clinician-rated Scale to assess Unawareness of Mental Disorders (SUMD) introduced by Amador et al, and self and clinician-rated hypothetical vignettes developed by McEvoy et al (2). The SUMD has three global items assessing awareness of a mental illness, its response to medications and its social consequences. In addition, awareness of current symptoms and attribution of these symptoms to the disease is assessed. The vignettes include 9 hypothetical scenarios exemplifying a person with positive and negative symptoms. Patients rate their resemblance to that person (awareness). The clinician also rates the patient's resemblance to the person in the vignette. Patients are asked whether the description in each vignette is a sign of mental illness (attribution). Scoring for both instruments is on a 1-5 scale with lower scores indicating better awareness. In the SUMD, global awareness was generally good (M = 1.7). In the vignettes, awareness was also good with no significant difference between self and clinician ratings in 8 out of 9 symptom areas. However, patients' attribution of symptoms to mental illness was less accurate, and poorer on the vignettes compared to the SUMD (M = 2.7 and 2.1 respectively, p = 0.06). Within instruments, awareness and attribution of symptoms did not correlate. In between instruments, awareness of symptoms correlated significantly (r = .5, p = .02) while attribution did not correlate. These findings support the proposal that insight is multi-dimensional. Interventions should include all aforementioned dimensions. 1. Amador XF, Strauss DH, Yale SA, Flaum MM, Endicott J, Gorman JM. Assessment of insight in psychosis. *Am J Psychiatry*. 1993;150:873-879. 2. McEvoy JP, Schooler NR, Friedman E, Steingard S, Allen M. Use of psychopathology vignettes by patients with schizophrenia or schizoaffective disorder and by mental health professionals to judge patients' insight. *Am J Psychiatry*. 1993;150:1649-1653.

CONTRIBUTION OF NEUROCOGNITIVE FUNCTIONING AND SYMPTOMATOLOGY TO EMOTION RECOGNITION PERFORMANCE IN PATIENTS WITH SCHIZOPHRENIA

T. Nienow,* N. Docherty, A. Cohen, T. Dinzeo
Department of Psychology, Kent State University, Kent, OH, USA

The aim of this study was to examine the contributions of neurocognitive functioning and symptomatology to emotion recognition performance in patietns with schizophrenia. It was hypothesized that symptom severity would not make a contribution to emotion recognition performance independent of neurocognitive functioning. Approximately 60 patients were recruited from an inpatient facility. Emotion recognition performance was assessed with the Facial Emotion Identification Test (FEIT) and the Bell-Lysaker Emotion Recognition Task (BLERT). The neurocgnitive assessment included measures of vigilance, visual processing, verbal ability, and abstract reasoning. Symptom severity was assessed with the SANS and SAPS. Three symptom dimensions were created: disorganization/thought disorder, psychotic symptoms, and negative symptoms. Regression analyses were conducted to examine the unique and overlapping contributions of symptom severity and neurocognitive functioning to emotion recognition performance. Contrary to expectations, negative symptom severity and disorganization/thought disorder made independent contributions to its prediction. Results suggest that both symptom severity and neurocognitive impairment underlie deficits in this area of functioning.

CONCURRENT VALIDITY OF A COMPUTERIZED NEUROCOGNITIVE ASSESSMENT SYSTEM FOR USE IN CLINICAL TRIALS OF ANTIPSYCHOTIC MEDICATIONS

J. P. O'Halloran,* L. S. Schneider, P. Farhadi,
G. M. Simpson, A. S. Kemp
NeuroComp Systems, Inc., Irvine, CA, USA

Neurocognitive assessment is an integral component of controlled clinical trials of candidate antipsychotic treatments, as well as a wide range of research protocols. However, manual administration of large neurocognitive batteries is often inefficient, error prone, and frequently inconsistent across multiple sites. As such, the Computerized Multiphasic Interactive Neurocognitive Diagnostics System (CMINDS) was developed, with funding from the National Institute of Mental Health (NIMH), to provide a unique dual-monitor platform for comprehensive administration of various protocols utilizing contemporary multi-media capabilities for automated presentation of instructions, electronic data capture and report generation. Purpose: To conduct a preliminary comparison of traditional administration of a representative battery of neurocognitive assessments, selected by the NIMH-sponsored CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) consortium, with computerized administration of the same battery on CMINDS, in a sample of patients diagnosed with schizophrenia. Method: 32 stable, medicated outpatients provided informed consent to participate at the Schizophrenia Outpatient Clinic of the University of Southern California Keck School of Medicine. All participants received both the CMINDS and CATIE batteries at each of two visits, approximately 30 days apart, with the order of

administration counterbalanced across participants. Results: Intraclass Correlation Coefficient (ICC) and General Linear Model comparisons between all individual tests on the CMINDS and CATIE batteries yielded highly significant levels of absolute agreement (see Table 1), with no significant mean differences. Conclusions: These results provide clear support for the concurrent validity of the CMINDS battery and highlight its potential for time/cost savings in clinical trials of putative antipsychotic medications.

Table 1: Means and ICCs

THEORY OF MIND IMPAIRMENT IN SCHIZOPHRENIA: A META-ANALYSIS

T. M. Oh,* P. J. McKenna
Department of English Language & Literature, National University of Singapore, Singapore

Impaired theory of mind (ToM) has been proposed as a cognitive deficit in schizophrenia that is capable of explaining symptoms of the disorder, including delusions and formal thought disorder. We performed a meta-analysis of studies comparing ToM test performance in schizophrenic patients and normal controls. We also examined the neuropsychological specificity of the ToM impairment by comparing the magnitude of the deficit to that of overall intellectual impairment, as indexed by current IQ measures in the studies. Finally, we meta-analyzed the correlations of ToM impairment with positive, negative and disorganisation symptoms. The pooled effect size for ToM impairment from 14 studies was -1.11 (CI -1.27/-0.95), i.e. in the 'large' range. This was considerably larger than the pooled effect size for current IQ decrement in the studies (ES for 7 studies = -0.60, CI -0.80/-0.40). The pooled correlation between ToM performance and positive symptoms (reality distortion) was -0.14, in the 'small' range for correlations, whereas that with negative symptoms was -0.25, and that with disorganisation was -0.29, both in the 'medium' range. The findings indicate that ToM impairment is a robust finding in schizophrenia, which has an unusually large effect size, and appears greater than can be accounted for by overall intellectual impairment. However, like other neuropsychological deficits in schizophrenia, ToM impairment appears to be associated primarily with negative and disorganisation symptoms, rather than with delusions and hallucinations.

MAKING FACES: A BEHAVIORAL AND DIFFUSION TENSOR IMAGING (DTI) STUDY OF IMITATION AND *MIRROR NEURON* MECHANISM IN SCHIZOPHRENIA

S. Park,* C. Gibson, B. Folley, J. Lee, A. Anderson
Psychology, Vanderbilt University, Nashville, TN, USA

Schizophrenia patients (SZ) have difficulties in generating and guiding their behavior by internal representations. Since mental representation and imitation of others' actions and emotions form the core of social understanding, deficits in *mentalising* are likely to have a significant impact on social-cognitive functions including theory of mind (ToM), emotion recognition and language use. A neural mechanism has been proposed to account for action understanding and imitation in primates. Analogous to the mirror neurons in the monkey premotor cortex (F5) that support action understanding, human mirror mechanism is mediated by a direct mapping of the observed action and its motor representation in the circuit that includes Broca's area (human homolog of F5) and the right parietal cortex. The aim of this study was to examine imitation ability in SZ in relation to: 1. Active use of internal representations (working memory, ToM); 2. Social function and 3. White matter integrity and connectivity between frontal and posterior regions using DTI. *Method:* SZ and matched controls (NC) were asked to imitate lip movements, manual gestures and facial expressions of others. Working memory (WM) was also assessed. ToM was assessed by a *false belief* task. Connectivity of the white matter tracts was examined by DTI using indices of fractional anisotropy (FA) and mean diffusivity (D) from ROI analyses. *Results:* SZ were significantly impaired on all imitation tasks even when they correctly identified the acts. Imitation accuracy was correlated with WM, especially verbal WM but not with ToM. Emotion imitation was associated with social functioning and negative symptoms. DTI showed greater FA of corpus callosum in SZ than NC, and a trend towards an asymmetry of frontal white matter integrity in NC (left > right FA) but not in SZ. Imitation accuracy was associated with the diffusivity of the frontal and cingulate cortices. *Discussion:* Imitation requires simulating mental states of others and is central to all forms of learning including language acquisition, as well as understanding actions of others. Impaired imitation in SZ and its association with WM deficit suggest that generation of mental representations and mirror neuron mechanism may be at the core of abnormal social cognition in SZ. Although relating brain structure to behavior requires great caution, altered cortical connectivity in SZ may contribute to deficits in mapping observed action to its motor representation.

COGNITIVE COORDINATION: FUNCTION, PHYSIOLOGY, PATHOLOGY

W. A. Phillips
Psychology, University of Stirling, Stirling, United Kingdom

Cognitive neuroscience is dominated by evidence for semantic specialization. Different regions and different cells within regions process information about different things. We now need to understand how these diverse activities are coordinated. Coordination is necessary to enhance activity relevant to the current context, to combat noise, to make coherent choices, and to organize activity into coherent subsets. These computational requirements lead to

processes of contextual modulation and dynamic grouping in perception, attention, and working memory for which there is evidence from various cognitive paradigms. I will summarize evidence that these coordinating interactions are implemented by a distinct family of physiological mechanisms that include various sub-types of NMDA receptor together with mechanisms that regulate the balance between activity mediated by NMDA and non-NMDA glutamate receptors. It will be argued that NMDA receptors are uniquely suited for selective amplification of contextually relevant activity because of their distinctive voltage-dependent and ligand-gated mode of operation. It will be noted that genes encoding these mechanisms are susceptibility genes for schizophrenia, and that it is likely that processes of cognitive coordination can malfunction in many different ways. At the level of scalp potentials, Gamma oscillations have been seen as evidence for the hypothesis that dynamic grouping, or 'binding', is signalled by synchronization of the spiking activity that needs to be grouped. While supporting this general hypothesis I will note important ways in which it needs to be modified. Evidence for the relevance of coordinating interactions to cognitive disorganization in psychosis comes from several different sources. These include studies of perception, attention, and working memory in disorganized subjects which show them to have reduced context-sensitivity, reduced ability to distinguish between relevant and irrelevant signals, and specific impairments of dynamic grouping. They also include studies of the effects of NMDA antagonists, along with other evidence for the NMDA-hypofunction hypothesis of schizophrenia. The potential of new methodolgies relevant to these issues, such as NMDA receptor subtype-specific antagonists, and transgenic animals with pharmacologically inducible and reversible sub-unit expression, will be noted.

EXECUTIVE AND THEORY OF MIND IMPAIRMENT IN SCHIZOPHRENIA VERSUS ASPERGER SYNDROME

E. Pomarol-Clotet,* C. Rice, E. T. Bullmore, P. J. McKenna, S. Baron-Cohen
Psychiatry, University of Cambridge, Cambridge, United Kingdom

Executive function and theory of mind (ToM) have been implicated as key deficits in two otherwise unrelated disorders, schizophrenia and autism/Asperger syndrome. We investigated the profile of neuropsychological impairment in 33 patients with schizophrenia and 24 adults with Asperger syndrome, using a battery of tests covering visual/visuospatial function, language, memory and executive function. The patients were also administered three ToM tests. Patients were selected on the basis that they were generally intellectually intact (schizophrenic patients) or high functioning (Asperger patients), in both cases as indexed by a current WAIS-R IQ of 85. Thirty normal subjects matched for estimated IQ were also tested. In the schizophrenic patients, impairment on the neuropsychological tests predominated in memory and executive function, with relative sparing of visual/visuospatial function and comprehension of syntax. In contrast the Asperger patients showed a more uniform pattern of mild impairment across all tests, and there was no disproportionate deficit in executive function. Both patient groups showed equivalent levels of impairment on the ToM tests. The findings suggest that ToM impairment characterises intellectually preserved patients with both disorders, whereas executive impairment is only a feature of schizophrenia.

SCHIZOPHRENIA PATIENTS' USE OF FEEDBACK IN THE WISCONSIN CARD SORTING TEST

K. J. Prentice,* J. M. Gold, R. W. Buchanan, W. T. Carpenter
Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD, USA

Schizophrenia (SZ) patients show impaired performance on the Wisconsin Card Sorting Test (WCST). Low scores are often attributed to patients' frequent perseverative errors, a pattern typically interpreted as a failure to shift from previously rewarded behavior in response to negative feedback. Such perseverative behavior, however, cannot account for errors early in the task before any reward, or positive feedback, is received. We hypothesized that SZ patients are fundamentally impaired in their use of feedback to guide behavior, and that this impairment is (1) evident in performance on the earliest WCST learning trials, prior to any rule-switching, and (2) predictive of overall task performance. We analyzed WCST data from 100 SZ patients and 64 healthy controls, focusing on the use of feedback on the first four trials of the test (i.e., cards 1-4). SZ patients were less effective than controls in their use of feedback to arrive at a rewarded response. As early as card 2, where 69% of controls were able to use verbal feedback as a guide to the correct response, only 44% of SZ patients were able to do so [$t(162)=3.18$, $p<.01$]. Differences of similar magnitude were seen at cards 3 (89% vs. 61%) and 4 (92% vs. 70%). There was a strong relationship between accuracy on the first 4 cards and overall task performance. Total score on cards 1-4 was significantly correlated with overall perseverative error rate in SZ patients ($r=-.47$, $p<.001$) and also in controls ($r=-.46$, $p<.001$). Similarly, SZ patients who were correct on at least 3 of the first 4 cards were able to complete the maximum number of categories 48% of the time. Among patients who were correct on 2 or fewer of the first 4 cards, only 5% were able to complete the maximum number of categories (more than 40% of these early low-scorers completed 0 categories). SZ patients' poor performance on these first WCST trials cannot be due to a failure to release a previously-rewarded behavior, but is more likely to reflect a fundamental impairment in the ability to use feedback (reward information) to guide behavior. Recent data from both humans and primates suggest that reward-based learning processes like those employed in the WCST are driven by phasic changes in midbrain dopamine (DA) activity. It might, therefore, be possible to interpret higher order executive dysfunction in schizophrenia as a manifestation of altered DA signaling.

COGNITIVE FUNCTION IN FIRST-EPISODE PSYCHOSIS: RELATIONSHIP TO DIAGNOSIS, TREATMENT, AND TIME

T. Proffitt,* S. J. Wood, M. A. McConchie, W. J. Brewer, C. Pantelis, P. D. McGorry, G. E. Berger
ORYGEN Research Centre, University of Melbourne, Parkville, VIC, Australia

Since the mid 1990s our groups have been conducting comprehensive neuropsychological assessments of first-episode psychosis patients recruited into the research program at the Early Psychosis Prevention & Intervention Centre at ORYGEN. The data collected has been both cross-sectional and longitudinal in nature. The initial aim was to shed light on the pathophysiology of schizophrenia, however, we have more recently begun a more fine-grained analysis of the cognitive profiles of different diagnostic subgroups, defined

either by phenomenology, response to treatment, or biology i.e., measures of niacin sensitivity (a proxy for lipid metabolic status), structural and functional imaging, and genetic polymorphisms. Data will be presented showing a lack of specificity of several traditional neuropsychological measures in differentiating bipolar and schizoaffective patients, and groups of affective and non-affective psychosis patients will also be compared. Finally, we will examine the utility of the newer biological measures in predicting cognitive outcome following a first episode of psychosis. The implications of these findings to our understanding of the trajectory and nature of cognitive change occurring in young people with psychosis will be discussed.

A TEMPORAL SEQUENCE TO RECOVERY IN FIRST EPISODE PSYCHOSIS

R. Purvis,* R. Ohlsen, L. Pilowsky, R. Brown
Psychology, Institute of Psychiatry, London, United Kingdom

Altered levels of physical activity, impaired circadian cycling and reduced goal-directed behaviour are characteristic features of many psychiatric and neurological disorders, including schizophrenia. Such changes involve neurocognitive and behavioural impairment, frequently with a dominance of negative symptoms. The monitoring of clinical, neurocognitive and behavioural features of the disease offer important means of understanding and predicting outcome. However, besides symptom management, the promotion of real-world social, occupational and recreational outcome is also a significant challenge to practitioners working with schizophrenia. A framework is presented for examining real-world functional outcome in first episode psychosis. Some novel methods of time-budget interviewing have been employed, in addition to traditional clinical and neurocognitive measures of symptomology and functioning. Further, objective measures of physical activity and circadian cycling have been obtained using discreet actigraphy techniques. The research presents the findings from a longitudinal study of nineteen patients with first episode psychosis assessed at baseline (whilst drug naive), and again after six weeks, twelve weeks, six months and one year of treatment Results of an independent clinical assessment showed a statistically significant reduction in symptoms occurred within six weeks (Brief Psychiatric Rating Scale $t=2.76$ $p<.05$; Clinical Global Impression $t = 2.31$ $p<.015$; PANSS $t = 3.07$ $p<.05$). These clinical improvements were later matched by improvements in neurocognitive functioning at 12 weeks (BADS Rule Shift $t=2.64$ $p<.05$; Trails B errors $t=3.13$ $p<.05$; Wisconsin Modified Card Sort errors $t=2.73$ $p<.05$). However, it was not until 6 months that significant increases in levels of raw activity ($t=2.17$ $p<.05$), wake minutes ($t=3.64$ $p<0.05$) and more settled circadian sleep patterns became evident. The results indicate a specific temporal sequence to the recovery process in first episode psychosis with clinical symptoms remitting first, followed later by an improvement in neurocognitive functioning. It is suggested that improvements in the clinical and neurocognitive domains may be necessary but not sufficient precursors of favourable functional outcome.

VISUAL PROCESSING IN SCHIZOPHRENIA: STRUCTURAL EQUATION MODELING OF VISUAL MASKING PERFORMANCE

Y. Rassovsky,* M. F. Green, K. H. Nuechterlein, B. G. Breitmeyer, J. Mintz
Psychiatry and Biobehavioral Sciences, UCLA Neuropsychiatric Institute, Los Angeles, CA, USA

Schizophrenic patients consistently demonstrate performance deficits on visual masking procedures. In visual masking, the subject's ability to process a target stimulus is reduced by another stimulus (mask) presented either before (forward masking) or after (backward masking) the target. Several experimental paradigms have been used to study visual masking in schizophrenia. Most early studies have used high-energy masks (i.e., the mask is stronger than the target) and spatially overlapping target and mask. More recently, studies have begun to employ relatively weak (i.e., low-energy) masks, as well as masks that surround, but do not spatially overlap, the target. These paradigms typically produce non-monotonic (U-shaped) functions that demarcate the minimum as the point of the strongest masking effect. Despite the theoretically plausible distinctions among the various paradigms, it remains unclear whether these procedures provide different information regarding visual processing deficits in schizophrenia. The purpose of the present study was to address this issue by examining the underlying structure of visual masking parameters, based on theoretical distinctions among physiological processes involved in these procedures. Data for forward and backward masking components of four masking conditions (target location and identification with a high-energy mask, target identification with a low-energy mask, and target identification with equal energy paracontrast/metacontrast) was collected from 75 patients with schizophrenia and 56 normal controls. Based on the aforementioned distinctions, we compared four models of visual masking using structural equation modeling. Although high zero-order correlations were found among the masking parameters, a four-factor model, in which factors were separated on the type of response (target location and identification), the shape of the function (monotonic and non-monotonic), and the overlap of the stimuli (overlapping and non-overlapping), provided the best fit for the data. The pattern of results was virtually identical for patients and controls. These findings suggest that the four masking procedures used in this study may tap unique effects on visual processing and are not redundant. The results also support distinctions in the mechanisms underlying performance on these measures.

WORKING MEMORY FACILITATES LEARNING ON THE WISCONSIN CARD SORTING TEST

M. Rempfer,* C. E. Brown
Kansas City VA Medical Center, Kansas City, MO, USA

Schizophrenia is increasingly recognized as a neurocognitive disorder (Green & Nuechterlein, 1999). A large literature indicates that schizophrenia is associated with cognitive difficulties in areas such as attention, memory and executive functioning. However, not all individuals with schizophrenia display cognitive impairment, and even among those who do, the specific patterns of cognitive functioning vary. Wiedl and colleagues (Wiedl, 1999; Wiedl et al., 2001) have used the concept of learning potential to help explain this observed variability in cognition. Broadly defined, learning potential is the ability to attain and utilize cognitive skills, sometimes referred to as cognitive modifiability. Learning potential is measured with dynamic assessment methods, which combine instruction with test administration. The extent to which an individual can take advantage of the instruction to improve performance is taken as an index of learning potential. In recent work, we have used dynamic assessment to establish learner subtypes on the Wisconsin Card Sorting Test (WCST), a widely used neuropsychological measure of executive function. We identified the three learner subtypes initially reported by Wiedl (1999): *high scorers* who do not have significant impairment on the test, *learners* who initially perform poorly but improve performance subsequent to enhanced training, and

nonlearners who perform poorly initially and do not improve after training. The present study was intended to identify the cognitive processes that differentiate learners from nonlearners on the WCST. To date, over 60 participants with SCID confirmed diagnoses of schizophrenia/schizoaffective disorder have completed this project. Participants completed a test-train-test version of the WCST and a battery of other neurocognitive measures, including tests of attention, memory, and executive functioning. Our data show that although learner subgroups do not differ in type or severity of symptoms, there are group differences in several domains of cognitive functioning. Of particular interest, *working memory* distinguishes learners from nonlearners. To our knowledge, these are the first data to show cognitive distinctions between WCST 'learners' and 'nonlearners.' The results have implications for understanding the cognitive requirements of the WCST and for understanding the role of basic cognitive functions in predicting learning ability and perhaps, ultimately, rehabilitation potential.

NEUROCOGNITIVE PROFILE IN ADOLESCENTS WITH EARLY-ONSET SCHIZOPHRENIA: CLINICAL CORRELATES

J. P. Rhinewine,* T. Lencz, E. P. Thaden, K. L. Cervellione, K. E. Burdick, L. Keehlisen, I. Schvartz, S. Bhaskar, J. Kane, G. S. Fisch, S. Kumra
Psychiatry Research, North Shore Long Island Jewish Health System—Zucker Hillside Hospital, Glen Oaks, NY, USA

The purpose of this study was to provide information about the severity and pattern of neurocognitive deficits in adolescents with early-onset schizophrenia (EOS; onset of psychotic symptoms by age 18) and the relationships between these deficits and syndromal characteristics. We administered comprehensive neurocognitive assessments, including tests assessing motor skills, attention, memory, visuospatial abilities, language and executive functions, to 45 adolescents with EOS after initial stabilization of psychosis and to 28 healthy controls. Profiles of patients' neurocognitive functioning were compared to those of controls. Relationships between neurocognitive deficits and a range of historical and clinical characteristics were explored. We found a significant generalized neurocognitive deficit of 1.4 standard deviations in EOS patients compared to healthy controls. In addition, patients demonstrated specific, relative deficits in the domains of executive functioning and motor skills. Language skills were found to be relatively spared. The degree of generalized neurocognitive impairment was predicted by premorbid adjustment and by the severity of negative symptoms at the time of testing (Adjusted $R^2 = .40$). These results document a significant generalized deficit, as well as differential deficits, in clinically stabilized adolescent patients with EOS. Global deficits were related to severity of negative symptoms at the time of test administration and to premorbid adjustment. The generalized neurocognitive deficit we observed in this sample of EOS patients is similar in magnitude to those found in prior studies of EOS, as well as those found in studies of adults with a first episode of schizophrenia. Our data support significant cognitive impairment across multiple ability domains as a core characteristic of EOS and may indicate widespread brain dysfunction in this disorder. This research was supported by NIMH grants MH-60221 to Dr. Kane; MH-64556 and a NARSAD award to Dr. Kumra; NSLIJ Research Institute General Clinical Research Center, Grant # M01 RR018535.

NEGATIVE SYMPTOMS OF SCHIZOPHRENIA AND THE DYSEXECUTIVE SYNDROME

C. D. Rice,* P. J. McKenna
Department of Psychology, University of Hertfordshire, Hatfield, United Kingdom

Weinberger and others have proposed that the negative symptoms of schizophrenia are similar to the frontal-lobe syndrome in neurological patients. However, an association between poor frontal, or executive test performance and negative symptoms has not been found consistently. Some studies have also found associations between non-executive test impairment and negative symptoms. One reason for these inconsistent findings might be that schizophrenic patients commonly show general intellectual impairment, which could obscure a specific association between an executive deficit and symptoms. In addition, conventional tests of executive function may not be particularly sensitive to executive impairment, inadequately capturing the types of situations that people encounter in their everyday life. The Multiple Errands Test (MET) and all six tests that comprise the Behavioural Assessment of the Dysexecutive Syndrome (BADS) were administered to 2 groups of RDC schizophrenia patients, 16 with negative symptoms and 13 without negative symptoms, plus 16 normal controls. Carer ratings of everyday dysexecutive behaviours were also collected for both patient groups on the DEX and FrSBe. All three groups were matched for age and NART-R IQ. Only patients with a current WAIS-R IQ of at least 85 were included. Patients with negative symptoms were significantly impaired compared to those with positive symptoms on two of the tests (MET, plus the Modified Six Elements Test from the BADS battery). They were also rated by their carers on both scales as showing significantly greater dysexecutive behaviours in daily life. In contrast, there was no significant difference between the two patient groups on the Rivermead Behavioural Memory Test. The results suggest that ecologically valid tests of executive function that are loosely structured and require multi-tasking are linked to negative symptoms. The findings with respect to carer ratings suggest that patients with negative symptoms have dysexecutive disturbances commonly associated with frontal-lobe patients.

DECISION MAKING PROCESS IN FIRST EPISODE SCHIZOPHRENIA

J. Rodriguez-Sanchez,* B. Crespo-Facorro, C. Gonzalez-Blanch Bosch, M. Alvarez, O. Martinez, M. Ramirez, J. Vazquez-Barquero
Psychiatry, Hospital Universitario Marques de Valdecilla, Santander, Spain

Decision making process is an emotion based mechanisms, related to orbitofrontal cortex, that guides daily behavior specially in social context. Emotional and social disturbances in schizophrenic patients as long as abnormalities found in their orbitofrontal cortex makes study of decision making process highly interesting in this group of patients. The current work pretends to assess decision making process in a large sample of first episode schizophrenia patients A decision-making task (Gambling Task) was applied to 91 first episode schizophrenic patients and 18 healthy controls. Clinical scales (SAPS and SANS) were used to measure symptoms severity and to cathegorize patients into three clinical

subgroups: Positive, negative and disorganized. Part of the sample did not fullfil criteria and could not be included into these subgroups. Nevertheless analysis related to schizophrenia as a unitary group included all the sample. Between and within subject ANOVA were made for the whole task score and for five periods of the task in order to assess global decision making score and learning process of patients on such kind of task. Correlational studies between decision making and clinical scales were also performed. No differences were found between patients and controls in the total score on the decision making task, neither for the whole group of patients nor for the clinical subgroups. The whole group of patients and the control group performed increasingly better along the task. However patients included in the clinical subgroups did not improve their performance. There were significant negative correlations between severity of symptomatology and decision making task performance. Patients included in the clinical subgroups were found to be significantly more severely ill than those not included. Our results show that there is not impairment in the general performance of first episode psychotic patients in their decision making capability. However it seems that patients have difficulties to change their pattern of response to adapt to changes on environmental contingencies. This would involve a deficitary ability of decision making capacity in these patients that may be related to clinical state and is not apparent unless the evolutive performance of the tasks is examined. The role of clinical dimensions remains unclear and further investigation controlling for the effect of severity would be required.

HEALTH, OPTIMISM, NEUROCOGNITION, AND SOCIAL FUNCTIONING IN SCHIZOTYPY

R. P. Rosenberg,* M. J. Sergi, C. S. Jahshan, A. Pangilinan, M. A. Parvand, L. DeLazari
Psychology, California State University Northridge, Northridge, CA, USA

Health is often impaired in persons with schizophrenia. The present study extends the study of impaired health to persons with schizotypy. Twenty-one psychometric schizotypes and 18 persons low in schizotypy were identified from a screening of 1054 undergraduates with the Schizotypal Personality Questionnaire-Brief (SPQ-B). Schizotypy status was confirmed with the Perceptual Aberration Scale (PAS and SPQ-B scores were highly correlated, $r(38) = .70$, $p < .001$) All participants were administered a test battery designed to assess health-promoting behaviors (Health-Promoting Lifestyle Profile II), health-related quality of life (RAND 36-Item Health Survey), optimism (Life Orientation Test), secondary verbal memory (California Verbal Learning Test), social functioning (Social Adjustment Scale - Self Report) and executive functioning (Wisconsin Card Sorting Test). Analyses of group differences found that the schizotypes were impaired relative to their healthy counterparts in role limitations due to physical problems ($F(1, 38) = 10.72$, $p = .02$), overall health promoting lifestyle ($F(1, 38) = 3.70$, $p = .06$), stress management ($F(1, 38) = 3.2$, $p = .080$) and optimism ($F(1, 38) = 4.16$, $p = .000$). Group differences in neurocognition were not observed. Also, for the schizotypes, neurocognition was not associated with the health-related constructs; however, optimism was associated with social functioning, health promoting behaviors, energy/fatigue, and reported pain. This study, to our knowledge, is the first to report impaired health in schizotypy.

WHAT PREDICTS THE COURSE OF NEUROCOGNITIVE FUNCTIONING IN FIRST-EPISODE PSYCHOSIS?

B. R. Rund,* I. Melle, S. Friis, U. Haahr, J. O. Johannessen, T. K. Larsen, L. J. Midboe, S. Opjordsmoen, E. Simonsen, P. Vaglum, T. H. McGlashan
Psychology, University of Oslo, Oslo, Norway

Purpose: A renewed interest has emerged in the question whether schizophrenia is a neurodevelopmental or a neurodegenerative disorder.The aim of the present study was to determine the longitudinal course of cognitive functioning in first-episode psychoses within schizophrenia spectrum; and to examine whether premorbid adustment, duration of untreated psychosis (DUP) or any clinical variables are associated with the course of cognitive functioning. Methods:Consecutive patients with a DSM-IV diagnosis of nonorganic, nonaffective psychosis coming to their first treatment in the study health care areas in Norway and Denmark between Januar 1, 1997, and December 31, 2000 were included. A total of 207 patients were assessed neuropsychologically at baseline, 138 were reassessed 1 year later and 111 2 years later. Eight neurpsychological (NP) tests were used for assessing neurocognitive function. Five dimensions were identified through principal component analysis of a subset of measures from the NP tests: Working Memory, Executive Function, Verbal Learning, Impulsivity, Motor Speed. Results: No major changes were found in the level of neurocognitive functioning from baseline to the 1-year and 2-year follow-up on any domain or any subtest, although a certain improvement was seen in most domains, especially during the first year. There were few consistent patterns of association between any demographic or clinical measures and NP measures. Patients with good initial levels of premorbid academic functioning had consistently better scores on Working Memory at all three test points. No association was found between DUP and the longitudinal course of neurocognitive function. Significant associations were revealed between Working Memory and Verbal Learning at 1 and 2 year and number of relapses during the first year. Conclusions: The longitudinal NP data do not support a neurodegenerative model. Number of relapses during the first 2 years of treatment is significantly associated with Working Memory, and at a trend level with Verbal Learning. DUP is not related to neurocognitive functioning at all. The process involved in psychotic breakdown may have a detrimental effect on cognitive functioning in itself while the effect of being in a psychotic state is less damaging. Supported by: The Research Council of Norway, The Norwegian Department of Health and Social Affairs, and The National Council for Mental Health/Norwegian Foundation for Health and Rehabilitation.

VERBAL WORKING MEMORY IN SCHIZOPHRENIA: FRACTIONING OF EXECUTIVE PROCESSES

C. Schimming,* M. Rapp, A. Furst, A. Reichenberg
Psychiatry, Mount Sinai School of Medicine, New York, NY, USA

Background: There is abundant evidence that schizophrenia patients perform poorly on tests of working memory. It has previously been suggested that working memory tests be characterized as either transient ‘online’ storage and retrieval tasks (where short-term storage and retrieval of information is required) or executive tasks (where

manipulation of information is also required). There is, nevertheless, strong evidence for distinct manipulation functions. Thus, the working memory deficit in manipulation needs to be more precisely defined. Methods: Subjects were 20 chronic schizophrenia patients and 20 healthy controls. They were assessed with a battery of neuropsychological tests. Five measures of verbal working memory were used, selected to vary in their degree of 'online storage' and type of 'manipulation' required: the digit span forward and backward, and the letter-number sequencing from the WMS-III, and digit sequencing and ordering span tests. Results: Patients performed significantly worse than controls on all measures of verbal working memory. Differences were not due to general intellectual ability or processing speed. There was considerable heterogeneity in working memory deficits. However, impairments in patients were more severe in tasks requiring 'manipulation' than those requiring 'storage' only. Conclusions: The data support the fractionation of manipulation functions in working memory. In selecting measures of working memory for clinical or genetic studies, it is important to clearly identify the distinct aspects of working memory that are assessed. The distinction between 'storage' and 'manipulation' tasks is insufficient as there is evidence for dissociations of different manipulation tasks.

NEUROPSYCHOLOGICAL FUNCTIONING IN SCHIZOPHRENIA VS. BIPOLAR DISORDER

D. J. Schretlen,* N. G. Cascella, S. M. Meyer, L. R. Kingery, C. A. Munro, P. Rivkin, V. Rao, C. M. Diaz-Asper, A. E. Pulver, G. D. Pearlson
Department of Psychiatry, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Despite the historical and current nosological distinction between bipolar disorder (BD) and schizophrenia (SZ), emerging evidence suggests that these conditions might share some genetic susceptibility. Consequently, determining whether they are characterized by similar or different neuropsychological profiles could be useful, especially if the latter prove robust enough to constitute "endophenotypes." The aim of this study was to compare the nature and severity of cognitive deficits shown by patients with SZ and BD. The participants included 61 adults with schizophrenia, 31 adults with bipolar I disorder, and 152 healthy individuals who were matched to each patient group in terms of age, sex, race, years of education, and estimated "premorbid" IQ. All participants completed a cognitive test battery that yielded 19 measures. Their performances on each were z-transformed using the distributions produced by healthy controls. After assigning each test score to one of eight cognitive domains, the mean domain z-scores for each patient group were derived for statistical comparison. Patients with SZ performed significantly worse than their matched controls on every cognitive measure and domain. Those with BD performed significantly worse than their healthy controls on six individual cognitive measures and four of the eight cognitive domains (attention, verbal learning/memory, design fluency and recognition memory). Moreover, the cognitive profiles produced by patients with SZ showed negligible correlation with those produced by the BD patients (Spearman's rho = -.19, ns, for the 19 individual test measures and -.07, ns, for the 8 cognitive domains, respectively). These findings suggest that relatively stable outpatients with bipolar I disorder suffer from cognitive deficits that are less severe, more selective, and qualitatively different from those shown by relatively stable outpatients with schizophrenia. Because these data are cross-sectional, the temporal stability of the cognitive "profiles" found for both patients groups, but perhaps especially those with BD, remains unclear.

SPANISH ADAPTATION OF THE BACS (BRIEF ASSESSMENT IN COGNITION IN SCHIZOPHRENIA)

N. Segarra,* M. Bernardo, F. Gutierrez
Fundacio Clinic, Barcelona, Spain

Introduction: The duration of standard cognitive evaluation in schizophrenia usually takes over 2 hours time. The BACS (Brief Assessment of Cognition in Schizophrenia,) is a instrument created by Dr. Keefe 1999, recently validated in English Language and recognized sensitive to cognitive impairment which in advantage to previous standard cognitive test requires less than 35 minutes to be completed. As Spanish is spoken by 400 millions people around the world, its adaptation and validation to this language seems clearly appropriate. Objective: In this pilot study, a Spanish version of the BACS was tested as for viability, compressibility and duration. Method: A sample of 30 schizophrenic patients (diagnosed according DSM IV-TR criteria) was assessed in two separate days to asses by means of the BACS. The Spanish BACS the same test as the English versions: Verbal memory (List learning), Working memory (Digit sequencing task), Motor speed (Token motor task), Verbal Fluency (Category instances, Controlled oral word association test), Attention and speed of information processing (Symbol coding). Executive functions (Tower of London). Conclusions: The Spanish adaptation of the BACS scale is suitable for uses it in Spanish schizophrenic patients. All items and instructions resulted undertandable, and duration was as expected. These preliminary results allow us as the next step to Spanish validation of the BACS.

STRUCTURAL EQUATION MODELING SUPPORTS SOCIAL PERCEPTION AS A MEDIATOR OF RELATIONS BETWEEN EARLY VISUAL PROCESSING AND COMMUNITY FUNCTIONING IN SCHIZOPHRENIA

M. J. Sergi,* Y. Rassovsky, S. Davidson, S. M. Crosby, M. F. Green
Department of Psychology, California State University, Northridge, Northridge, CA, USA

Support for social cognition as a mediator of relations between neurocognition and community functioning in schizophrenia mainly comes from correlational studies that link neurocognition and social cognition or, alternatively, social cognition and community functioning. The present study employed structural equation modeling to examine the potential mediating role of social cognition more directly. Using data collected from 75 outpatients with schizophrenia, the present study examined whether a social cognitive variable, social perception, mediated relations between a neurocognitive variable, early visual processing, and community functioning. Two conditions of visual masking were used to estimate early visual processing, the Half Profile of Nonverbal Sensitivity was used to estimate social perception, and two subscales of the Role Functioning Scale, independent living and work functioning, were used to

estimate community functioning. All indicators had moderate-to-high loadings on their respective latent variables, and all were significant at the .05 level. Social Perception was both significantly predicted by Early Visual Processing (standardized coefficient = .56, $p < .05$) and significantly predictive of Community Functioning (standardized coefficient = .54, $p < .05$). Stated otherwise, the indirect path from Early Visual Processing to Community Functioning that passes through Social Perception was significant (standardized coefficient for indirect effect = .30, $p < .05$). The direct path from Early Visual Processing to Community Functioning, on the other hand, was not significant (standardized coefficient = .06, ns). It is worth noting that the direct path from Early Visual Processing to Functioning was significant when Social Perception was not included in the model (standardized coefficient = .33, $p < .05$). The present findings offer direct support for social cognition as a mediator of relations between neurocognition and functioning in schizophrenia.

EMOTION VERSUS CONTEXT: A BEHAVIOURAL TEST OF THE HIPPOCAMPAL-GATING MODEL OF SCHIZOPHRENIA

K. Smolewska,* B. Christensen
Clinical Psychology, University of Waterloo, Waterloo, ON, Canada

Recent neurobiological theories of SCZ have focused on the dysregulation between neural pathways that control emotion versus those that govern goal-directed action (e.g., Grace, 2000). In the present study, we will be investigating this interaction using a novel computerized task (i.e., the Emotional Gating Task [EGT]), which was developed to behaviourally test this model of emotion/cognition regulation in SCZ. This model is based on single neuron recording studies in rodents, which suggest that the hippocampus (HIP) provides a gating influence over information flow from the prefrontal cortex (PFC) at the level of the nucleus accumbens (NAcc). In this model, the PFC provides multiple motor plans by which it drives goal-directed action. The most effective plan is then selected within the NAcc via the inputs from both the HIP and amygdala (AMG). In the face of affectively salient stimuli, the AMG can over-ride the HIP and direct behaviour to effectively deal with the affective material. In SCZ, it is hypothesized that the AMG not only fails to facilitate PFC throughput, but actually drives NAcc cell activity in a competitive fashion (Grace, 2000). As a result, goal-directed action is replaced by impulsive responding based on the affective state of the individual. While the neural characteristics of this model are well established, there exist no cognitive or behavioural studies that directly test the validity of this model among patients with psychotic symptoms. Thus, the EGT was developed to test the primary tenets of this model - i.e., that affective characteristics will disproportionately influence behaviour in the face of contextual cues that signal an alternative action - among individuals with schizotypal personality disorder. This competition is operationalized as a motor response to positively or negatively valenced digitized photographs under different contextual constraints. The two responses that the task attempts to manipulate are: 1) accelerating a motor response and 2) inhibiting a motor response. Participants' movements will be tracked by a magnetic movement tracking system. It is hypothesized that, compared to controls, schizotypal individuals will experience a greater disruption in performance when the task demands signal a response inhibition to negative emotional pictures. In other words, that emotion will disproportionately oppose contextually-driven responses among individuals with schizotypal traits.

THE IMPACT OF INVARIANT AND CHANGEABLE ASPECTS OF FACIAL STRUCTURE ON FACIAL RECOGNITION IN PATIENTS WITH SCHIZOPHRENIA

B. Soholm,* R. C. Gur, H. Lublin, B. Y. Glenthoj
Department of Psychiatry, Center for Neuropsychiatric Schizophrenia Research, University of Copenhagen, Bispebjerg Hospital, Copenhagen, Denmark

Schizophrenic patients exhibit facial processing deficits that likely contribute to their social functioning. However, the specific nature of facial processing deficits is unclear. The ability to glean social meaning from facial displays requires integration of changeable facial aspects (emotional expression) with invariant (identity) features of facial configuration. The study was designed to test the hypothesis that people with schizophrenia are impaired specifically in processing variant facial features. We constructed a test of facial identity recognition, PICAF (Processing of Invariant and Changeable Aspects of Faces), modelled on the Benton Test of Facial Recognition. We used standardized black and white straight angle photographs from a pool of 174 photographs of Caucasian actors exhibiting happy, sad and neutral faces (Erwin et al., 1992). Test items consisted of a target photograph and six others arranged in a non-delayed match-to-sample design. Invariant processing was assessed by a task of matching identical inverted or upright frontal view photographs and variant processing was measured by matching same identities depicting varying intensities of happy, sad or neutral facial expressions. PICAF was pretested in 36 healthy participants in order to develop tasks equated for psychometric power. The PICAF was then administered to 16 patients (13 men, 3 women, mean age 31.8 years) with schizophrenia ICD-10 F20 and 24 healthy controls. Patients performed worse on the variant task compared to the invariant task ($p=0.001$), while this difference was not significant for controls. Patients with schizophrenia performed worse than controls on the variant condition ($p=0.000$), but there were no significant differences between groups on the invariant task. These findings support the notion that deficits in facial processing in schizophrenia reflect difficulties in the co-processing of changeable and invariant facial features. Such difficulties likely impair the ability to keep stable impressions of facial identity. Future studies may further establish the specificity of deficits by incorporating facial horizontal rotation. Such efforts may help refine hypotheses on the neural systems underlying face processing deficits in schizophrenia. References Erwin RJ, Gur RC, Gur RE, Skolnick B, Mawhinney-Hee M, Smailis J. Facial Emotion Discrimination I:Task Construction and behavioral Findings in normal subjects. *Psychiatry Res* 1992; 42:231-240.

THE CONSORTIUM ON THE GENETICS OF SCHIZOPHRENIA (COGS): PRELIMINARY FINDINGS OF IMPAIRED LEARNING AND MEMORY ON THE CALIFORNIA VERBAL LEARNING TEST, SECOND EDITION (CVLT-II) IN SUBJECTS WITH SCHIZOPHRENIA AND THEIR RELATIVES IN A MULTISITE STUDY

W. Stone,* A. H. Roe, S. V. Faraone, M. T. Tsuang, L. J. Seidman
Harvard Medical School/Massachusetts Mental Health Center, Boston, MA, USA

Introduction: COGS is a 7-site (Harvard, Mt. Sinai, U. Penn., UCH-SC, UCLA, UCSD, U. Wash.) consortium studying schizophrenia

genetics using multiple endophenotypes, including verbal learning and memory, attention, PPI, P50 suppression and antisaccade measures. Data herein were collected across all 7 sites. Probands (PRO), relatives (REL) and normal comparison subjects (NCS) are assessed carefully using structured clinical and neuropsychological instruments. In total, COGS will test 420 schizophrenia pedigrees (1680 subjects) and 525 NCS over 5 years. Due to the complexity and scope of this project, interim analyses of endophenotypes will be used to identify expected response patterns and potential site-specific anomalies in data collection. Methods: Five months of consortium-wide training and quality assurance (QA) efforts, standardization of equipment and test protocols, and database development preceded 10 months of data collection. Administration of the CVLT-II and DNA collection were completed on 279 subjects across the 7 COGS sites (PRO=55, REL=124 and NCS=100; Male (M)=137, Female (F) =142). Data were analyzed using 2x3 ANOVAs, with post hoc Tukey HSD tests where appropriate. Results: The COGS QA process, including on-site inspections, detected and corrected several relatively minor methodological differences across sites. Initial comparisons showed that NCS learned more words than did either REL or PRO, and REL learned more than PRO (all p's < 0.001). The same pattern of results occurred in Short- and in Long-Delay Free Recall (p's < 0.035-0.001). In addition, F consistently performed better than M (all p's < 0.001), with no significant group x gender interactions. All groups used more (i.e., semantic clustering) and less (i.e., serial clustering) efficient learning strategies. PRO, REL and NCS all used the less efficient strategy to the same extent, but NCS and REL used the more efficient strategy to a greater extent than PRO (p < 0.001). A tendency of F to use the efficient strategy more than M approached significance (p=0.53). Discussion: PRO and REL deficits on the CVLT-II and superior performance in F across groups are consistent with previous studies using the CVLT. These findings show the feasibility of testing across 7 sites, and of using the newer version of the CVLT to assess verbal learning and memory in schizophrenia. Additional analyses of all COGS endophenotypes and diagnostic classifications are ongoing. Supported by MH 65571.

THE EFFECT OF MONETARY REINFORCEMENT ON WORKING MEMORY IN SCHIZOPHRENIA SPECTRUM DISORDER

A. Thornton,* S. Y. Griffiths, V. G. Boudreau, T. M. Fawkes-Kirby, T. S. Woodward, M. Howey, W. G. Honer
Psychology, Simon Fraser University, Burnaby, BC, Canada

We prospectively evaluated the impact of monetary incentive on the working memory abilities of schizophrenia spectrum disorder patients while accounting for the differential contribution of psychomotor poverty symptoms to incentive response. Forty-eight patients with schizophrenia (n = 38) or schizoaffective disorder (n = 10) were recruited from a tertiary psychiatric hospital. The mean age of this sample was 36.5 years and their mean education level was 11.4 years. Our research was based on the observations of others which suggest that 1) negative symptoms (i.e., psychomotor poverty) of schizophrenia involve reduced drive and motivation 2) persons with negative symptoms exhibit greater cognitive impairments than patients with other symptom complexes 3) working memory appears to be a core neuropsychological deficit that underlies other cognitive impairments in schizophrenia, and 4) monetary reward induces increased neuronal activation of areas implicated in working memory and moderates working memory performance in healthy individual. We were specifically interested in determining whether patients with greater psychomotor poverty, as assessed by the Signs and Symptoms of Psychotic Illness (SSPI) rating scale, were capable of improving their working memory performance in response to rewards that presumably increase motivation to perform well. At the two levels of monetary reward our results failed to reveal an overall improvement in working memory relative to the non-rewarded baseline condition on an n-back task. Furthermore, symptoms of psychomotor poverty were not associated with a differential working memory response to rewards. These findings suggest that decreased motivation, and dysfunction of the associated neuronal circuits, do not account for schizophrenia-related deficits in working memory. Nor does it appear that working memory impairments can be addressed by increasing patient motivation through monetary incentive.

LEARNING POTENTIAL AS A DIFFERENTIATING VARIABLE IN SCHIZOPHRENIA

A. Vaskinn,* A. B. Birkenaes, J. Engh, H. Jonsdottir, P. A. Ringen, S. Opjordsmoen, S. Friis, O. A. Andreassen, K. Sundet
Department of Psychiatry, Ulleval University Hospital, University of Oslo, Oslo, Norway

Learning potential describes the level of optimal capacity given structured aid, rather than actual performance. The construct has been proposed as a mediating variable between neurocognition and functional outcome in schizophrenia, and as such of more predictive value than standard test scores. The aim was to study the validity of learning potential as a differentiating variable in a Norwegian schizophrenia sample, i.e. whether the groups could be defined and if so, their characteristics. At present (September 2004) learning potential has been measured in 24 subjects with DSM-IV schizophrenia using a test-train-test 64-card manual version of the WCST with instruction and continuous feedback on the second trial. In addition, neuropsychological tests and symptom measures were administered. In accordance with previous research, subjects were divided into three groups based on their performance on trial 1 and 3 on the WCST. The 'non-learning group' is characterized by low performance on both trials, the 'learning group' shows improvement of test results from trial 1 to trial 3, and the group of 'high-achievers' has good performance on both trials. Subjects with more than 50 correct responses on trial 1 were considered 'high-achievers' (n=12). Of the remaining 12 subjects, 2/3 showed improvement from trial 1 to trial 3, defining them as the 'learning group' (n=8). The 'non-learning group' (n=4) obtained low performance on both trials. The groups do not differ statistically on background variables such as symptom level, age, education or premorbid IQ. A comparison of the three groups' test profiles shows that the 'learning group' is more similar to the 'high-achievers' than to the 'non-learners' even though they score equally impaired on the WCST. Our data confirms that learning potential is differentially distributed in schizophrenia and shows that the three trial administration of the WCST gives more information than a single administration. Given help, low-achieving subjects may be split into 'learners' and 'non-learners'. Based on the initial WCST trial, the 'learners' will wrongly be characterized as having executive impairments. The results may have implications for real life functioning, suggesting that learning potential can be used as a predictor of rehabilitation success.

THE VIRTUAL WATER MAZE, P50 SENSORY GATING, AND COGNITIVE FUNCTIONING

M. C. Waldo,* L. A. Woodward, E. M. Cawthra, L. E. Adler
VISN 19 MIRECC, Denver VAMC, Denver, CO, USA

Schizophrenics are known to have deficits in both the anatomy and functioning of the hippocampus. However, most tests of hippocampal functioning include other cognitive factors, most commonly verbal ability. The virtual water maze test (VMWT) is a computerized version of the Morris water task for rodents, a test that measures spatial learning and navigation. In the rodent task an animal is placed into a circular pool of opaque water and must escape by climbing onto an invisible (submerged) platform. This form of spatial learning is often referred to as "place learning" and can be contrasted with "cued navigation" in which a single stimulus marks the platform location. These two forms of learning can be dissociated in rats based upon lesion, pharmacological, and behavioral studies. In animals, the Morris Water Maze is known to be a sensitive indicator of hippocampal functioning. The purpose of the VMWT is to provide a human task analogous to this widely used memory task. Because of the basic similarities in human and rodent behavior and neurobiology, we believe that the VMWT provides a unique method to measure learning and memory in humans and allows for better generalization of findings across species. This is likely to be particularly important for evaluating animal models of human clinical syndromes and in establishing or improving neuropsychological and behavioral profiles of human clinical disorders. We have completed a pilot study of 12 subjects, normal subjects and schizophrenic patients, using the virtual water maze. In this group of subjects we found that P50 gating was highly correlated with functioning on the water maze (r=.69, p=0.013). We also found that functioning on the water maze was correlated with tests of verbal fluency, a series of tests which are associated with hippocampal dysfunction (Gleissner and Elger, 2001). These findings corroborate the findings of Astur et al (1999; 2002) using the fMRI and water maze, which demonstrated that subjects with hippocampus damage display severe spatial memory impairments in a virtual water maze, and also that schizophrenics showed significantly less hippocampal activation than controls when completing the test (Astur et al, 2004).

DISSOCIATING RESPONSE INHIBITION AND HIGHER ORDER RULE USE IN INDIVIDUALS WITH SCHIZOTYPAL PERSONALITY DISORDER

C. M. Wilson,* B. K. Christensen
Psychology, University of Waterloo, Waterloo, ON, Canada

The Dual Trends Theory (DTT) is an evolutionary model that uses cytoarchitectonics to characterize brain development across phylogeny. The DTT posits that all mammalian cortex has derived from two seperate primitive brain structures which have, in turn, given rise to two related, but independent, neural pathways or trends: the archicortical trend (originating from the hippocampus) and the paleocortical trend (originating from pyriform cortex). Collectively, studies of cognition, regional blood flow, and brain morphology suggest that Schizophrenia (SCZ) is preferentially associated with archicortical impairment, in the context of intact paleocortical function. The purpose of the current study is to test this model among healthy individuals and those with schizotypal personality disorder. The integrity of the archicortical and paleocortical trends will be measured via a novel motor response inhibition task (RIT) designed to orthogonally measure response inhibition (RI) (i.e., a paleocortical function) and higher order tule use (HORU) (i.e., an archicortical function). This dissociation of constructs is important given that many experimental paradigms purporting to measure RI have routinely conflated RI and HORU (e.g., GO/NO-GO tasks). Importantly, Zelazo, Frye, and Rapus (1996) have successfully dissociated these two constructs (i.e., RI and HORU) across stages of development in children. The task employed in this study is a modified GO/NO-GO task in which the discriminant stimuli vary in their perceptual similarity one to another. Participants make an imperative button press to the presentation of a green circle. HORU is operationalized as the perceptual similarity between the discriminative stimuli (e.g., "P" and "R" vs. "N" and "Q"). In order to manipulate RI difficulty, the time interval between the imperative stimulus (i.e., green circle) and the discriminative stimulus (i.e., letter) is varied (e.g., 150ms vs. 350ms). The prediction of interest is a group x condition interaction, whereby increasing the HORU demands will result in a discrepant performance between healthy and schizotyal participants. In contrast, it is hypothesized that between-groups performances will remain invariable across RI conditions.

ASSESSMENT AND DYNAMICS OF NEUROPSYCHOLOGICAL PROFILE IN PATIENTS WITH DEPRESSIVE AND SCHIZOPHRENIC DISORDERS: OUR FIRST EXPERIENCES

H. Kucerova,* R. Prikryl, T. Kasparek, E. Ceskova
Department of Psychiatry, Brno, Czech Republic

a)Our study is focused on acquiring information about the existence of cognitive deficit and its profile in depression and schizophrenia. b)We used a comprehensive battery of neuropsychological tests. Depression:9 inpatient men for F32,F33 according to the ICD 10; cognitive function were assessed at the beginnig of treatment and after 28 days Schizophrenia:66 men for the first episode of F20.x according to ICD 10; cognitive function were assessed at admission and after one year c)Comparison cognitive dysfunction in depression and schizophrenia depression: in acute phase of illness is present most serious and deeper cognitive dysfunction than in patients with schizophrenia, but this cognitive deficit had quicker improving and with remision we found gradual trend to normal level with the exception of higher executive functions and aimed concentration of attention. schizophrenia: the existence of cognitive deficit already during the first schizophrenic episode was proved, after one year we found a certain trend toward gradual improvement and return to an adequate standard but any parameter of cognitive function after one year did not reach the standard level and henceforth cognitive deficit especially mild impairment of executive function is present. d)We believe that monitoring the level of cognitive functions in either of the two disorders should not be neglected because cognitive deficit seems to be the factor restricting not only social, but also work-related functioning and involvement of patients, and thus to affect the quality of their common daily lives in a most serious way. Acknowledgement:This work was supported by the Ministry of Education Czech Republic(CEZ J07/18/141100001) and International Grant Agentury of Ministry of Health Czech Republic(NR7990-3/2004). Bibliography Albus,M.,Hubmann,W.,et al.Contrasts with first-episode schizophrenia and first episode affective disorders,1996,*Acta Psychiatr Scand*,94,87-93. Goldberg,T.,Gold,J.,Greenberg,R.,et al.Contrasts between patients with affective disorders and patients

with schizophrenia on a neuropsychological test battery,1993,*Am J Psychiatry*,150,1355-1362. Jeste,D.,Heaton,S.,Paulsen,J.,et al.Clinical and neuropsychological comparison of psychotic depression with non psychotic depression and schizophrenia,1996,*Am J Psychiatry*,153,490-496. Lezak,M.,D.*Neuropsychological Assessment*,3rd ed.New York,Oxford University Press,1995.

THE EFFECT OF NEUROLEPTIC WITHDRAWAL ON NEUROLOGIC PERFORMANCE IN SCHIZOPHRENIA

R. D. Sanders,* S. D. Forman, M. E. Kelley, D. P. van Kammen
Dayton VA, Dayton, OH, USA

Neurologic examination abnormalities (NEA) are potentially useful in clinical psychiatry, but we need to better understand their determinants. We now have an NEA battery with demonstrated test-retest reliability, enabling us to assess state influences longitudinally, thereby clarifying the effects of these factors on neurologic performance. We examined 24 patients with chronic schizophrenia twice: while stabilized on haloperidol (9.6 + 3.5 mg/day), and after haloperidol had been discontinued for at least 19 days (47.0 + 30.5 days). Patients were male, 25-49 (mean 39.3 + 7.5) years old, and free of other psychiatric, medical or neurologic disorder. Psychotic symptoms (Bunney-Hamburg) increased 47% (p=.003) and EPS ratings (Simpson-Angus) decreased 51% (p=.022). AIMS and BPRS total scores increased, but did not reach statistical significance. Total NEA scores, subscale scores and individual test scores were unchanged. Covarying for psychiatric symptoms and looking separately at those who did and did not relapse off medication had no effect on results. Blink rate during visual fixation increased from 6.0 to 17.9 bpm, regardless of relapse status, and persisting after covarying for positive psychotic symptoms (F=4.89, p=.03). Blink rate at rest did not change. Other than decreasing Parkinsonian signs, haloperidol withdrawal had no impact on the neurologic examination in chronic schizophrenia.

SPECIFIC IMPAIRMENTS IN THE PERCEPTION, REGULATION, AND PSYCHOPHYSIOLOGY OF EMOTION PROCESSING IN SCHIZOPHRENIA

M. Van 't Wout,* A. Aleman, B. Bermond, R. P. Kessels, E. H. de Haan, R. S. Kahn
Psychonomics, Helmholtz Research Institute, Utrecht, Netherlands

Disturbances in the processing of emotional material are a hallmark of schizophrenia. More specifically, patients with schizophrenia seem to be especially impaired in the recognition of facial affect. These facial affect recognition deficits seem to be most pronounced in the recognition of negative emotions, such as fear and anger. As the ability to recognize emotions is relevant for social functioning in daily life, deficits in affect recognition might contribute to social isolation, hamper independent living and negatively affect professional functioning in schizophrenia. Besides impairments in the recognition of facial affect, patients with schizophrenia also seem to inadequately express emotions. However, the abnormal expression of emotions does not necessarily imply that the subjective experience of emotions is affected. In the present study, we compared 40 patients with schizophrenia with healthy matched control subjects on tasks measuring facial affect recognition, affect regulation that include both the expression and experience of emotions, and skin conductance in response to affective faces. There were no differences in age, sex and years of education. Patients with schizophrenia were worse in the recognition of fear on a facial affect recognition task and this correlated with negative symptoms. In addition, patients with schizophrenia reported more difficulties in identifying and verbalizing emotions. On the other hand, patients reported to be more easily aroused by emotion-inducing events. With regard to the psychophysiology of facial affect, we observed correlations between skin conductance responses on fearful faces and impairments in the regulation of affect in schizophrenia and increased psychopathology. We suggest that patients with schizophrenia show specific abnormalities in the processing of threatening faces and this may relate to affect regulation impairments.

12. Psychology, Cognitive

SOCIAL COGNITION: IS IT A MEDIATOR BETWEEN COGNITION AND OUTCOME IN FIRST EPISODE PSYCHOSIS?

J. Addington,* B. Christensen, H. Saeedi, D. Addington
Psychiatry, University of Toronto, Toronto, ON, Canada

Social cognition has been implicated in the relationship between cognition and social functioning. Individuals with schizophrenia have demonstrated impairments in all three domains (Addington & Addington, 1998; 1999; 2000). This one-year longitudinal study tested the hypothesis that social cognition mediates between cognitive and social functioning. The sample included three groups - 50 first-episode (FE) subjects, 59 multi-episode schizophrenia subjects (ME) and a non-psychiatric comparison group (NPC) (n=66). Subjects were assessed on a range of measures within each of the domains of cognition, social cognition and social functioning. Results of ANOVA demonstrated that both the FE and ME subjects were clearly impaired (significance ranged from 0.01 to 0.0001) relative to NPCs in cognition, social functioning and social cognition (social problem solving, social perception & facial affect). The predictive value of cognition and social cognition for outcome in each of the groups was examined. There were few significant associations for the NPCs. In the patient groups there were robust significant associations amongst the three domains (cognition, social cognition, social functioning). However, using the mediation model of Baron & Kenny, 1986 we were unable to demonstrate in a series of hierarchical regressions that social cognition mediates between cognition and social functioning. Our results suggest that social cognition is not a mediator between cognition and social functioning. Rather, it is an important deficit of psychotic disorders which, although related to cognitive and social functioning, is a distinct construct. Funded through a grant to Jean Addington from Canadian Institutes of Health Research. References Addington J. & Addington D. 1998 Facial affect recognition and information processing in schizophrenia and bipolar disorder. *Schiz Res* 32:171-181 Addington J. & Addington D. 1999 Neurocognitive and social functioning in schizophrenia. *Schiz Bull* 25:173-182 Addington, J. & Addington D. 2000 Neurocognitive and social functioning in schizophrenia, a 2.5 year follow-up. *Schiz Res* 44: 47-56.

FACIAL AFFECT EVALUATION IN PATIENTS WITH SCHIZOPHRENIA—AN IMPLICIT STUDY

S. An,* J. I. Kang, E. Lee, J. J. Kim, J. H. Seok, S. H. Park, H. S. Lee
Department of Psychiatry, Severance Mental Health Hospital, Yonsei University College of Medicine, Gwangju-si, Gyeonggi-do, South Korea

To determine the nature of affect perception impairment, we assessed the implicit evaluation of the simulatnesously presented two facial photographs, depiciting happy and happy, fearful and fearful, neutral and neutral, and happy and fearful expressions in schizophrenia. Twenty three patients with schizophrenia and 21 normal controls saw black and white photographs that were classified on the basis of the intrinsic stimulus valence and also saw color filtered pictures that were classified on the basis of the color. All stimuli were selected from the pictures of facial affect (Ekamn and Friesen, 1976). Normal controls classified the pictures with happy and happy expressions significantly more accurately when the response according to the color were the same response, which were also assigned to the positive black and white pictures than the opposite response, which were assigned to the negative black and white pictures. For fearful and fearful, neutral and neutral trials, the reverse was true. For happy and fearful faces, there was no significant difference in normal controls. However, under the same conditions, for happy and happy, fearful and fearful, and happy and fearful expressions, there was similar findings to those of normal controls, while for neutral and neutral trials there was no significant difference in patients with schizophrenia. These findings suggest that patients with schizophrenia might suffer from the perception impairment of the neutral facial affect, which could be implicitly evaluated as negative expression by normal controls, at a relatively early emotional processing stage.

LONGITUDINAL CHANGES IN NEUROCOGNITION DURING THE FIRST DECADE OF SCHIZOPHRENIA ILLNESS

N. C. Andreasen,* D. J. Moser, D. S. O'Leary, B. C. Ho
Department of Psychiatry, The University of Iowa, Iowa City, IA, USA

Background: Although cognitive dysfunction is a core feature of schizophrenia, its severity varies widely. While few patients go on to develop Kraepelinian severe, progressive cognitive deterioration, current neurodevelopmental concepts of schizophrenia would predict that cognitive dysfunction peaks by early adulthood, and remains stable thereafter. Methods: We studied 84 schizophrenia patients early in the course of their illness, and repeated a comprehensive battery of standardized neuropsychological tests 2, 5 and 9 years later. Fifty patients were initially tested during their first psychiatric hospitalization; 45 of whom were neuroleptic naïve. All test results were transformed to z-scores based on means and standard deviations from the intake assessments. Tests were further grouped into 6 cognitive domains. Longitudinal changes in cognitive domain scores were examined using mixed models and post hoc paired t-tests. Results: Statistically significant changes were seen in five of the six cognitive domains during the 9 years of follow-up ($F's \geq 3.71$; $p's \leqq 0.006$). Verbal memory, speed/attention, problem solving, language and visuospatial abilities improved significantly at 2 years compared to intake assessment ($T's \geq 2.13$, $p's \leq 0.04$). When the mixed models analyses were restricted to only follow-up data, longitudinal changes in verbal memory, problem solving and motor skills remained statistically significant ($F's \geq 3.11$; $p's \leq 0.03$), with speed/attention and language domains being at trend levels. Cognitive functioning remained relatively stable between 2- and 5-year assessments. However, by 9 years, cognitive performance had reverted to levels observed at intake. Verbal memory and problem solving skills at 9 years worsened significantly compared to at 5-year follow-up ($T's \geq 2.18$, $p's \leq 0.03$). Verbal memory, language and motor skills at 9 years were also significantly lower than test scores at 2 years ($T's \geq 2.05$, $p's \leq 0.04$). Conclusions: After initial improvement and stability, cognitive deficits in schizophrenia may worsen during the latter half of the first decade of illness. These findings are consistent with recent longitudinal MRI studies, which have found progressive brain volume reductions after illness onset. Longer durations of follow-up will be necessary to ascertain the evolution of cognitive deficits in schizophrenia. Longitudinal within-subjects studies will also assist in reassessing our current concepts of schizophrenia.

METAMEMORY KNOWLEDGE AND BELIEFS IN SCHIZOPHRENIA

E. Bacon,* N. Huet
INSERM, Strasbourg cedex, France

Patients with schizophrenia suffer a wide range of deficits affecting their insight of several aspects of daily living. This includes memory function. Subjective reports and theories about memory are important because they often provide the basis for regu lating one's performance. They can also exert powerful influences on other beliefs and behaviours. Metacognitive knowledge refers to the explicit knowledge and beliefs that one possesses about our own cognitive strength and weaknesses in particular, and a bout human cognitive functioning in general. This study examined the metamemory knowledge profile of patients with schizophrenia. Methods: Patients with schizophrenia (N=34) and their matched healthy controls answered the 120 Likert-type questions of the Metamemory Inventory in Adulthood (MIA, Dixon et al., 1988). This multidimensional questionnaire gives a rating of metamemory beliefs and knowledge concerning seven domains of daily cognitive function: Strategy (knowledge and reported use of strategies), Task (knowledge of basic memory processes), Capacity (beliefs regarding one's own memory capacities), Change (perceived change in the capacity to remember), Anxiety (perception of the relationship between anxiety and memory performance), Achievement (perception of one's motivation to perform well on memory tasks), and Locus (perc eived sense of control over memory skills). Results: The profile of metacognitive knowledge in patients with schizophrenia differed on some respects from that observed in healthy controls. Patients reported a lower use of Strategies, either internal or e xternal. They also expressed a higher level of Anxiety relative to memory. Furthermore, they perceived themselves as having lower Capacity and less Controllability over their memory abilities. Nevertheless, their Knowledge about what a memory task was, as well as their Motivation to succeed in a memory task were normal. Finally, the way they feel the age-related decline of memory (Change) was also similar to controls. Conclusion: Patients do not suffer a general and non specific impairment of their metacognitive knowledge. These results may provide perspectives for cognitive remediation.

INTERVENTION FOR TOBACCO DEPENDENCE AMONG PEOPLE WITH A PSYCHOTIC ILLNESS—RESULTS FROM A RANDOMISED CONTROLLED TRIAL

A. L. Baker,* V. Carr, R. Richmond, M. Haile, T. Lewin, R. Taylor, K. Wilhelm
Centre for Mental Health Studies, University of Newcastle, Newcastle, NSW, Australia

The prevalence of smoking among people with schizophrenia is much greater than in the general population (90% vs 25%). Smoking related diseases rate second in frequency to suicide as the greatest contributor to early mortality among people with schizophrenia. The financial and health costs of smoking among this population are serious. Existing studies investigating smoking cessation treatments for smokers with a psychotic illness are inadequate, although recommendations for smoking cessation interventions with this group are becoming common. This study investigates the efficacy of a smoking cessation intervention for people with a psychotic illness in comparison to routine psychiatric care. Specifically, we conducted a randomized, single-blind controlled comparison of an eight session, individually administered, smoking cessation intervention consisting of nicotine replacement therapy (NRT), motivational interviewing (MI) and cognitive-behaviour therapy (CBT) with routine care among 298 people with a psychotic illness. Outcome variables included: rates of smoking cessation; and secondarily, psychiatric symptomatology. Major analyses were on an intention-to-treat basis. Of smokers with a psychotic illness who completed all treatment sessions, a significantly higher proportion had quit smoking at all follow-up occasions compared to those in the routine care control group (point prevalence rates: 3-months, 30.0% vs 6.0%; 6-months, 18.6% vs 4.0%; and 12-months, 18.6% vs 6.6%). Smokers who completed all treatment sessions were also more likely to have achieved continual abstinence from their quit date to the 3-month follow-up (22.9% vs 4.0%). There was a strong dose-response relationship between abstinence rates and group attendance, with no treatment participants attending fewer than five sessions achieving abstinence at any time point. There was no change in psychotic symptomatology and no significant improvement in measures of anxiety, depression and general mental health over time. These findings demonstrate the potential effectiveness of an individually administered smoking cessation intervention consisting of NRT, MI and CBT among people with a psychotic illness.

NEUROCOGNITIVE DEFICITS IN HEALTHY SIBLINGS OF SCHIZOPHRENIC PATIENTS

N. Barrantes-Vidal,* M. Aguilera, M. Fatjo-Vilas, M. J. Munoz, S. Campanera, S. Miret, L. Navarro, L. Fananas
Un Antropologia (Dep Biologia Animal), Facultat de Biologia, Universitat de Barcelona, Barcelona, Spain

Background: Sitskoorn et al. (2004) have recently conducted a meta-analysis confirming that the cognitive deficits found in schizophrenic patients are also present in non-affected relatives. The largest differences were found on verbal memory recall and executive functioning. However, as the authors stated, other neurocognitive domains that may be of interest could not be included in the analysis because of the lack of studies. Aims: To compare healthy siblings and normal controls on an extended array of neurocognitive domains. Only adult siblings were included in order to reduce the age-linked stratification bias produced by pooling all relatives (Saoud et al. 2000). Methods: 24 full-siblings of schizophrenic patients (14F,10M) and 50 healthy controls (21F, 29M) were compared on neurocognitive functions (intelligence, sustained attention, verbal fluency, executive functioning, verbal and visual memory). Neither age [sibs (28.1/7.8), controls (25.7/6.8)] nor education [sibs (13.9/3.6), controls (15/3.7)] differed between groups. Results: T-test comparisons between siblings and controls were significant for estimated IQ (sibs=110.3/14.4, controls=93.3/16.2, $p<0.0001$), CPT-IP numbers d'(sibs=0.17/0.51, controls=2.02/0.89, $p<0.0001$), both semantic (sibs=19.6/4.7, controls=23.9/6.9, $p=0.003$) and phonemic fluency (sibs=14.3/3.5, controls=17.2/4.7, $p=0.006$), WMS-R visual span forward (sibs=8.77/1.7, controls=9.7/1.7, $p=0.03$) and backward (sibs=7.3/1.9, controls=8.8/1.9, $p=0.004$). Differences on the WCST and verbal memory did not reach statistical significance. Discussion: These results support that subtle neurocognitive deficits in the relatives of schizophrenic patients may be an indicator of genetic liability for the disorder. This study extends previous work by showing that spatial attention and spatial working memory, which have been scarcely analysed, are also lower in healthy relatives. These results are in line with the view of neurocognitive deficits as promising endophenotypic candidates in molecular genetic studies. Acknowledgements: This work has been funded by Fundacio La Marato de TV3 de Catalunya (014430/31).

EMOTIONAL INTENSITY JUDGMENTS ARE NOT INFLUENCED BY CONTEXT IN SCHIZOPHRENIA

J. A. Barrett,* D. C. Glahn, D. I. Velligan, M. J. Green
Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

Poor contextual processing may be central to the cognitive fractionation found in schizophrenia (SCZ). Although a reduced ability to use contextual cues to guide ongoing behavior has been proposed to underlie a variety of behavioral and neuropsychological impairments found in SCZ, to date most studies of contextual processing have focused on attentional or working memory measures designed to be devoid of social or emotional valiant stimuli. To assess the effects of context on social cognition in SCZ, we adapted an emotion discrimination paradigm where subjects are asked to make judgments about the intensity of a given emotion of an individual in and out of context. Healthy subjects (CT) tend to utilize contextual information to moderate their assessment of emotional intensity. We hypothesize that patients will be unable to use these cues to the same extent as healthy subjects. 30 patients with SCZ and 21 demographically matched CT completed our emotion contextual processing task. In the first condition of our task, subjects are shown an image of a single person presented on a blue background and asked to assess one of five emotions (anger, disgust, happiness, sadness, and fear) on a 5-point Likert scale. A total of 14 images were used and 3 separate emotion assessments were made for each image. For Condition 2, subjects are presented with the same images used in Condition 1, however, the blue background was replaced with a visually informative scene. Differences between the first and second ratings provide an index of the extent contextual information is used to judge emotional intensity. With the exception of disgust, patients with SCZ did not differ from comparison subjects when rating the intensity of emotion for individuals without contextual cues ($F[1,49]=0.34$, $p=0.5$). However, while CT significantly altered their ratings in the face of contextual information, patients did not ($F[1,49]=9.93$, $p=0.002$), suggesting that patients with SCZ did not utilize contextual information to help judge emotional intensity. We find that contextual information has less influence on social cognitive decisions made by patients with SCZ than similar decisions made by CT. Our findings extend current models of contextual processing deficits in SCZ to emotion processing and social cognition. A better understanding of the core social cognitive processes disrupted in SCZ could help in developing remediation strategies for patients and potentially lead to better outcomes.

PERCEPTUAL TIMING AND NEUROCOGNITIVE FUNCTION IN SCHIZOPHRENIA

R. S. Bhaker,* M. V. Ashok, K. H. Lee, R. W. Parks, P. Birkett, P. W. Woodruff
Academic Clinical Psychiatry, University of Sheffield, Sheffield, South Yorkshire, United Kingdom

OBJECTIVE: Timing dysfunction may be fundamental to many of the cognitive deficits of schizophrenia. The aim of this study was to investigate internal clock speed and temporal sensitivity, and their relationship with neuropsychological frontal lobe function. METHOD: Twenty-four patients with schizophrenia and twenty-four healthy controls matched by age and gender participated. There was no group difference in NART IQ. All subjects completed the temporal bisection task which involves categorising durations as long or short. We employed two interval ranges (400-800ms and 1000-2000ms). A battery of neuropsychological tests was also used. RESULTS: Patients showed significantly delayed bisection point (decreased internal clock speed) in both interval ranges. The patients also had a widened difference limen (decreased sensitivity) in both interval ranges compared with healthy controls. Impaired executive function measured by the Wisconsin Card Sorting Test in patients was significantly associated with delayed bisection point and impaired temporal sensitivity. Other measures of prefrontal function (Digit Spans and Continuous Performance Test) showed similar associations. DISCUSSION: Patients judge objective durations to be longer. They also show a reduced ability to discriminate between intervals. Moreover, these impairments were associated with executive and working memory dysfunction. CONCLUSION: Time perception is impaired in schizophrenia. This impairment is closely associated with working memory and executive function in schizophrenia.

ARE AUDITORY-VERBAL HALLUCINATIONS ASSOCIATED WITH AUDITORY EMOTIONAL PROCESSING DEFICITS?

C. L. Boundy,* S. L. Rossell
MACCS, Macquarie University, Sydney, NSW, Australia

It has long been established that people with schizophrenia exhibit difficulties when processing emotion. However, most of this literature has focused on the perception of visual affective stimuli (e.g. faces). Whilst some research has investigated the perception of prosody, no study to date has examined this deficit as a function of positive symptomology, specifically the presence of Auditory-Verbal Hallucinations (AVH). We hypothesised that patients with a history of AVH would demonstrate a greater overall deficit in processing affectively-laden sound/speech stimuli in comparison to patients with no history of AVH and controls. Controls (C), schizophrenia patients with a history of AVH (AVH) or with no history of AVH (NAVH) completed four perceptual auditory affect tasks. The tasks used either verbal/semantic or non-verbal/non-semantic (i.e. sounds) stimuli. AVH patients had significantly impaired perception specifically on the non-verbal task, with the affective, and not the neutral valance stimuli. There were no emotion specific deficits, i.e. no differences in accuracy between any of the four categories of emotion tested: fear, sad, angry and happy sounds. Both patient groups showed impairments on tasks with verbal/semantic stimuli, as these tasks require proficient semantic processing we speculated that semantic impairments in schizophrenia masked differences between AVH and NAVH patients on these tasks. In conclusion the results on the non-verbal task support the notion that patients with AVH have increased liability for auditory affect perception deficits. We speculate altered sensitivity to affective sounds/speech predisposes individuals to unusual auditory perceptions and/or AVH.

AGE-ASSOCIATED DECLINES IN COGNITIVE FUNCTIONING IN SCHIZOPHRENIA PATIENTS WITH A CHRONIC VERSUS STABLE COURSE OF ILLNESS

C. R. Bowie,* A. Reichenberg, P. D. Harvey
Psychiatry, Mt. Sinai School of Medicine, New York, NY, USA

The course of cognitive functioning in schizophrenia is controversial. While many chronic patients have deterioration in late life, studies

of ambulatory patients suggest a more stable course. Cross-sectional analyses of cognitive test performance were performed for older (age>=65) and younger (age <65) ambulatory and institutionalized schizophrenia patients. The measures included naming, fluency, episodic memory, and constructional praxis. A multivariate analysis of variance revealed significant a main effect for patient group [$F(6,373)=20.9$, $p<.001$], with chronic patients manifesting more severe impairments on all measures, and a significant interaction between age group and patient group [$F(6,373)=2.4$, $p<.05$], with the chronic patients performing more poorly in late-life and ambulatory patients showing stability into late-life. However, even for the ambulatory patients, age-related differences were found for constructional praxis, a measure of complicated information processing. A further analysis of letter-number sequencing, a measure of working memory that was only conducted in the ambulatory cohort, revealed a trend for poorer performance in ambulatory patients in late-life, $t(58)=1.84$, $p=.07$. The worsening in late-life on these measures was not due to normal age-associated declines, as indexed by comparisons with data from demographically matched healthy controls or normative data. Consistent with previous work, chronic schizophrenia inpatients demonstrated poorer functioning than ambulatory patients across the lifespan, with these impairments more pronounced in late life. Ambulatory patients manifested less severe cognitive deficits that remained stable across a number of domains, including verbal skills, learning, and memory. However, deficits in complex information processing were greater in older ambulatory patients. These data suggest that dynamic change processes may occur in late-life schizophrenia, regardless of lifetime course and outcome. These changes vary by lifetime outcome, with poor-outcome patients deteriorating across domains and ambulatory patients worsening only in complex cognitive skills.

THE INDEPENDENCE OF ATTENTIONAL NETWORKS IN SCHIZOPHRENIA

J. G. Braun,* D. C. Gooding
Psychology, UW-Madison, Madison, WI, USA

Schizophrenia and its spectrum disorders are characterized by attentional deficits. In the current study, we compared the efficiency of three attentional networks (alerting, orienting, and executive functioning) in outpatients (diagnosed with schizophrenia or schizoaffective disorder) and healthy controls. We used the Fan et al. (2002) Attentional Network Task (ANT), a cued reaction time task using one central arrow plus four flankers. Participants were required to identify the direction of a centrally presented arrow that was surrounded by either arrows or dashed lines. On some trials, the stimulus array was preceded by a warning cue. The experimental design was factorial, with two within-subject factors: cue type (no cue, center cue, double cue, and spatial cue) and flanker type (neutral, congruent, and incongruent). Performance was assessed in terms of reaction time and accuracy. The efficiency of the attentional networks was assessed by measuring how response latencies were influenced by alerting cues, spatial cues, and flanking stimuli. Although the patients were slower and less accurate than the controls, the reaction times of both groups were similarly influenced by the presence or absence of an alerting cue and/or orienting cue. The patient group showed a significantly greater flanker effect, suggesting less effective executive control of attention. Furthermore, the flanker effect was influenced by the focal nature of attention. The magnitude of the flanker effect did not significantly differ between the two groups when attention was extrinsically focused on one specific location (e.g. on trials with central or spatial cues). However, under diffuse-attention conditions (e.g., trials with no cue or a double cue), the patient group exhibited a significantly greater flanker effect as compared to the controls. These results suggest that schizophrenia-spectrum patients can avoid abnormally large flanker (interference) effects when given external cues to focus their attention but have more difficulty when their attentional resources are more widely distributed. Additionally, we also found that the efficiency within each of the three networks was not correlated with one another for either the outpatient group or the control group. These results support the Posner and Petersen (l990) model of relatively independent attentional networks in schizophrenia-spectrum patients as well as healthy controls.

THE SENSE OF AGENCY: A PROCESS PRIMARY TO MOTOR EXECUTION

V. Bulot,* Y. N. Delevoye-Turrell, P. Thomas
Psychiatric Unit, CHRU, Lille, France

Introduction: In healthy controls, self imposed (S) forces are reported as being smaller than externally imposed (E) forces of similar magnitude. In patients with schizophrenia, S and E-forces are judged as similar (Blakemore et al. 2000). These results, even if subjective, have been put in parallel with the abnormal sense of agency that characterizes schizophrenia; they have lead to the theory that the sense of agency is based on sensory attenuation and thus, is secondary to motor execution. In the present study, we examined the predictive scaling of grip force in S and E collisions in a learning paradigm. Our aim was to obtain an objective measure of the sense of agency before and after motor execution, in order to assess whether the abnormal sense of agency in schizophrenia is primary or secondary to movement production. Methods: Twenty-two patients with schizophrenia and healthy controls were required to arrest the fall of a pendulum with a load cell which measured the grip force level used throughout the trial. The pendulum was released either by the subject (S=self imposed) or by the experimenter (E=externally imposed). To succeed in the task, grip force had to be increased in anticipation of the impact. For each individual, the sense of agency was objectively taken as the difference between S and E. Half of the subjects received feedback on the efficiency level reached, at the end of each trial. Results: The sense of agency was present in controls prior to movement production: grip force was scaled at the time of impact, more efficiently in S than in E. Efficiency improved with trial repetition for both S and E at a similar rate. Feedback improved overall efficiency but again similarly for S and E. The sense of agency was absent in patients: grip force was scaled as efficiently in S and in E. Trial repetition and feedback improved efficiency at the same degree than for controls and similarly for S and E. Conclusion: For the first time, we have objectively demonstrated an abnormal sense of agency in schizophrenia. This deficit is quantifiable in the predictive scaling of grip force, which suggests that it occurs prior to movement execution. Consequently, we suggest here that the sense of agency is (1) a process primary to motor execution and (2) not based on sensory attenuation. Our results further indicate that the sense of agency is not sensitive to motor awareness which suggests an automatic nature for the process.

VISUAL PROCESSING IMPAIRMENT AND EMOTION RECOGNITION DYSFUNCTION IN SCHIZOPHRENIA

P. D. Butler,* R. C. Gur, M. Jalbrzikowski, J. Loughead, A. M. Saperstein, I. Schechter, E. M. Weiss, V. Zemon, D. C. Javitt
Cognitive Neuroscience and Schizophrenia, Nathan Kline Institute, Orangeburg, NY, USA

Several studies have shown that patients with schizophrenia have deficits in emotion perception. Such deficits have been related to poor performance on visual processing tasks. Given the importance particularly of the magnocellular pathway in visual processing deficits, this study examined relationships between visual pathway impairments and emotion processing dysfunction in schizophrenia. Emotion processing was examined using the PENN Emotion Differentiation, Emotion Recognition, and Emotion Acuity Tasks. Magnocellular and parvocellular visual pathway function were assessed using both steady-state visual evoked potentials (ssVEPs) and psychophysically-determined contrast thresholds. Luminance contrast and stimulus size (i..e, spatial frequency) were utilized in the ssVEP and contrast threshold tasks to bias processing towards the magnocellular vs parvocellular pathways. Patients with schizophrenia (n=30) performed significantly more poorly than controls (n=19) on the Emotion Differentiation Task on both number of happy and number of sad faces differentiated correctly ($p<0.001$), as well as on total number correct for the Emotion Recognition and Emotion Acuity tasks ($p<0.001$). Poorer performance on magnocellular- and parvocellular-biased ssVEPs and on magnocellular-, but not parvocellular-, biased behavioral contrast threshold tasks was significantly correlated with poorer performance on all four emotion processing variables ($p<0.05$) for patients and controls combined. However, significant relationships were not found when patient and control data were analyzed separately, perhaps due to decreased variability on task performance within each group than in the two groups combined. These data show significant relationships between visual pathway, particularly magnocellular, dysfunction and emotion processing performance. The results support the hypothesis that dysfunction in early-stage, low level processing in the visual system may upwardly generalize to erode higher-level processing.

EVIDENCE FOR A WORKING MEMORY DOMAIN BY DIAGNOSIS INTERACTION: DISSOCIATING SCHIZOPHRENIA AND BIPOLAR DISORDER

S. Cakir,* D. C. Glahn, J. C. Soares, J. A. Barrett, D. I. Velligan
Psychiatry, University of Texas Health Science Center, San Antonio, San Antonio, TX, USA

Objective: Although unique diagnostic entities, schizophrenia (SC) and bipolar disorder (BP) may have overlapping etiologies, leading to potential similarities in neuropsychological functioning. The evaluation of the congruence and incongruence of neurocognitive processing in SC and BP could provide insights into the pathology and progression of both disorders. The disturbed working memory (WM) is thought to be fundamental to the cognitive impairments seen in SC, but little is known about similar impairment in BP. Here, we evaluated verbal and spatial WM in demographically matched groups of SC, BP and healthy comparison subjects. Method: 45 clinically stable SC patients, 52 BP patients and 46 healthy subjects completed a neuropsychological evaluation including the verbal (forward and backward digit span) and spatial (spatial delayed response task) WM measures. In addition, clinical symptoms at the time of assessment were conducted. Data were analyzed with a 3 x 3 mixed model assessing the effects of WM measure and diagnostic group while statistically controlling IQ, sex, race and education level. Results: There were significant main effects for WM and group and a WM index by group interaction suggested that while both patients groups were impaired, the extent of this impairment differed across WM measure. Planed contrasts indicated that verbal WM was equally impaired in both patients groups. However, only the SC group showed spatial working memory deficits. Clinical symptoms at the time of assessment were not correlated with WM performance in either group. Conclusions: SC and BP patients showed similar impairments for verbal WM. Yet, while SC patients were impaired on a standard spatial WM test, BP patients were intact. These results suggest that either (1) a common neuropsychological process serving verbal WM is disrupted in both illnesses and that SC patients have a separate unique abnormality creating their spatial WM difficulties or that (2) the verbal WM deficits common to the two disorders have different neural roots. Future neuroimaging and neuropsychologic studies could be useful in evaluation of the each subcomponents of the WM in SC and BP patients to address the pathology specifically.

PROCESSING SPATIAL INFORMATION IN SCHIZOPHRENIA: A STUDY OF SHORT-TERM MEMORY FOR SERIAL ORDER AND ITS SUSCEPTIBILITY TO DISTRACTION

C. Caroline,* S. Tremblay, C. Lehoux, M. Roy
Groupe de recherche en psychologie cognitive, Universite Laval, Quebec, QC, Canada

Memory impairment is a core feature in schizophrenia (SZ). The aim of this study was to investigate short-term memory (STM) for serial order and its sensitivity to distraction in the spatial domain. This study comprised 18 schizophrenic patients and 19 healthy controls. The degree of disruption upon recall from interleaving irrelevant items within a sequence of to-be-remembered items (the sandwich effect) was examined with visuo-spatial material. This well established paradigm in experimental cognitive psychology is very similar to the Digit span distractibility test, a task widely used in verbal STM in SZ (Oltmanns & Neale, 1975). In the current study, recall performance, whether in the presence or absence of distraction, was poorer in SZ compared to healthy controls. Disruption of recall was significant but of similar magnitude in both groups. Our results suggest that STM capacity is impaired in SZ rather than attentional control, which is not in line with the pattern of distraction observed in the verbal domain.

DIFFERENCES IN COGNITIVE PERFORMANCE BETWEEN MEDICATED AND NON-MEDICATED SCHIZOPHRENICS AND NORMALS ON THE TRANSITIVE INFERENCE TASK

R. B. Chin,* K. E. Youens, C. A. Tamminga
Psychiatry, UT Southwestern Medical Center, Dallas, TX, USA

Objective: The transitive inference task requires the construction of a mental hierarchy A>B>C>D>E, using arbitrarily selected patterns, in order to make an "inference" about dominance between pairs of

patterns selected from that hierarchy. Thus, the TI task tests subjects' ability to organize information and to make logical operations based upon that organization (Eichenbaum et al 2001). It is hypothesized that people with schizophrenia will not perform as well as normals on the TI task due to abnormalities in the hippocampus (Titone et al 2003). The objective of this study is to investigate differences in performance on the TI task between schizophrenics off and on medication and normals. *Methods:* Three groups are recruited: normals (n=9) and schizophrenics off (n=2) and on (n=7) medication. Subjects perform a computerized task whereby an arbitrarily-arranged hierarchy of stimuli is learned. In the training phase, subjects see repeated presentations of pairs of abstract color patterns (A>B,B>C,C>D,D>E). Subjects learn the dominant pattern within each pair until criterion (95% accuracy) is reached. In the test phase, subjects indicate dominance among the stimulus pairs from the training phase along with two new pairs: a non-transitive pair (A>E) and a transitive pair (B>D). A follow-up questionnaire is administered to evaluate awareness of the hierarchy when performing the TI task. *Results:* Schizophrenics require more trials to reach the 95% criterion (SZ off-med 14+/-3 trials, SZ on-med 7+/-1 trials, normals 3.67+/-1.56 trials). Schizophrenics are also less successful in performing the transitive inference (SZ off-med 55+/-45.0% correct, SZ on-med 68.3+/-17% correct, normals 84.4+/-18% correct). All groups perform fairly well on the non-transitive inference (SZ off-med 100%, SZ on-med 88.6+/-21%, normals 85.5+/-28%. Very few subjects from either group are able to correctly rank-order the stimuli hierarchy (SZ off-med 0:2 correct, SZ on-med 1:7 correct, normals 2:9 correct). *Conclusion:* Preliminary results suggest that schizophrenics on and off medication have more difficulty in learning the hierarchy, indicated by a greater number of training trials required to reach criterion. Schizophrenics also have more difficulty in making the transitive inference, as seen in the smaller percent accuracy on the TI pair when compared with normals. The hierarchical awareness seems to have no bearing on the success of the transitive inference.

EVIDENCE FOR IMPAIRED MNEMONIC STRATEGY USE AMONG PATIENTS WITH SCHIZOPHRENIA USING THE PART-LIST CUING INHIBITION PARADIGM

B. K. Christensen,* A. Benjamin, P. Vidailhet, T. Girard
Centre for Addiction and Mental Health, University of Toronto, Toronto, ON, Canada

Episodic memory is among the most impaired cognitive functions associated with schizophrenia (SCZ). A prominent characteristic of this deficit is poor utilization of mnemonic strategies, such as organizing material by semantic category. Studies have demonstrated that patient's recall improves disproportionately as a function of the semantic structure of word lists at study (i.e., better recall for categorized lists that are blocked by category rather than presented randomly). However, these conditions are typically confounded by task difficulty (i.e., blocked lists are easier), which undermines interpretations of a differential deficit. A potential solution is the use of experimental paradigms in which the presence of a deficit improves performance. Part-list cuing inhibition (the detrimental effect of presenting a subset of learned items on the recall of remaining items) is hypothesized to reflect the disruptive effects of these cues on retrieval strategies. Therefore, given that persons with SCZ often fail to invoke retrieval strategies, part-list retrieval cues should improve their memory relative to healthy controls, thereby revealing mnemonic strategy deficits unencumbered by a difficulty confound. In the current study, patients with SCZ (n=19) and healthy controls (CON; n=16) studied words from 48-item lists that were either semantically unrelated (U), categorized but presented randomly (CR), or blocked by category (CB). Word lists and categories were matched for psycholinguistic attributes. After a 90-second delay, participants recalled previously studied words under both uncued and cued (i.e., the provision of 30 randomly chosen studied words) conditions. Repeated measures ANOVA revealed significant main effects for group (CON>SCZ), list type (U<CR<CB) and retrieval condition (uncued>cued). Importantly, a significant group x list type x retrieval condition interaction indicated that the cuing effect diminished with increasing semantic structure at encoding for controls (i.e., U>CR>CB), whereas the opposite was true for SCZ. Possibly, increasing internal structure of word lists mitigates the necessity for control subjects to impart the same degree of retrieval strategy. In contrast, while providing structure aids memory in SCZ, it may also instantiate the use of increased retrieval efforts. These results generally support the hypothesis that patients with SCZ are impaired in their ability to impart mnemonic strategies in the aid of recall.

EVIDENCE OF INDEPENDENCE BETWEEN ANTISACCADE AND WORKING MEMORY TASK PERFORMANCE IN SCHIZOPHRENIA

S. Clarke,* G. Donohoe, A. Corvin, R. Reilly, H. Garavan, M. Gill, D. Morris, K. McGee, J. M. Nangle, S. Schwaiger, B. Greene, S. Meredith, I. H. Robertson
Dept of Psychiatry, Trinity College Dublin, Dublin, Ireland

Introduction: The high heritability of impaired antisaccade performance has lead to its identification as a potential endophenotype for schizophrenia. However, the neurocognitive correlates of the task remain uncertain. This study investigated the competing theories that impaired performance is related to a general working memory deficit or to a separate cognitive function of inhibitory control. Method: Antisaccade performance of 26 patients with schizophrenia or schizoaffective disorder were assessed using an overlap design (antisaccade cues occurring randomly at +/-16 degrees either side of a constantly illuminated central fixation point) and portable EOG apparatus. Patients were also assessed on CANTAB spatial episodic and working memory, pre-morbid and current IQ and on a simple go-no go task. Results: In addition to showing a similar pattern of compromised antisaccade performance as previously reported, the percentage of successful antisaccades negatively correlated with age (r=-.52; p=.007), spatial episodic memory performance errors (r=-.60;p=.001) and working memory performance errors (=r-.47; p=.025), and correlated positively with correct responses on the go/no go task (r=.503; p=.02). To parse the contribution of working memory to inhibitory control, we performed a partial correlation between antisaccade performance and go-no go performance controlling for spatial working memory and age. Results revealed a significant relationship between the two measures of inhibitory functioning (r=.54; p=.034) Discussion: In the present study working memory performance was associated with antisaccade performance. However the fact that antisaccade performance correlated with our other inhibitory task even when working memory performance was partialled out suggests that there may be a "distinct" inhibition process common to these tasks not explainable by working memory alone. These findings are discussed in terms of the competing theories of antisaccade performance.

ATTENTION AND MOVEMENT PRODUCTION: DYSFUNCTIONAL MODULATION IN SCHIZOPHRENIA

Y. N. Delevoye-Turrell,* P. Thomas, A. Giersch
Psychology, Lille 3 University, Villeneuve d'Ascq, France

Introduction: The control of simple motor actions is considered to be automatic by nature. The present study was conducted in order to (1) evaluate the attention demands of basic motor planning and execution in healthy controls and (2) to assess whether the motor sequencing deficits previously reported in schizophrenia are associated to executive dysfunction. Methods: A dual task paradigm was used in 24 patients with schizophrenia and 24 healthy controls. Their task was to respond to an auditory probe while holding an object in midair, which recorded the grip force levels used throughout three gripping actions: increase the grip force applied on the object (grip); grip before moving the object (sequence); grip and move the object simultaneously (synchronize). The percentage of reaction time increase between single and dual-task conditions (ΔRT) was the indicator of the amount of attention allocated for motor planning, execution and resetting, depending on whether the probe occurred before, during or after action production, respectively. Results: ΔRT was significantly different from zero for all subjects. For controls, ΔRT was increasingly shorter when the probe occurred before, during and after action execution, respectively; this pattern of attention allocation was modulated in function of the nature of the gripping action. For patients, ΔRT was the largest when the probe occurred during action execution; this pattern was identical for all actions. Conclusions: Our results demonstrate that motor planning is attentional demanding even in healthy controls. They suggest that optimal motor performance is reached thanks to a constant modulation of attention allocation and that this function is perturbed in patients. Further work is nevertheless required to determine the causal relationship between motor and executive dysfunction in schizophrenia.

LIFE EVENTS AND PERCEIVED STRESS IN SCHIZOTYPIC YOUNG ADULTS: A THREE-YEAR FOLLOW-UP STUDY

M. A. Diaz,* L. A. Dickerson, T. R. Kwapil
Psychology, UNCG, Greensboro, NC, USA

The present study examined the experience of significant life events and perceived stress in a three-year follow-up assessment of schizotypic young adults (n = 52) and control participants (n = 47) identified by the Revised Social Anhedonia Scale (RSAS). Numerous studies have supported the validity of the RSAS for identifying schizotypy. Life events were assessed at the follow-up assessment using the Recent Life Changes Questionnaire and perceived stress was examined using the Perceived Stress Scale. The Social Anhedonia group exceeded the control group on ratings of perceived stress during the follow-up period, although the groups did not differ on rates of significant life events. Perceived stress, but not life events, accounted for significant variance (over variance accounted for by anhedonia group membership) in the prediction of schizotypal and psychotic-like symptoms at the follow-up, as well as the diagnosis of schizophrenia-spectrum disorders. In addition, the three-way interaction of anhedonia group membership, high perceived stress, and low levels of significant life events accounted for significant variance in the prediction of schizotypal symptoms and spectrum disorder, suggesting that schizotypic individuals who experience high stress and are disengaging from life seem to have especially poor outcomes.

COGNITIVE IMPAIRMENTS PREDICT COMMUNICATION FAILURES IN SPEECH MORE CLEARLY THAN THEY PREDICT "THOUGHT DISORDER" OR CONCEPTUAL DISORGANIZATION

N. M. Docherty
Psychology, Kent State University, Kent, OH, USA

Schizophrenia patients have neuropsychological impairments that could be expected to have marked effects on the capacity for coherent speech production. However, associations between cognitive impairments and speech disorder have tended to be relatively small. This may be due partly to the ways in which speech disorder has typically been measured. The present study tested (1) whether deficits in sustained attention and sequencing capacity are related to speech disorder, and (2) whether these impairments are more highly related to a communication-oriented speech measure than to speech measures that target underlying thought disorder or structural disorganization. Forty-seven schizophrenic inpatients and 36 control participants were tested for low and high load sustained attention, and simple, complex, and conceptual sequencing ability. Their speech was rated using measures of communication disturbance, thought disorder, and conceptual disorganization. Hierarchical regressions tested the contributions of the cognitive variables to each of the three measures of speech disorder. The findings suggest that (1) impairments in basic cognitive processes contribute substantially to schizophrenic speech disorder, (2) the associations between cognitive impairments and speech disorder are stronger when the speech disorder is measured in terms of communication disturbance than when it is measured in terms of thought disorder or structural disorganization.

RECOGNITION OF AFFECT AND ORIENTATION OF FACES IN SCHIZOPHRENIA PATIENTS IN RELATION TO THE DEFICIT SYNDROME: WHAT IS IN A FACE?

M. L. Doop,* S. Park
Psychology, Vanderbilt University, Nashville, TN, USA

Affective deficits may be core features of schizophrenia (SCZ) that are associated with cognitive dysfunction and clinical symptoms, especially the deficit syndrome. However SCZ also have a wide range of perceptual deficits. Since most studies of emotion recognition use faces as stimuli, it is unclear whether emotion deficits observed in SCZ may be secondary to perceptual impairments. The aim of this study was to determine whether emotion deficits reflect impairments of affective processing or a broader perceptual deficit that prevents accurate processing of visual information. SCZ and matched controls (NC) participated in three matching tasks. In the emotion-matching task, the facial expression of the target face had to be matched to one of the three choices. In the face orientation and car orientation matching tasks, the orientation of the target had to be matched to one of the three choices. Accuracy and response times were recorded. Deficit symptoms were scored from BPRS using the Proxy for Deficit Syndrome (PDS; Kirkpatrick et al, 1993). NC were given the Schizotypal Personality Questionnaire (SPQ). SCZ were impaired on all three tasks compared with NC, which suggests that in addition to affect processing, there are clear perceptual deficits. Deficit symptoms were correlated with emotion matching errors but not with orientation-matching errors, suggesting a more specific rela-

tionship between emotion identification and deficit syndrome. Similarly in NC, the constricted affect subscale of SPQ and emotion matching errors were associated. Moreover, the Zigler social functioning score was correlated with emotion matching errors across both groups. These results suggest that SCZ have affect recognition deficit over and above perceptual deficits and that these deficits are linked to deficit symptoms and poorer social functioning.

SEMANTIC MEMORY IMPAIRMENT IN SCHIZOPHRENIA—DEFICIT IN STORAGE OR RETRIEVAL OF KNOWLEDGE?

O. Doughty,* V. A. Lawrence, A. Al-Mousawi, D. J. Done
Psychology, University of Hertfordshire, Hatfield, Hertfordshire, United Kingdom

The purpose of the study was to see if semantic memory impairment in schizophrenia results from a deficit in stored semantic knowledge, or from abnormal retrieval of otherwise intact semantic knowledge. According to the criteria established by Warrington and Shallice (1979), semantic storage disorder includes i) consistency of errors for the same items across tests, ii) a linear increase in errors as more detailed item knowledge is accessed. This pattern is particularly noted in people with dementia (Hodges, Salmon and Butters, 1992) using the Hodges' semantic memory battery. In the current study 18 patients with schizophrenia, 20 patients with Alzheimer's dementia (AD) and 20 non-psychiatric controls completed the Hodges' battery. The group with schizophrenia also completed the Behavioural Assessment of Dysexecutive Syndrome (BADS). The groups were matched on pre-morbid IQ as measured by the NART. It was found that the profile of errors differed substantially between the groups, in that the AD sample were significantly impaired on all subtests whereas the schizophrenia sample performed at ceiling level for 4 of the 7 subtests (naming, category comprehension, and categorizing at both superordinate and base levels), but were noticeably impaired on the other 3 subtests (picture - picture semantic associations, word - word semantic associations, and subordinate categorisation). Whereas the AD subjects demonstrated a high level of consistency of errors, together with the linear error pattern (superordinate < base level < subordinate categorization), the schizophrenia sample showed inconsistency of errors and a significantly different, non-linear pattern of errors (only on subordinate level) as more specific semantic knowledge is accessed. This pattern suggests that loss of semantic knowledge is not a primary explanation for semantic memory impairment in schizophrenia. Furthermore, although a substantial number of people in the schizophrenia sample met criteria for executive dysfunction (based on the BADS test), this did not correlate with the profile of errors. Thus executive dysfunction (in the form of atypical retrieval strategies) appears not to explain semantic memory impairment either. In conclusion, we propose that patients with schizophrenia adopt inappropriate criteria for responding in some semantic tasks. An explanation is offered which suggests dysfunction may result more in the orbito-frontal rather than dorsolateral prefrontal circuit.

ASSOCIATIONS OF SELF HARM IDEATION FOLLOWING FIRST PRESENTATION WITH NON-AFFECTIVE PSYCHOSIS

R. J. Drake,* N. Tarrier, G. Haddock, S. W. Lewis
School of Psychiatry & Behav. Sci., University of Manchester, Manchester, United Kingdom

Identifying and treating ideas of deliberate self harm (DSH) is important for suicide prevention in early schizophrenia, when rates are highest. We investigated the relationships between insight, self esteem, symptoms and DSH ideas in a cohort followed-up as part of the SOCRATES trial of CBT in early DSM IV non-affective psychosis. Patients were recruited from consecutive first admissions to in & day patient units covering 3 catchment areas in England over 26 months. All were 16-65 and had DSM IV schizophrenia spectrum psychoses. Initial interview - with the PANSS, Birchwood Insight Scale (BIS), Rosenberg Self Esteem (RSE) scale and HoNOS global outcome scale - was followed by interviews at 6 weeks, 3, 9 & 18 months. The outcome measure was a dichotomised form of the HoNOS DSH item. 257 were recruited. BIS & RSE had weak but significant correlations with degree of DSH ideation. DSH ideation at succeeding stages always correlated moderately. Factor analysis of DSH ideas with the PANSS at each stage showed a consistent loading onto depression and psychosis factors. Multi-dimensional scaling at each stage showed PANSS items appeared to mediate the relationship between RSE, BIS and DSH ideas. Including selected PANSS items, therapy and demographic variables in logistic regression at each stage left almost no independent relation of BIS & RSE to DSH. Depression consistently predicted DSH ideas; as did residual persecutory ideas during recovery and hallucinations at 18 months. DSH ideas from previous stages were not significantly related, nor did they much improve the fit of the models, except by improving sensitivity. Depression and paranoia mediated the effect of insight and self esteem on DSH ideas. Including past DSH ideas marginally improved prediction of current ones; demographic variables were not predictive in this sample.

IMPAIRED VISUAL SEARCH IN SCHIZOPHRENIA REFLECTS DEFICITS IN ATTENTIONAL CONTROL

R. L. Fuller,* S. J. Luck, E. L. Braun, B. M. Robinson, R. P. McMahon, J. M. Gold
Maryland Psychiatric Research Center, University of Maryland SOM, Baltimore, MD, USA

Many of the cognitive deficits in schizophrenia (SC) are often attributed to impairments in attention. The goal of this study was to identify the specific attention-related processes that are impaired by using 4 visual search tasks which varied on the degree of perceptual difficulty and working memory (WM) involved. Each search array contained one of two possible targets. The target was a square with a gap on the left or right side. In the feature task the distractors were squares without a gap, so the target contained a feature that was absent in the distractors. In the large-gap task the distractors had a gap on the top or bottom and in the small-gap task the gaps were smaller to increase perceptual difficulty. The comparison task increased the working memory (WM) load by requiring subjects to search for the pair of squares containing gaps on the same side among pairs of squares with gaps on opposite sides. The set size for each task varied among 4, 8 or 12 items. Accuracy and reaction time (RT) were recorded in 22 SC patients and 16 controls. For each task SC and control accuracy reached 98% or above. Slope of RT as a function of set size is the best measure of the efficiency of search and an ANOVA using slope as the dependent variable found significant effects of group, task and group X task interaction ($p < 0.01$). We examined the proportional change in slope to see which tasks were the most proportionally impaired. SC slopes were slower than control slopes by the greatest magnitude in the feature task (109%), followed by the comparison task (91%) and the large gap task (68%) while the two groups' slopes differed the least in the small gap task (34%). Thus SC

performance was most proportionally impaired in the least perceptually challenging condition and least impaired in the most perceptually challenging condition. These data implicate an abnormality in the efficient control of attention. Further studies are needed to determine if the SC attentional control deficit is due to an impairment detecting likely target candidates during search or to inefficient search caused by WM impairments that result in repeated visits to previously searched locations.

NEUROCOGNITIVE EFFECTS OF TYPICAL AND ATYPICAL ANTIPSYCHOTICS

A. Gibbs,* C. Harte, D. Titone, M. Coleman,
O. Krastoshevsky, H. Gale, P. Holzman, D. Levy
Psychology Laboratory, McLean Hospital, Belmont, MA, USA

Schizophrenic patients perform poorly on a variety of cognitive and motor tasks. The effects of typical and atypical antipsychotic medications on performance are not well understood, in particular, whether performance is stable or varies over time and whether various medications differ in their performance. We carried out a longitudinal study of schizophrenic outpatients taking clozapine (CLZ), olanzapine (OLZ), or typical (TYP) antipsychotic medications as well as nonpsychiatric controls (NC) who were taking no antipsychotic medication. Subjects were tested three times over the course of a year. The test battery included smooth pursuit eye movements, the Stroop color-word task, and a spatial working memory task. On the Stroop test, patients taking CLZ and patients taking a TYP antipsychotic showed a speed-accuracy tradeoff. Specifically, patients on TYP antipsychotic medication had the slowest reaction time and the highest accuracy, indicating that performance benefited from slowed responding. Patients on CLZ, on the other hand, had the fastest reaction time and the worst accuracy, indicating that performance suffered from responding quickly. Patients on OLZ had both significantly delayed reaction time and low accuracy relative to the other groups, indicating that, unlike the patients taking TYP antipsychotics, accuracy did not benefit from slowed responding. On the spatial working memory task, in which rapid speed of response is not specifically encouraged, patients taking CLZ and NC performed significantly better than patients taking a TYP antipsychotic and patients taking OLZ. Thus, CLZ seems to interfere with accuracy only when rapid responding is encouraged. Eye tracking performance was stable across trials in all groups. This study was supported in part by grant MH31340 and a grant from Eli Lilly and Company.

FUNCTIONAL NEUROANATOMY OF CREATIVE THINKING PROCESS IN MUSICIANS IN RELATION TO SCHIZOTYPAL PERSONALITY: A NEAR INFRARED OPTICAL TOMOGRAPHY (NIROT) STUDY

C. Gibson,* B. Folley, S. Park
Psychology, Vanderbilt University, Nashville, TN, USA

There is much speculation concerning a possible link between creativity and psychosis. However, past studies have relied on historical and biographical analyses rather than empirical evidence to examine the relationship between creativity and psychosis. The present study examined creativity and schizotypal personality in individuals of a "creative" profession. Past research suggests that musicians are more likely to have reduced functional laterality and greater connectivity between hemispheres compared to nonmusicians (Hassler, 1990; Jäncke, 1997), perhaps due to a unique neurodevelopmental trajectory supported by music training. There is evidence of enlarged corpus callosum in musicians, possibly due to early musical training, which often relies on a dispersed network of different areas of the brain (Schlaug, 1995). Furthermore, musical talent requires integration of motor functions of both the left and right hemispheres (Christman, 1993; Hassler, 1990) and depends on efficient and fast communication between hemispheres, which is also important to, and may facilitate, creative thinking processes. To examine psychosis-proneness and functional neuroanatomy of creative thinking in musicians, we assessed 21 musicians and 21 age and sex-matched nonmusicians on schizotypal personality and handedness. To measure creative thinking, participants were given tests of divergent thinking and associative processing. Musicians showed superior performance on creativity tasks and elevated schizotypal personality. These results suggest that music training is associated with increased psychosis-proneness and creativity. We then used NIROT to examine the neural bases of creative thinking in a sub-group of the original participants. Musicians showed reduced left hemisphere activation during a divergent thinking task, which may suggest efficiency during creative thinking and/or reduced reliance on language.

RELATIONSHIP BETWEEN TOP-DOWN CONTROL, BINDING PROCESSES, AND MEMORY IN PATIENTS WITH SCHIZOPHRENIA

A. Giersch,* V. Rhein
Psychiatry, INSERM, Strasbourg, France

We derived a new paradigm from a study by Beck & Palmer (2002, *JEP:HPP* 28:1071-84) in order to test the relationship between top-down control, binding processes and memory in patients with schizophrenia. 18 patients with schizophrenia and 18 matched controls were tested with perceptual and memory tasks. Stimuli were identical in all tasks, i.e. squares of 0.7 deg of visual angle including varying geometrical features. In perceptual tasks, 7 squares were drawn on an horizontal axis and displayed on a computer screen. The squares were separated by a distance of 1 or 2 deg, so that they composed three pairs of two squares and one single square. In half trials two adjacent squares, belonging to the same pair or to different pairs, included identical features; in half trials all squares were different. Subjects pressed on a right response key when there was two identical squares, and on a left response key when all squares differed. Like in Beck & Palmer study, controls and patients were faster and more accurate when the two identical squares were part of the same pair rather than different pairs. This advantage varied in controls with the relative proportion of trials in which identical squares were part of the same or different pairs. Patients, however, were unable to lower their percent errors when the two identical squares belonged more frequently to two different pairs. The results suggest that patients have a selective difficulty to adapt when information is not automatically bound. We explored the consequences of such an impairment by running a memory task after each perceptual block. In the memory task, 5 squares were displayed for 2.5 s, i.e. two pairs and a single square. After a delay of 1 s, one of the three central square was shown in the centre of the screen, with a question mark on the right or on the left. Subjects were asked to remember the square that was in the location of the question mark, and to choose between two alternatives, the correct pair of squares or a pair composed of the target square and the square located on the opposite side relative to the

question mark. Patients with schizophrenia showed impaired memory performance as compared to controls. Moreover, patients performance in the perceptual task predicted performance in the memory task that followed when squares were part of different pairs. In patients, part of the memory deficit appears to be related to a difficulty to consider figures that are physically separated.

EARLY COGNITIVE RESPONSE IN FIRST EPISODE PSYCHOSIS

C. Gonzalez-Blanch,* B. Crespo-Facorro, R. Perez-Iglesias, J. M. Rodriguez-Sanchez, M. Alvarez-Jimenez, J. L. Vazquez-Barquero
Psychiatry, Hu Marques de Valdecilla, Santander, Cantabria, Spain

The aim of the study is to examine cognitive functions in the early course of first episode drug-naive patients with schizophrenia spectrum disorders. In this prospective, naturalistic design a total of 42 patients (range of age 16-45 years), admitted to a first episode psychosis program available for the community of Cantabria (Spain), and a group of 43 healthy volunteers similar in age, gender, educational level completed a brief battery of 5 neurocognitive tests (Ruff 2 & 7 Selective Attention Test; RBMT Story Recall; Letter-numbering sequencing; Colour Trails Test; Stroop Colour Word Test) four times (baseline, 2-week, 6-week, and 3-month) over 3 months. Baseline assessment occurred within the first 72 hours after the treatment was initiated, then parallel forms of the tests where applied in all assessments. The testing cognitive domains comprise attention, visuomotor speed, declarative memory, working memory and executive function. Between-group comparisons of continuous variables were analysed with analysis of variance (ANOVA). Repeated measures ANOVA was used to examine the patients sample performance across the four moments. Compare to the control group, patients performed significantly worse on all cognitive tasks at baseline, 2-week, 6-week and 3-month assessments, except for the Stroop Colour Word Test at 6-week ($p=0.192$) and 3-month ($p=0.637$), and the RBMT Story recall [immediate ($p=0.682$) and delayed ($p=0.118$)] at the 3-month assessment, where no difference was found. An overall improvement was observed in the patients group through the 3 months period ($p>0.000$ to $p=0.03$). All variables improved significantly by the 6-week with regard to baseline assessment ($p=0.001$ to $p=0.05$). The first 2 weeks of drug therapy yielded improvements in all cognitive variables ($p>0.000$ to $p=0.02$), with the solely exception of executive function related tests (CTT-B and Stroop Colour Test). In conclusion, first-episode patients with schizophrenia show a significant improvement in cognitive functions through the very early phases of antipsychotic treatment, but there are specific patterns and timing for each neurocognitive domain. In some domains patients reach an optimal level of performance in relation to the matched healthy controls.

TWO-YEAR LONGITUDINAL STABILITY OF VISUAL INFORMATION PROCESSING IMPAIRMENTS IN OLDER PATIENTS WITH SCHIZOPHRENIA

E. Granholm,* S. Verney, S. Fish, D. Perivoliotis, T. Miura
Psychology Service, VASDHS, San Diego, CA, USA

Information processing impairments on the Span of Apprehension Task (SOA), Visual Backward Masking Task (VBM), and Degraded Stimulus Continuous Performance Test (DS-CPT) may be stable genetic vulnerability trait markers of schizophrenia. Deficits on all three tasks have been found in younger patients, family members of probands, and high-risk populations, but little is known about the stability of impairments on these tasks into middle age and late life. The present longitudinal study examined performance on these tasks at annual visits over two years in 75 middle-aged and older (age range=45-75) patients with schizophrenia (M age = 55) and 64 age-comparable nonpsychiatric controls (M age = 56). These older patients with schizophrenia showed the same well-known pattern of impairments on all tasks (SOA 10-letter array accuracy; VBM accuracy in 717 msec stimulus onset asynchrony; DS-CPT d-prime) at baseline and one- and two-year follow-ups. Moreover, mixed-model random regressions showed similar level of impairment at all time points on these variables (no significant group X time interactions). Subgroups of patients experiencing an increase, decrease or no change in symptoms over the two years also did not differ significantly in rate of change over time on any task. These early visual information-processing tasks, therefore, may be useful genetic vulnerability trait markers of schizophrenia that are relatively stable across the lifespan.

FUNCTIONAL INTEGRITY OF BRAIN SYSTEMS UNDERLYING SPECIFIC WORKING MEMORY COMPONENTS IN SCHIZOPHRENIA

O. Gruber,* D. Zilles, E. Gruber, P. Falkai
Department of Psychiatry, Saarland University Hospital, Homburg (Saar), Germany

Recent functional neuroimaging studies indicate that distinct brain systems underlie different working memory components in humans. A presumably phylogenetically older, multimodal working memory system, which is also present in non-human primates, is implemented by several domain-specific prefronto-parietal and prefronto-temporal networks. Another system, which probably developed later in the context of the evolution of language, is supported by mainly left-hemispheric speech areas mediating explicit verbal rehearsal (Gruber, 2001; Gruber & von Cramon, 2001, 2003; Gruber & Goschke, 2004). The aim of the present study is to identify specific dysfunctions of these networks in patients suffering from schizophrenia. So far, 37 schizophrenic patients and 47 healthy controls have been tested experimentally with respect to specific components of phonological and visuospatial working memory using a modified Sternberg paradigm (Gruber & von Cramon, 2003). Total group analysis revealed significant impairment of schizophrenic patients in each of these working memory components. However, we were able to identify subgroups showing different patterns of selective deficits. In six patients we observed a selective deficit of the verbal rehearsal mechanism while four other patients showed a selective deficit of visuospatial working memory processes. These selective deficits can be attributed to impaired functioning of distinct brain systems which have been identified recently using fMRI. Furthermore, we found preliminary evidence that in some patients disturbances of the verbal rehearsal mechanism were associated with pronounced symptoms of thought insertion and thought broadcast as well as delusions of alien control. Overall the findings of this ongoing study suggest a high degree of heterogeneity in schizophrenic patients with respect to the presence or absence of dysfunctions of specific neuronal networks involved in working memory. References: Gruber, O. (2001) *Cerebral Cortex*, 11, 1047-1055. Gruber, O. & von Cramon, D.Y. (2001) *Neuroscience Letters*, 297, 29-32. Gruber, O. & von Cramon,

D. Y. (2003) *NeuroImage*, 19, 797-809. Gruber, O. & Goschke, T. (2004) *Acta Psychologica*, 115, 105-121.

NEUROCOGNITIVE AND SOCIAL DYSMATURATION DEFICITS ASSOCIATED WITH 'THEORY-OF-MIND' DEFICITS IN SCHIZOPHRENIA

G. L. Haas,* B. L. Hart, L. Tran, P. Huang
Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Deficits in social functioning represent a prominent feature of schizophrenia; however, little is yet understood about the nature of these deficits or their relationship to neurocognitive function and the underlying pathophysiology of the disorder. Evidence that social dysfunction often predates the onset of psychotic symptoms would suggest that it represents a core feature of the disorder. However, the remarkable variance in the social development of individuals with this disorder presents a challenge to our current understanding of the fundamental nature of social dysfunction in schizophrenia. Preliminary findings from our lab suggest that the emergence of social deficits in early childhood and the timing and course of social dysfunction predicts a specific constellation or pattern of neurocognitive deficits among individuals presenting with their first episode of psychosis. In a recent series of studies, we investigated the relationship between laboratory-based measures of social cognition and non-social neurocognitive functioning with a battery of cognitive measures (including the Wisconsin Card Sort Test, Continuous Performance Test, digit span test and others) in 20 adults with DSM-IV (SCID-diagnosed) schizophrenia and their age- and sex-matched healthy control subjects. Deficits on Theory-of-Mind tasks were observed in schizophrenia as compared with healthy control subjects ($p<.04$) and associated with signal detection errors ($p<.01$), working memory deficits ($p<.01$), set-learning ($p<.03$) and perseverative ($p<.01$) and non-perseverative ($p<.01$) errors. Whereas deficits in making inferences regarding the mental state of another individual were characteristic of individuals with schizophrenia as a group, profound deficits in making more basic inferences regarding the perspective another person were characteristic of a subgroup of individuals with schizophrenia and associated with a history of early pre-pubertal social dysfunction. Implications of these findings for a neurodevelopmental model of social dysfunction in schizophrenia will be presented. This project was supported by a grant from the National Alliance for Research on Schizophrenia and Affective Disorders (NARSAD).

PERSECUTORY DELUSIONS AND THE PERCEPTION OF TRUSTWORTHY FACES IN SCHIZOPHRENIA

K. Haut,* A. W. MacDonald
Psychology, University of Minnesota, Minneapolis, MN, USA

Patients with schizophrenia show deficits in social cognition and the ability to make judgments about the emotions and intentions of others. Assessment of trustworthiness in unfamiliar faces is one aspect of these judgments and is correlated with emotion and attractiveness. Regions of the brain identified in perception of trust have also been implicated in the processing of attractive faces (Winston et al, 2002, *Nature Neuroscience*, 5, p. 277-283. We hypothesize that the relationship between the networks underlying trust and attractiveness perception is compromised in patients with schizophrenia. Using a modification of the procedure developed by Winston, 43 control subjects and 22 patients with schizophrenia rated 100 non-famous, neutral faces on trustworthiness, attractiveness, and six emotional dimensions using an anchored Likert scale. As predicted, both groups showed significant average correlations between trust and attractiveness. However, controls' average correlation was significantly greater ($r=.33$) between trust and attractiveness than patients' correlation ($r=.23$, $T[63]=1.897$, $p=.062$). Importantly, the severity of persecutory delusions (as rated on the SAPS) predicted a decreased relationship between trust and attractiveness ratings ($p=.023$). The correlation did not appear to be the result of a response bias across participants. These results are consistent with the interpretation that schizophrenia patients with active paranoia symptoms use idiosyncratic cues when making trustworthiness judgments and support theories of disrupted social cognitive networks in the etiology of positive symptoms in schizophrenia.

PREDICTING SOCIAL BEHAVIOR AMONG INDIVIDUALS WITH SCHIZOPHRENIA

E. Heerey,* K. Humber, C. M. Wilk, M. LeDuc, A. S. Bellack, J. M. Gold
MPRC, University of Maryland Medical School, Baltimore, MD, USA

The purpose of this study was to investigate how aspects of social cognition relate to social behavior and outcome. Difficulties with emotion and social interaction have long been considered a hallmark of schizophrenia (Kee et al., 1998). Research suggests that deficits in theory of mind (ToM), the ability to understand the mental states including beliefs, desires, and intentions of others, may explain some of the social difficulties experienced by individuals with schizophrenia (Frith, 1992). Emotion perception deficits are thought to play a role in social functioning as well (Adolphs, 2001). Although clinical ratings of social functioning, such as social adjustment, have been linked to ToM among individuals with schizophrenia (Roncone et al., 2002), little is known about how ToM and emotion perception relate to actual social performance in this population. To better understand the link between ToM and social performance, 31 schizophrenia patients completed tests of ToM, cognitive functioning, and emotion perception. They also completed the Maryland Assessment of Social Competence (MASC), a measure of social skill developed for individuals with schizophrenia (Bellack et al., manuscript under review). The MASC assesses social skill on the basis of behavior exhibited during of a series of social interactions. Finally, each patient's quality of life was rated by his or her therapist using a semi-structured interview. Cognitive ability was related to ToM ($r = .48$; $p < .01$), MASC score ($r = .49$; $p < .01$), and emotion perception ($r = .37$; $p = .04$). Hierarchical regression analyses, statistically controlling for cognitive ability, demonstrate that ToM predicts MASC score (ΔR square $= .16$; $p = .02$). Emotion perception ability added significantly to the predictive power of the model, over and above the effects of cognition and ToM (ΔR square $= .21$; $p = .04$). In turn, MASC scores were correlated with quality of life ratings ($r = .38$; $p = .03$). Social cognition, including ToM and emotion perception, was predictive of social skill in individuals with schizophrenia. Social skill, as assessed during interaction, related positively to quality of life. These findings suggest that 1) social cognition is an important facet of more general cognition, with the ability to account for unique variance in social functioning, and 2) that it relates to outcome and is thus an important target for future research and treatment.

EFFECTS OF ANTIPSYCHOTIC TREATMENT ON EMOTION PERCEPTION DEFICITS IN FIRST EPISODE SCHIZOPHRENIA

E. Herbener,* S. K. Hill, R. W. Marvin, J. A. Sweeney
Psychiatry, University of Illinois at Chicago, Chicago, IL, USA

Cognitive deficits are typically present at the onset of schizophrenia and show limited responsiveness to treatment. However, it remains to be established whether emotion processing deficits are present at illness onset and whether antipsychotic treatment reduces such deficits. The current study addresses these issues by assessing emotion recognition in first episode schizophrenia before and after treatment. Method: Emotion perception of patients presenting with their first episode of schizophrenia was tested during an unmedicated state and again following clinical stabilization. Healthy individuals were evaluated over a similar time interval. All subjects completed tests of the ability to perceive and discriminate emotional expressions from the Penn Computerized Neuropsychological Battery. The Emotional Acuity Test requires individuals to rate 40 black-and-white pictures of adult faces along a 7-point continuum of emotional intensity (happy-to-sad). The Emotion Differentiation Task requires individuals to identify which of two faces in 40 pairs of black-and-white photographs of faces shows more intense emotion. Results: First episode patients demonstrated impairments in emotion perception prior to treatment, and no significant improvement after treatment. Emotion perception deficits were correlated with negative symptoms after clinical stabilization. Conclusions: Deficits in emotion perception are present at illness onset in schizophrenia, and show minimal response to effective antipsychotic treatment. While the severity of emotional processing deficits was minimally related to symptom presentation during acute illness, they were strongly linked to negative symptom severity after clinical stabilization. Because medication effectively reduced some aspects of negative symptoms, it may be that residual core persistent negative symptoms have a stronger linkage to emotional processing deficits.

MOTIVATION AND SOCIAL COGNITION IN SCHIZOPHRENIA: DIFFERENTIAL ASSOCIATIONS WITH DISTINCT ASPECTS OF COMMUNITY FUNCTIONING

W. P. Horan,* M. F. Green, M. Sergi, Y. Rassovsky, K. S. Kee, P. Nori, S. L. Davidson, B. Deng, M. McGee
Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, CA, USA

Background: Functional impairments are among the most debilitating and treatment refractory features of schizophrenia. There has been good progress in identifying basic neurocognitive deficits that influence how well individuals with schizophrenia function in the areas of social relationships, work, and the ability to live independently. However, neurocognitive deficits do not fully account for the variance in functional outcome seen among affected individuals, indicating that additional determinants remain to be identified. While certain motivational factors, such as anhedonia/approach motivation, and social cognitive abilities, such as social perception, show promise as determinants of functional outcome in schizophrenia, their relationships with each other and with distinct aspects of functional outcome have not been systematically investigated. Methods: 50 stabilized individuals with schizophrenia who were residing in the community completed self-report measures of trait anhedonia, a performance measure of social perception, and functional outcome assessments of social relationships, work functioning, and independent living abilities. Two alternative models of the relationships among anhedonia, social perception, and functional outcome were evaluated: 1) a 'mediation model', predicting that social perception mediates the relationship between anhedonia and functioning, and 2) a 'distinct correlates model', predicting that anhedonia and social perception are minimally correlated with each other, but are each significantly correlated with aspects of functioning. Results: Correlational analyses supported the 'distinct correlates model.' Anhedonia and social perception were not significantly correlated with each other, but were significantly correlated with different aspects of functional outcome. Specifically, higher anhedonia was associated with lower social functioning whereas lower social perception abilities were associated with lower work functioning. Conclusion: Motivational and social cognitive variables may help account for unexplained variance in community functioning among individuals with schizophrenia. These variables may be particularly important for explaining different components of functional outcome. Further clarification of the factors that lead to functional impairments will facilitate the development of more effective treatment interventions.

MOTOR AND EXECUTIVE INHIBITORY FUNCTION IN A SCHIZOPHRENIA: THE WEST LONDON FIRST EPISODE STUDY

V. C. Huddy,* A. R. Aron, L. Clark, T. W. Robbins, M. Kapasi, S. H. Mutsatsa, I. Harrison, T. R. Barnes, E. M. Joyce
Psychiatry, Imperial College London, London, United Kingdom

Background: Deficits are typically reported in studies that probe the ability of people with schizophrenia to inhibit thoughts and actions. Such abnormalities have been demonstrated using a variety of tasks, from perceptual to executive levels of processing. The current study aimed to provide a comprehensive assessment of inhibitory function in schizophrenia by using novel and diverse tasks, each probing different areas of inhibitory functioning Method: First-episode patients with DSM IV schizophrenia, schizoaffective or schizophreniform disorder and matched controls performed four tests: i) a novel subliminal motor priming task that has been shown to tap early response inhibition processes; ii) the stop signal paradigm where an executive measure of motor inhibition can be extracted; iii) an attentional set shifting task, where high-level inhibition of acquired stimulus response contingencies are assessed iv) a novel gambling type task where the degree of impulsivity in decision making can be probed. Results: Schizophrenia patients demonstrated intact functioning on the subliminal motor priming task. They did, however, show evidence of impairment on executive motor inhibition as indexed by the stop signal task. While more patients tended to fail the critical stage of the attentional set shifting task than the controls, this was not accompanied by increased errors in those that passed, suggesting generally intact set shifting ability in a subgroup of patients, with others showing evidence of impairment. Although patients made more errors overall on the impulsivity task, they failed to show impulsive decision making in terms of their response latencies, by making decisions without recourse to available information or by risk taking behaviour. Discussion: On the tests of inhibitory function reported here, differences in the integrity of separate areas of inhibitory processes emerged in schizophrenia. Clear evidence for dysfunction was found using the stop signal paradigm, a task that has been closely linked to prefrontal cortex function. There was also evidence of impairment in a subgroup of patients, on another task sensitive to

prefrontal function, attentional set shifting. Outside this, patients showed generally intact performance on subliminal motor inhibition and impulsivity of decision making. One interpretation is that inhibitory deficits in schizophrenia are confined to those tasks mediated by the prefrontal cortex.

COGNITION IN SCHIZOPHRENIA NEUROPSYCHOLOGICAL CORRELATES OF ANTISACCADES AND FRONTAL FUNCTIONING

C. Hughes,* V. Kumari, U. Ettinger, T. Crawford, W. Soni, T. Sharma
Psychology, Institute of Psychiatry, London, London, United Kingdom

Objectives: The prefrontal cortex has been implicated in cognitive deficits associated with schizophrenia such as attention, working memory and executive dysfunction. Control of anti-saccadic eye movements is disrupted in schizophrenia and is hypothesised mainly to be due to dysfunctions of the frontal lobe. These cognitive impairments occur in patients, their healthy first-degree relatives and healthy subjects with high schizotypy scores, suggesting they may be vulnerability markers for schizophrenia. This study aimed to identify relationships between anti-saccadic performance and a comprehensive battery of neuropsychological tests thought to assess frontal lobe functioning in schizophrenia. Methods: Anti-saccade performance on eye movement tasks was assessed in thirty patients with DSM-IV schizophrenia or schizoaffective disorder. In addition, patients completed a neuropsychological test battery comprising tasks of attention, working memory and executive function and were rated for symptoms. Symptom ratings, together with neuropsychological performance, were used in multiple regression models to predict anti-saccadic performance since negative symptoms of schizophrenia are also thought to reflect frontal lobe deficits. Results: Anti-saccadic latency was predicted by negative symptoms. Anti-saccadic error rate was most strongly predicted by spatial strategy performance on a test of executive function. Spatial strategy performance, however, explained only 16% of the total variance in anti-saccadic error rate. Conclusions: These observations provide support for the hypothesis that the cortical locus of anti-saccade abnormalities in schizophrenia is in the frontal lobes and demonstrate evidence for a multimodal approach to the identification of vulnerability factors for schizophrenia.

SOCIAL COGNITION AND FUNCTIONAL OUTCOME IN SCHIZOPHRENIA

K. Humber,* C. M. Wilk, M. Leduc, J. M. Gold
Outpatient Research Program, Maryland Psychiatric Research Center, Baltimore, MD, USA

While previous research has documented that neurocognitive deficits in schizophrenia (SC) are associated with functional outcome, models that exclusively emphasize the role of neurocognition account for only a modest amount of outcome variance. It is likely that the cognitive impairments found in SC diminish the ability to effectively process socially relevant information and generate socially appropriate behavioral responses. It is also widely believed that the ability to understand the mental state of others (theory of mind) is impaired in SC populations and this deficit may be particularly salient to functional outcome. The present work examines the relationship between social cognition, general intellectual capacity and two types of functional outcome: social functioning and instrumental functioning (work and living status). Fifty outpatient SC and thirty healthy control subjects were given measures of neurocognitive functioning (processing speed, episodic and working memory, executive functioning, general ability) and social cognition as determined by Facial Emotion Recognition measures (BLERT, PEAT, PERT, EDT) and Theory of Mind measures (TOM stories and cartoons). Results show that SC subjects perform significantly worse than controls on all measures of neurocognition and social cognition, particularly on TOM measures. TOM was found to be associated with both social functioning (Stories: $r=.379$, $p<.01$; Cartoons: $r=.313$, $p<.05$) and instrumental functioning (Stories: $r=.477$, $p<.01$; Cartoons: $r=.294$, $p<.05$). TOM deficits persist even when generalized cognitive deficits are controlled, suggesting that social cognition impairment is at least partially domain specific. Our findings suggest that deficits in TOM may be important targets for treatment development.

SOCIAL COGNITION: A POTENTIAL MEDIATOR OF RELATIONS BETWEEN NEUROCOGNITION AND SOCIAL FUNCTIONING IN SCHIZOTYPY

C. S. Jahshan,* M. J. Sergi, R. P. Rosenberg, C. Levy, S. Borghei, S. Gross, R. Coutin
Psychology (Clinical), California State University, Northridge, Northridge, CA, USA

The present study is the first to examine neurocognition, social cognition and social functioning in schizotypy concurrently. Screening of 1054 undergraduates with the Schizotypal Personality Questionnaire-Brief (SPQ-B) identified 21 psychometric schizotypes and 18 persons low in schizotypy. Schizotypy status was confirmed with the Perceptual Aberration Scale (PAS and SPQ-B scores were highly correlated, $r = .70$, $p < .001$). All participants were administered a test battery designed to assess two elements of neurocognition, secondary verbal memory (California Verbal Learning Test) and executive functioning (Wisconsin Card Sorting Test), two elements of social cognition, emotion perception (The Awareness of Social Inference Test-Part 1) and theory of mind (The Awareness of Social Inference Test-Parts 2 and 3), and social functioning (Social Adjustment Scale-Self Report). The schizotypic participants were impaired in their social functioning ($F(1, 37) = 48.83$, $p < .001$), but not in theory of mind, emotion perception, secondary verbal memory, or executive functioning. The lack of social cognitive deficits in the schizotypes is consistent with the results of previous studies. The current findings cast doubt on social cognition's role as a mediator of relations between neurocognition and social functioning in schizotypy.

VERBAL SELF-MONITORING IN PEOPLE AT HIGH RISK OF PSYCHOSIS

L. C. Johns,* P. Allen, M. Broome, J. Woolley, N. Vythelingum, T. Wykes, P. McGuire
Psychological Medicine, Institute of Psychiatry, London, United Kingdom

Patients with schizophrenia and positive symptoms show impaired verbal self-monitoring and tend to misattribute their own distorted voice to an external source (Johns et al., 2001). To examine whether this effect is evident before the onset of full-blown psychotic symptoms, we tested 16 individuals with an 'at risk mental state' (ARMS)

and 16 healthy volunteers matched for age and verbal IQ. The ARMS participants had attenuated or brief psychotic symptoms, as measured by the Comprehensive Assessment of At Risk Mental States. Participants read out single words (complimentary, derogatory, or neutral adjectives) under the following conditions: reading aloud, reading aloud with acoustic distortion of their own voice, reading aloud with alien feedback (hearing someone else's voice), and reading aloud with distorted alien feedback. Participants judged whether the speech they heard was their own voice or not. When reading aloud and hearing their own voice distorted, ARMS participants made more misidentification errors than controls when the words presented were complimentary ($p = 0.044$). There were no significant differences between the ARMS and control groups when reading aloud and hearing someone else's voice. The results suggest that defective self-monitoring may precede the onset of frank psychotic symptoms and contribute to their development. Johns LC et al. (2001). Verbal self-monitoring and auditory verbal hallucinations in schizophrenia. *Psychological Medicine*: 31: 705-715.

Group means and standard errors for the percentage of misidentification errors when reading aloud with distorted feedback

SELECTIVE IMPROVEMENT OF PHYSICAL, BUT NOT MENTAL STATE INFERENCE IN PARANOID SCHIZOPHRENIA USING A VERBAL/ATTENTIONAL REMEDIATION STRATEGY

A. B. Joiner,* T. A. Russell, J. Carter, R. Corcoran, M. L. Phillips
Medical School, GKT School of Medicine, London, United Kingdom

Subjects with paranoid schizophrenia have difficulties on tasks requiring them to make inferences about other peoples mental states: i.e.: theory of mind tasks (ToM). These individuals also have abnormalities in their data gathering style, notably, a restricted viewing pattern for faces and other complex social stimuli, and increased attention to irrelevant aspects of the stimulus. In a previous study we demonstrated abnormalities in a group of paranoid subjects on a cartoon task requiring the inference of mental and physical states. The paranoid group found both mental and physical state cartoons difficult and one explanation for this finding relates to abnormal data gathering strategies. It is suggested that these patients fail on both types of inferences due to insufficient visual attention to the pertinent details. As an empirical test of this suggestion, 20 subjects with paranoid schizophrenia and 20 healthy controls completed Happes ToM cartoon task, which requires subjects to state why a series of cartoons are funny, relying on either mental, or physical, state inference. Paranoid subjects were then prompted, using an attentional/verbal remediation strategy, to improve their data gathering. This strategy required the experimenter to give a series of structured prompts, drawing the subjects attention to the relevant parts of each cartoon, ie: the parts that would help them to understand the joke. Paranoid subjects accuracy scores before and after prompting were compared to that of healthy controls (who did not receive any prompts). Prior to prompting, paranoid subjects were significantly less accurate in their descriptions of the cartoons. There was a significant improvement in the paranoid performance after prompting as compared to before prompting. There was a trend for the paranoid subjects to still find the mental state inferences more difficult (compared to controls) while their performance on the physical state cartoons did not differ significantly from controls after prompting. These data provide evidence to suggest that a remediation strategy that helps paranoid subjects attend to the relevant details can help to improve performance on this type of ToM task. While improvements are evident, there does still remain, a specific impairment in mental state inference. Abnormalities in ToM in this group of subjects, are not, therefore, solely attributable to problems in attending to, and processing, the relevant aspects of the stimulus.

BASELINE NEUROCOGNITIVE ASSESSMENT OF 1364 PATIENTS WITH SCHIZOPHRENIA IN THE CLINICAL ANTIPSYCHOTIC TRIALS FOR INTERVENTION EFFECTIVENESS (CATIE) PROJECT

R. Keefe,* R. M. Bilder, P. D. Harvey, S. Davis, B. Palmer, J. P. McEvoy, T. E. Goldberg, J. M. Gold, M. F. Green, M. Swartz, S. Stroup, R. Rosenheck, D. O. Perkins, H. Y. Meltzer, D. Miller, J. Canive, T. M. Walker, J. A. Lieberman
Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC, USA

Background: Neurocognitive deficits are an important predictor of functional outcome, and cognitive improvement may be associated with treatment effectiveness. The CATIE schizophrenia trial was designed to compare the effectiveness of currently available atypical and conventional antipsychotic medications through a randomized clinical trial involving 1493 patients treated for schizophrenia at multiple sites, including academic and community providers. Methods: Prior to the initiation of study medication, 1446 patients were assessed with a battery of neurocognitive tests, and 1364 patients met criteria for completeness in that meaningful data were collected on at least eight of the eleven tests, listed here by domain: processing speed (Letter fluency, Category instances, Grooved pegboard, WAIS-R digit symbol), reasoning and problem solving (Wisconsin Card Sorting Test, WISC-III Mazes), verbal memory (Hopkins Verbal Learning Test), working memory (Computerized visuospatial working memory test, Letter-number sequencing), vigilance (Identical Pairs CPT), and social cognition (Facial Emotion Discrimination Test). Z-scores were created for each test measure based on the baseline sample. Domain scores and a composite score were calculated from these z-scores. Results: Compared to published norms, schizophrenia patients performed worse on all measures, with z-scores ranging from 1.0 to 4.0 (all $P<.0001$). The Pearson correlations of the cognitive domain scores and the overall composite with demographic factors and clinical factors varied very little between cognitive domains. The size of correlations with age, education, and duration of illness were medium ($r \sim .30$), while correlations with PANSS negative symptoms were small to medium (.10 to .30). The correlations of the neurocognitive measures with PANSS positive symptoms were less than .05 (n.s.). The following variables significantly differentiated the composite scores: employment ($F=11.57$, $df=2, 1348$, $P<.0001$), with full-time and part-time employed patients

performing .40 and .31 standard deviations better than unemployed patients; and antipsychotic medication status at baseline (F=7.67, df = 2, 1302, P<.001), with patients on no antipsychotic medication or atypicals performing similarly, and those on typicals performing about .25 standard deviations below the others. Composite scores did not significantly differ by sex or whether a patient had an acute exacerbation in the past 3 months.

THE RELATIONSHIP BETWEEN METAREPRESENTATION AND DELUSIONS IN PATIENTS WITH SCHIZOPHRENIA

A. Kennedy,* N. Kilzieh, A. E. Wood, A. Tapp
MIRECC, VA PSHCS American Lake Division, Tacoma, WA, USA

Frith (1992) proposed that the common deficit underlying the symptoms of schizophrenia is a deficit in metarepresentation or theory of mind (ToM), hypothesizing that a deficit in ToM might be a causal factor in the formation of delusions. To date, the findings on the relationship between ToM and delusions have been inconsistent. In this study, we examined the relationship between representation of the mental contents of the self and other and delusions in 16 patients with schizophrenia or schizoaffective disorder. Three tests of metarepresentation were administered: 1) a ToM task, 2) the global rating scores from the Scale for the Unawareness of Mental Disorders, and 3) the empathy item from the Quality of Life Scale. The Peters et al. Delusion Inventory was administered to assess delusional beliefs. It was hypothesized that performance on the tests of metarepresentation would negatively correlate with delusions. Contrary to expectations, there was no relationship between performance on the Tom task and delusions. There were trend level negative correlations between the SUMD global scores for awareness of mental disorder and awareness of the social consequences of mental disorder and delusions, (r = -.45, p = .07 and r = -.47, p = .07, respectively). Surprisingly, there was a strong positive correlation between empathy and delusions (r = .62, p = .01). The lack of correlation between ToM and delusions supports other studies with similar findings, suggesting that there may not be a direct causal relationship between a deficit in ToM and delusions. The finding that awareness of a mental disorder is associated with better reality orientation has good face validity. The finding of a correlation between empathy and delusions is somewhat more perplexing. However, it may be that the capacity to empathize with another person requires a temporary loosening of ego boundaries that allows the affective state of the self to resonate in response to the affective state of the other. In individuals with delusions, the loosening of ego boundaries may constitute a trait rather than state phenomenon. Thus, empathy and delusions may both be situated on a continuum of the permeability of ego boundaries between the self and other. Frith, C.D. (1992). *The cognitive neuropsychology of schizophrenia*. Hillsdale, NJ: Lawrence Erlbaum.

BEHAVIORAL CHARACTERISTICS OF PATIENTS WITH SCHIZOPHRENIA DURING SOCIAL INTERACTION IN THE VIRTUAL SPACE

C. Kim,* J. J. Kim, H. J. Jang, S. H. Park, J. H. Ku, K. U. Kim, J. H. Kim, I. Y. Kim, S. I. Kim
Department of Psychiatry, Yonsei University College of Medicine, Seoul, South Korea

Introduction: Virtual avatar has been used for various applications which need to communicate with other person or to train or educate by showing humanlike behavior. Recently, many researches have shown that the virtual avatar technology has been enhanced and the avatar could be perceived like real human. Therefore, the avatar begins to be used for observing human behavior to a virtual avatar. This study concerns whether a virtual avatar could be perceived as real human by mental disease patient, particularly schizophrenic patient as well as whether a virtual avatar could be applied to acquiring patients′ behavior characteristics in a short conversation situation. Methods: For this, a virtual avatar standing in a virtual room was designed and a task to approach, initiate a talk, and answer to avatar′s questions was assigned to the 11 subjects with schizophrenia. As behavioral parameters in the virtual environment, the interpersonal distance and the verbal response time were acquired. In addition, Positive and Negative Syndrome Scale (PANSS) for patients was obtained in order to investigate a relationship between patients′ symptomatic characteristic and behavior parameters. Results: As the results of this study, the interpersonal distance was negatively correlated with the negative syndrome scale which is a subscale of PANSS, which is consistent result with previous research reporting the relationship between an interpersonal distance and real person′s image, while the verbal response time wasn′t correlated with any other subscale of PANSS. However, after analyzing with subscale of the negative syndrome of PANSS, two positive correlations were found, one was with blunted affect and the other was with poor rapport. Conclusion: When inferring based on these result, we could conclude that the virtual avatar could be perceived as a real human by schizophrenic patients and the avatar could draw the schizophrenic patients′ behavior characteristics.

SELF-INITIATED ATTENTION TO TARGET FACILITATES WORKING MEMORY ENCODING IN SCHIZOPHRENIA: IMPLICATIONS FOR THE ETIOLOGY OF WORKING MEMORY DEFICIT AND STRATEGIES FOR REMEDIATION

J. Kim,* S. Park, Y. Shin, K. J. Lee, J. S. Kwon
Psychology, Vanderbilt University, Nashville, TN, USA

Working memory (WM) deficit is a potential marker for schizophrenia (SZ) and is present in a majority of schizophrenia patients but it is unclear what components of WM are impaired in SZ. Past studies suggest that WM encoding may be compromised. One important determinant of encoding is the deployment of selective attention, which seems to be abnormal in SZ. We hypothesized that efficient deployment of attention to the target should improve WM encoding. Specifically we compared the effects of self–initiated attention vs. stimulus-triggered attention to target on WM. Thus, we investigated the effect of self-initiated encoding by presenting face targets in three different conditions. Subjects were asked to choose 1) one of the two identical faces (Non-preference condition), 2) one that is marked by a circle (Non-choice condition), and 3) one they prefer (Preference condition). In the preference condition, the two faces were of the same person but one had been graphically distorted. We recorded the target selection at the encoding and recall stages. Accuracy of WM for both location (SWM) and identity (OWM) was measured. Overall, SZ patients were less accurate and slower but the deficit was greater for OWM. But interactions indicated that SZ patients were significantly more accurate in OWM when they self-initiated attention to target during encoding (preference condition) than the other two conditions. Such effect of attention manipulation was not significant in SWM. These results suggest that active self-initiated attention to target may facilitate encoding of the object. These results also

implicate that attention may play different roles in encoding 'what' and 'where' at the early stage of WM as well as the potential role for motivational factors in WM deficits.

DISSOCIATING DORSAL AND VENTRAL VISUAL STREAM FUNCTIONS VIA WORKING MEMORY PERFORMANCE IN SCHIZOPHRENIA

J. P. King,* B. K. Christensen, A. B. Sekuler, P. J. Bennett
Psychology, University of Waterloo, Waterloo, ON, Canada

This study uses a model of brain evolution, the Dual Trends Theory (DTT), to understand anomalous neurodevelopment among patients with schizophrenia (SCZ). The DTT posits that mammalian cortex has derived from two separate primitive brain structures, which, give rise to two independent neural pathways or trends: the archicortical trend (originating from hippocampus) and the paleocortical trend (originating from pyriform cortex). The DTT also dovetails with the leading paradigm of primate vision, which also distinguishes between two neural pathways: one devoted to processing spatial/movement aspects of our visual world (i.e., dorsal trend), the other for processing features necessary for object identification (i.e., ventral trend). This duality also extends to prefrontal cortex where dorsolateral areas control spatial/kinetic working memory functions, while ventrolateral areas subserve object/feature working memory functions. Studies of cognition, regional blood flow, and brain morphology suggest that SCZ is preferentially associated with archicortical impairment and paleocortical sparing. The present study examined the integrity of these pathways using visual working memory tasks known to selectively activate these pathways. We hypothesized that patients would show disproportionate impairment on tests of spatial/kinetic versus object feature working memory, reflecting greater neural dysfunction in the dorsal stream. Patients with SCZ (n=23) and healthy controls (n=24) completed two dorsal (i.e., location and movement trajectory) and two ventral (i.e., spatial frequency and face) working memory tasks across 2- and 7-sec. delays. Threshold acquisition techniques were employed to ensure similar accuracy levels for each individual prior to introducing working memory delays. As predicted, patients demonstrated significantly worse accuracy across several dorsal task conditions but equivalent performance on one ventral working memory task (i.e., spatial frequency). Unexpectedly, patients performed worse on one face working memory condition. This result, however, may be consistent with research suggesting that face discrimination differs from object recognition. For example, if coding spatial relations of features in a face is required, this might necessitate dorsal stream recruitment. Overall, these results are consistent with previous studies suggesting that neurodevelopmental abnormalities in schizophrenia may disproportionately affect dorsal brain systems.

BINOCULAR DEPTH INVERSION CORRELATES WITH SUBTLE PSYCHOPATHOLOGY AND SIMPLIFIES DISTINCTION BETWEEN PRODROMAL AND EARLY STATES OF PSYCHOSIS

D. Koethe,* F. Schultze-Lutter, A. Juelicher, B. M. Nolden, C. Gerth, H. M. Emrich, J. Klosterkoetter, F. M. Leweke
Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany

The identification of individuals at high risk of developing schizophrenia has become a major goal because these individuals may benefit from an early intervention. Current criteria of prodromal states rely on sensitive rating scales assessing subtle, pre-psychotic psychopathology, e.g. the Structured Interview for Prodromal Syndromes (SIPS) or the Schizophrenia Prediction Instrument, Adult version (SPI-A). Impaired cognitive function is seen as an underlying core feature in schizophrenia. Although impairments of cognitive functioning are known in acute psychosis as well as in prodromal states, an association between psychopathology and cognition was rarely found. Binocular Depth Inversion (BDI) represents an paradigm for impaired visual perception in acute psychosis and was recently reported as impaired to a comparable degree already assumed in prodromal states of psychosis. We assessed the BDI, SIPS and SPI-A in two patient samples consisting of 13 first-episode, antipsychotic-naive paranoid psychotic (SZ) patients and 13 inpatients suffering from an assumed initial prodromal state (IPS) of psychosis according to the Melbourne 'ultra-high risk mental state' criteria. Whereas the BDI did not differ between SZ and IPS, the SIPS-subscores Positive and Disorganization Symptoms differed significantly. Correlations were found between the SPI-A subscores Cognitive Impediments and Cognitive Disturbances, the SIPS-Positive Symptoms, and BDI respectively for both groups. In IPS, SIPS-Negative Symptoms and, in SZ, SPI-A Cognitive Impediments and Cognitive Disturbances showed significant correlation with the BDI. A logistic regression analysis including the SPI-A Cognitive Impediments and Cognitive Disturbances, the SIPS Positive and Negative Symptoms, and BDI, revealed a perfect distinction between IPS and SZ. In conclusion we found a comparable impairment of visual perception in both groups, indicating that BDI reflects a potential early disturbance in psychotic disorders. Furthermore, we found a correlation of BDI to subtle psychopathology, predominantly to attenuated positive, negative and self-reported cognitive symptoms, their combination allowing a precise distinction between IPS and SZ. Being an easily to handle and time economic neurocognitive test, BDI may serve as an additional tool in clinical investigations. However, prospective studies are necessary to reveal the predictive power of BDI for the development of frank psychosis in prodromal patients.

THE COURSE AND NATURE OF INSIGHT CHANGE IN RECENT-ONSET SCHIZOPHRENIA: FROM UNAWARENESS TO DISAGREEMENT

D. Koren,* P. Viksman, L. J. Seidman, M. Poyurovsky, M. Goldsmith, E. Klein
Psychiatry Department, Harvard Medical School, Boston, MA, USA

The main aim of this study was to explore the course of insight change in recent onset schizophrenia. A secondary goal was to develop a reliable and valid method to distinguish between two types of poor insight: unawareness versus disagreement. Sixty four first-episode and 55 recurrent-episode patients were assessed with the Scale of Unawareness of Mental Disorder (SUMD) upon admission, at discharge, and six months later. In order to distinguish between unawareness (patients who believe they do not have a problem and their doctor does not see any either) and disagreement (patients who believe they do not have a problem but are aware that their doctor believes they do), we re-administered the SUMD asking our patients not about their own opinion, but rather about their best guess regarding their doctors opinion. To validate the unawareness vs. disagreement distinction we used the meta-cognitive version the Wisconsin Card Sorting Test (WCST) developed by Koren et al. (2000). Our

hypothesis was that level of neurocognitive impairment will be greater in patients who are unaware as compared to those who disagree (lower level of reality distortion), and this effect will be particularly noticeable at the meta-cognitive level. Overall levels of insight were poorer among recent-onset patients as compared to that of their chronic counterparts at all three time points, with no significant improvement over time. Strikingly, though, the proportion of disagreement among the recent-onset patients who continued to show poor insight significantly grew from 46% at baseline to 71% at six months. Consistent with our hypotheses, metacognitive measures were able to differentiate between patients who were classified as disagreement-type from those who were classified as unawareness-type. These results suggest that poor insight does not improve much over the first six month after first hospitalization. However, there is a significant change in the nature of poor from initial unawareness to disagreement. This change might reflect a gradual process of education and socialization to the psychiatric culture. Finally, these findings support the mediating role that deficits at the metacognitive level might play between basic neurocognition and poor insight in schizophrenia. Taken together, the current results suggest that more attention should be paid to the differential contribution of unawareness versus disagreement to poor insight in schizophrenia.

ACTION MONITORING IN PSYCHOSIS: EVIDENCE FOR ALTERATIONS IN PATIENTS, NON-PSYCHOTIC RELATIVES, AND SUBJECTS WITH PSYCHOTIC EXPERIENCES

L. Krabbendam,* D. Versmissen, I. Janssen, N. Franck, N. Georgieff, J. van Os
Psychiatry and Neuropsychology, Maastricht University, Maastricht, Netherlands

Self-monitoring is the capacity to distinguish the consequences of self-generated actions or thoughts from those of other-generated actions or thoughts. It has been suggested that a disorder of self-monitoring underlies the positive symptoms of psychosis. The cognitive mechanisms associated with psychotic symptoms may also operate at lower levels in individuals who have no clinical needs, but are at risk for psychosis. The aim of the present study was i) to investigate whether patients with psychosis show impaired self-monitoring, ii) whether this impairment is related to the presence of positive symptoms, and iii) whether this impairment can be detected in subjects with a liability for psychosis. The study included: i) 37 patients with a lifetime history of non-affective psychosis, ii) 41 first-degree relatives of patients with non-affective psychosis, iii) 40 subjects scoring high (>75pct) on the positive dimension of psychosis-proneness measured by the CAPE, and iv) 49 control subjects scoring in the average range on the positive dimension of the CAPE. All subjects performed an action-recognition task (cf. Franck et al, 2001) in which the image of a virtual hand was presented to the subjects superimposed on their own hand. Subjects executed discrete movements with a joystick. Angular biases and temporal delays were randomly introduced in some trials. Subjects had to decide whether the movement they saw was similar to the movement they had made. Patients made significantly more errors in the trials with temporal delays (OR=2.40, 95%CI 1.44, 3.97), but not in the trials with angular biases or the neutral trials. The number of errors in the temporal delay condition was associated with delusional ideation and the strength of this association increased with increasing levels of delusional ideation (summary OR over 3 levels of severity 1.62, 95%CI 1.25, 2.10; middle scores OR 1.49, 95%CI 0.81, 2.75; high scores 2.67, 95% CI 1.56, 4.59). Number or errors over all trials was associated with psychosis risk (OR linear trend 1.13, 95%CI 1.05, 1.22) with subjects with high levels of psychotic experiences and first-degree relatives having intermediate values between patients and controls. The findings support the hypothesis that an impairment of self-monitoring is part of the liability to psychosis. This impairment may be specifically associated with the presence of delusional ideation.

RELATIONSHIPS BETWEEN COGNITIVE FUNCTIONS AND CURRENT SOCIAL FUNCTIONING IN SCHIZOPHRENIA AND BIPOLAR AFFECTIVE DISORDER

J. Laes,* S. R. Sponheim, A. W. MacDonald
Psychiatry, University of Minnesota, Minneapolis, MN, USA

Relationships between cognitive deficits and decreased social functioning were investigated in schizophrenia (n=39), bipolar affective disorder (n=26), and nonpsychiatric control (n=37) participants to determine whether the associations between cognitive and social functioning differ across severe psychiatric disorders. The associations between social functioning (Social Adjustment Scale II; Schooler et al., 1979) and cognitive indices of verbal memory, verbal dexterity, attention/planning, and generalized cognitive functioning (Wechsler Adult Intelligence Scale-III; The Psychological Corporation, 1997) were examined. Preliminary results suggested that, of the cognitive indices, only the correlation between the Attention/Planning Factor and Social Adjustment Scale II Average scores exhibited significant group differences. Better performance on the cognitive index of attention/planning was associated with worse scores on the SAS-II Average in the schizophrenia group, but in the nonpsychiatric control and bipolar affective disorder groups, better performance on the cognitive index of attention/planning was associated with better scores on the SAS-II Average. Multiple regression analyses were used to determine the degree to which cognitive functioning explained the variance in social functioning in each group. The cognitive factors accounted for a larger proportion of the variance in the schizophrenia ($\Delta R^2 = 24\%$) and bipolar affective disorder groups ($\Delta R^2 = 38\%$) than in the nonpsychiatric control group ($\Delta R^2 = 9\%$). Further analyses will be performed including examination of associations of each cognitive and social functioning index with medications, treatment type, work type, and income type.

SOCIAL COGNITION IN FIRST-EPISODE SCHIZOPHRENIA

R. A. Langdon,* J. McLaren, M. Still
Macquarie Centre for Cognitive Science, Macquarie University, Sydney, NSW, Australia

Impairments of social cognition are well documented in chronic patients with schizophrenia and are important targets for treatment; less is known about the severity of these deficits at early stages of schizophrenic illness. This study investigated social cognition in 22 first-episode patients recruited from two early psychosis intervention services in New South Wales, Australia. Fourteen of the clinical participants had a DSM-IV diagnosis of schizophrenia, two were diagnosed with schizoaffective disorder, and six had a diagnosis of schizophreniform disorder. Nineteen age and sex-matched healthy

volunteers were also recruited from the general community. The capacity to ascribe mental states to others was assessed using three "theory-of-mind" tasks: a joke appreciation task (Corcoran, Cahill & Frith, 1997), a story comprehension task (Happe, 1994) and a false-belief picture-sequencing task (Langdon & Coltheart, 1999). IQ and verbal memory were also assessed. The first-episode patients showed evidence of selective theory-of-mind impairments on the joke appreciation task and the picture-sequencing task but not on the story comprehension task. Findings demonstrate that impairments of social cognition are present at early stages of schizophrenic illness, thus supporting the view that these impairments are a primary feature of schizophrenia, rather than a secondary consequence of the chronic asociality that is typically associated with long-term psychiatric illness. Findings also suggest that "indirect" theory-of-mind tasks that do not explicitly cue explanations of another person's behavior may be more sensitive measures of a spontaneous capacity to infer mental states in young adults at early stages of schizophrenic illness. Corcoran R, Cahill C, Frith CD (1997). The appreciation of visual jokes in people with schizophrenia: A study of 'mentalizing' ability. *Schizophrenia Research*, 24, 319-27. Happe, FGE (1994). An advanced test of theory of mind: Understanding of story characters' thoughts and feelings by able autistic, mentally handicapped, and normal children and adults. *Journal of Autism & Developmental Disorders*, 24, 129-54. Langdon R, Coltheart M (1999). Mentalising, schizotypy, and schizophrenia. *Cognition*, 71, 43-71.

DO OVERINCLUSION AND DISTORTED SEMANTIC CATEGORY BOUNDARIES ARISE FROM FRONTAL IMPAIRMENT?

V. A. Lawrence,* O. J. Doughty, A. Al-Mousawi, F. Clegg, D. J. Done
Psychology, University of Hertfordshire, Hatfield, Hertfordshire, United Kingdom

Semantic memory deficits have been reported extensively in patients with schizophrenia (McKay 1996, McKenna 1990) and it has been suggested that these deficits are the result of frontal lobe dysfunction which causes patients to use dysfunctional retrieval strategies (Zalla 2001, Goldberg 1989). In order to test this hypothesis we compared the performance of 18 patients with schizophrenia on a task measuring overinclusion (the Category Generation Task - CGT) with that of 12 patients with a traumatic brain injury in which frontal dysfunction was prominent. The CGT requires participants to sort a series of picture cards, which depict items from five semantic (i.e. taxonomic) categories, into "groups of items that go together". All participants completed the CGT, Behavioural Assessment of Dysexecutive Syndrome (BADS) test, NART, WASI and MMSE. According to the BADS classification 70% of the people with schizophrenia and 100% of the brain injured patients in this study met criteria for executive impairment. However the two groups performed significantly differently on the CGT. Whereas 67% of the patients with schizophrenia met criteria for overinclusion or distorted semantic category boundaries, this was true for only 17% of the brain-injured patients. In addition, no correlation was found between the BADS score and performance on the CGT in the schizophrenia sample. This pattern of neuropsychological findings suggests that overinclusion and distorted category boundaries do not result from a classical executive dysfunction.

CHANGES IN THE JUMPING-TO-CONCLUSIONS BIAS ARE ASSOCIATED WITH CHANGES IN DELUSIONS: A PILOT LONGITUDINAL STUDY INVOLVING COGNITIVE BEHAVIOURAL THERAPY

T. Lecomte,* T. S. Woodward, C. Leclerc
Psychiatry, University of British Columbia, Vancouver, BC, Canada

Individuals with delusions often display a cognitive bias referred to as the "jumping-to-conclusions" reasoning bias (Linney et al, 1998; Colbert & Peters, 2002; Moritz & Woodward, in press). The jumping-to-conclusions (JTC) bias is defined by insufficient information gathering prior to making a decision. Objectives: The present longitudinal study aimed at verifying whether changes in delusions would be associated with changes in the JTC bias. Method: 36 individuals who were taking part in a RCT comparing cognitive behaviour therapy (CBT) for psychosis to Skills Training and to a control group were asked to complete the JTC task as part of the assessment battery prior to being randomized, and at the end of treatment (3 months later). Participants all had a diagnosis of psychosis (67% schizophrenia, 14% schizoaffective, 10% bipolar, 9% other psychoses), had their first psychiatric consult for psychotic symptoms less than 2 years ago, had a mean age of 23 (SD: 4.9), a mean educations of 13 years (SD: 1.6) and were predominantly male (74%). Delusions were determined by the BPRS (Ventura et al, 1993). The JTC test involved the presentation of Lake A with 60% white fish and 40% black, and Lake B with the opposite proportion. The participants were shown a series of fish that were ostensibly being caught by a fisherman who was fishing from only one of the lakes, and were told to view the series until they felt they could decide on the fisherman's lake (A or B). Four independent series of fish were shown. Results: Of the 36, 13 received CBT, 4 Skills Training, 11 were controls, 7 'intention to treat', and 1 dropped-out of the study. 18 out of the 36 had changes in their delusion score from pre- to post-test. Two measures confirmed the association between the presence of delusions and the JTC bias. Namely, as delusions decreased, the number of series for which a decision was reached after only one draw decreased, $r(16) = .50$, $p < .05$, and the total number of draws requested before a decision was reached increased, $r(16) = -.47$, $p < .05$. In comparison, no such link was found for changes in hallucinations ($p = .94$, $p = .75$). Conclusions: This pilot longitudinal study provides evidence for a link between the JTC bias and the presence of delusions, such that the severity of the bias is positively associated with the severity of delusions. An increased sample size is however warranted in order to determine if this association might be enhanced by CBT for psychosis.

THE RELATIONSHIP BETWEEN EMOTIONAL EXPERIENCE AND EMOTIONAL EXPRESSION IN SCHIZOPHRENIC PATIENTS

W. K. Lee,* E. S. Han, T. Y. Hwang
Clinical Psychology, Yong In Mental Hospital, Yong In, Kyunggi-Do, South Korea

The purpose of this study was to examine the relationship between emotional experience and emotional expression. We assessed 77 clinically stable, medicated chronic schizophrenic inpatients. To measure habitual emotional experience, target participants completed the Positive and Negative Affect Schedule (PANAS). To measure dispositional expressivity, the patients completed the 16-item Berkeley

Expressivity Questionnaire (BEQ). Emotional experience and emotional expressivity correlated .41 for positive emotion and .34 for negative emotion in this patients. We also examined the relation between habitual emotion experience and nurse-rated expressive behavior. The results show that emotional experience was related to expressive behavior only for positive emotion. Patients who experience positive affects can perceive and express their emotion much better and form more empathic relationship with other people. To examine the independent and interactive effects of the related predictors, we conducted a multiple regression, predicting nurse-rated expressive behavior from PANAS positive affect, PANAS negative affect, BEQ positive expressivity, BEQ negative expressivity, and their interaction. Among the predictors, positive affect from PANAS and strong expressivity from BEQ related to nurse-rated expressive behavior. Their interaction was not significant, indicating that the nature of the relation between emotional experience and objectively coded expressive behavior did not depend on dispositional expressivity. These results are relevant considering that previous study (Blanchard et al, 1998) suggests that greater positive affect (PA) was related to better social functioning and poor social functioning in schizophrenia was associated with social anhedonia and greater negative affect (NA). These results indicated that multifaceted cognitive training program added with emotional perception task are promising. With these program, we can enhance positive affects and lessen negative affects so that schizophrenic patients may adapt to their surroundings better. KEY WORDS: dispositional expressivity, emotional experience, emotional perception.

WHERE IS MY FACE? SELF-RECOGNITION IN SCHIZOPHRENIA PATIENTS

J. Lee,* J. S. Kwon, Y. W. Shin, K. J. Lee, G. F. Woodman, S. Park
Psychology, Vanderbilt University, Nashville, TN, USA

Self-related information processing is associated with distinct patterns of behavior and neural activity in healthy individuals. Deficits in self-processing have been reported in schizophrenia patients (SZs) but it is unclear whether these deficits stem from general impairments of perceptual processes or from specific abnormalities of self-processing. In this study, we investigated self-face recognition in SZs in remission, using both behavioral and electrophysiological methods. The main question was whether SZs process their own face in a different way compared to healthy individuals. The first experiment used a visual search task that required subjects to find a target (self-face, famous face, or an object) among distractors as quickly and accurately as possible. Overall, SZs showed slower reaction time (RT) for detecting a target than normal controls (COs). However, when the self-face was a target, the group difference decreased as the set size increased, suggesting that in SZs self-face detection becomes more efficient at larger set sizes. Additionally, the difference in RTs for target-present vs target-absent trials was not affected by the target type in normal controls. But SZs showed a smaller RT difference between target-present and target-absent trials for self-face compared with the famous face target, due to comparatively faster RT in target-absent trials for self-face. These results suggest that while self-face processing may be relatively intact in SZs, there are subtle alterations in how they process self-face. In a second experiment, we sought to test for more subtle alteration of self-face processing in SZs using an electrophysiological technique. Event-related potentials (ERPs) were recorded from the same subject groups while they observed self-face, a famous face or a stranger face. We are currently analyzing data of the second experiment, mainly focusing on the comparison of P3 component for self-face vs famous face. The results of the ERP study will help us understand the nature of neural mechanism of self-face processing in SZ, in relation to behavioral data and clinical symptoms. This study has important implication for self-recognition in SZs in association with clinical symptoms on the behavioral level and on the neuronal level.

THEORY OF MIND DEFICITS IN SCHIZOPHRENIA

K. Lee,* M. Na, J. Oh, Y. Shin, T. Ha, J. Kwon
Department of Psychiatry, Seoul National University College of Medicine, Seoul, South Korea

A theory of mind (ToM) means the ability to appreciate mental states of people, which guides interactions with others. It has been proposed that ToM is impaired in schizophrenia and is related to the symptom severity of schizophrenia. However it is not clear whether ToM is the primary deficit or the secondary to the symptoms of schizophrenia. The purpose of this study was to evaluate the ToM deficits in the schizophrenic patients with mild symptoms who have little disability of communication. Twenty two patients with DSM-IV schizophrenia evaluated by PANSS to be in the mild symptom state and twenty matched controls participated the study. The patients (10 male and 12 female) had a mean age of 25.6 (SD, 5.5) years and a mean total PANSS score of 52.8 (SD, 13.3). ToM story tasks composed of four questions of false belief task and sixteen questions of strange story task were administered to the participants to evaluate their ToM deficit. As a result, the schizophrenic patients with mild psychotic symptom showed selective impairments on the ToM stories compared with controls, but not on the non-mental physical stories which do not require ToM. These findings indicate that regardless of the severity of psychotic symptom, the schizophrenic patients still have the ToM deficits and the ToM deficit is not the secondary to the symptoms of schizophrenia.

LANGUAGE AND ADJUSTMENT IN SCHIZOPHRENIA PATIENT

K. Lee
Neuropsychiatry, Wonkwang University School of Medcine, Iksan, Cheonbuk, South Korea

Purpose: This study aimed to investigate the relationship between ability of language and adjustmental state in schizophrenia patients. Methods: The subjects were 62 schizophrenia patients admitted in wards and 62 controls without any medical illness, who was matched to the schizophrenia patients by age and duration of education. We used the word-association responses to seven figures (horizontal line, vertical line, cross, triangle, square, circle, star) to evaluate the ability of language. The figures were showed to the subjects respectively. Then the subjects were asked to tell the words (up to ten words) to be associated after each figure. The induced words were classified to three categories: I-simple concrete words. II-more advanced words. III-complex abstractive words. The results of the word-association responses were compared between the patients and the controls. Global Assessment of Functioning Scale (GAF) in Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) was the scale to estimate the adjustment state of the schizophrenia patients(the best state during one year before admission-adjustment A and at the admission-adjustment B). The translated vocabulary scale of Wechsler Adult Intelligence Scale-Revised (WAIS-R) supplemented to evaluate the language of the patients. The realtions of adjustment,

the scores of vocabulary scale, word-association responses, present age, onset age, duration of education was checked via Pearson correlation coefficient. Results: 1. The schizophrenia patients showed less word-association responses in level II and total responses than the controls ($p<.00$). 2. The word-association responses had no direct correlations to the adjustment of the schizophrenic patients. 3. The scores of vocabulary scale of WAIS-R showed correlation to adjustment A of the schizophrenic patients ($p<.05$). 4. The level II in word-association responses showed correlation to the scores of vocabulary scale of WAIS-R. Conclusion: The schizophrenia patients showed more restricted association than the controls. But it seemed that this reduced association itself had no effect on the adjustment of the schizophrenia patients. Middle level of association might have some effects on the present adjustment of patients through the correlation of the vocabulary ability that effected the adjustment.

DISORDERS OF AGENCY IN SCHIZOPHRENIA CORRELATE WITH THE INABILITY TO COMPENSATE FOR THE SENSORY CONSEQUENCES OF ACTIONS

D. T. Leube,* A. Lindner, P. Schlotterbeck, A. Rapp, T. Kircher

Psychiatric University Hospital, University of Tuebingen, Tuebingen, Baden-Wuertemberg, Germany

Psychopathological symptoms in schizophrenia suggest that the self concept of these patients might be disturbed. Delusions of influence make them feel that someone else is guiding their actions and certain kinds of hallucinations seem to be misinterpretations of ones own voice as an external voice, the common denominator being that self-produced sensory information is perceived as if coming from outside. If this is true, image motion resulting from ones own smooth pursuit eye movements, might also be attributed to the environment rather than to oneself, giving rise to the percept of a moving world. In fact, we found a correlation between delusions of influence and the ability to cancel out such self-induced retinal information in motion perception. This shows for the first time, that delusions of influence in schizophrenia might be due to a specific inability to compensate for the sensory consequences of ones own actions.

SEX, GENDER, AND CORPUS CALLOSUM

R. Lewine

Psychological and Brain Sciences, University of Louisville, Louisville, KY, USA

Introduction: Interhemispheric dysconnectivity has been used to explain psychotic phenomena such as Schneiderian first rank symptoms. As a consequence, the corpus callosum has been of particular interest because of its role in the integration of inter-hemispheric information. Total corpus callosum area has been reported to be significantly smaller in schizophrenia patients, especially in men. The splenium is thought to be larger and more bulbous in women than in men. Such sex differences speak to possible differences in late neurodevelopment underlying schizophrenia in women and men. Inconsistencies in results can be attributed to imaging acquisition and analysis techniques, patient variables, and the indeterminate boundaries of the corpus callosum. We examine in this study the confusion of sex and gender as another potential source of variability in the study of sex differences. Sex and gender represent distinct conceptualizations. Sex refers to the demographic categories of female and male and gender to the sociocultural and psychosocial features of femininity/masculinity. This analysis was undertaken to determine the relative contributions of sex and of gender to differences in corpus callosum in schizophrenia. Methods: 213 schizophrenia/schizoaffective patients (141 men and 72 women) and 98 healthy controls (41 men and 57 women) were included in this analysis. Patients and healthy comparison subjects were divided into masculine and feminine groups based on the MMPI mf scale, yielding a 2 (diagnosis) by 2 (sex) by 2 (gender) classification scheme. Corpus callosum measurements were based on the MRI mid-sagittal slice that best visualized the splenium of the corpus callosum. Results: A 2 (Diagnosis) X 2 (Gender) X 2 (Sex) ANCOVA controlling for whole brain area revealed significant main effects for Diagnosis ($F1, 242 = 4.368$, $p = .038$) and Gender ($F1, 242 = 4.609$, $p = .033$) on total corpus callosum area. Controlling for age and illness severity did not affect the results. Effect sizes (d) for the main effects of Diagnosis and Gender were .19 and .39, respectively. Neither the main effect of Sex nor any of the interactions reached the .05 level of significance. Discussion: There was a sex-specific effect on the splenium and a gender-specific effect on total callosal area. Theoretical implications will be discussed. In particular, we will address the relationship between corpus callosum area and the cognitive style reflected in gender.

PSYCHOLOGICAL PROCESSES UNDERLYING THOUGHT INTERFERENCE IN PSYCHOSIS

Y. Linney,* E. R. Peters

Psychology, Institute of Psychiatry, Denmark Hill, London, United Kingdom

Morrison (2001) has suggested that auditory hallucinations are the result of cognitive intrusions being attributed to an external source. This study investigated the applicability of this model to symptoms of thought interference. Fifty psychotic patients with and without symptoms of thought interference were tested on (i) frequency of cognitive intrusions; (ii) metacognitive beliefs; (iii) source monitoring; and (iv) appraisals on an unrelated anomalous event (a Card Trick task). Individuals with symptoms of thought interference had increased cognitive intrusions, more negative interpretations of cognitive intrusions, an external attribution bias, and were more likely to endorse appraisals regarding 'permeability' of the mind and conspiracy on the Card Trick task, in comparison to individuals without such symptoms. When the patient group was divided into those who currently experienced auditory hallucinations, and those who did not, almost all significant differences disappeared. These findings suggest that previous studies may have been confounded by the presence of thought interference, and that Morrison's model is more appropriate for symptoms of thought interference, than for auditory hallucinations.

ELECTROPHYSIOLOGICAL MEASUREMENT OF VISUAL ATTENTION IN SCHIZOPHRENIA

S. J. Luck,* R. L. Fuller, B. M. Robinson, E. L. Braun, J. M. Gold

Psychology, University of Iowa, Iowa City, IA, USA

Schizophrenia is widely thought to involve impairments in attention. However, attention is an extremely broad theoretical construct, and it is important to understand exactly which attentional processes are impaired. In the present study, we examined the attentional processes that are used to facilitate the discrimination of objects in a visual

search task. To assess the status of attention, we measured the N2pc (N2-posterior-contralateral) component of the ERP waveform, which arises primarily from ventral occipito-temporal areas of visual cortex and is known to reflect the focusing of visual attention. The N2pc component is present at electrode sites contralateral to the current focus of attention, even when the overall stimulus array is bilateral, and this distinctive lateralization pattern makes it possible to isolate the N2pc component from the rest of the ERP waveform. The onset time of the N2pc component reflects the time required for a subject to find and shift attention to an object, and the amplitude of the N2pc component reflects the amount of attention allocated to the object. We tested 21 patients with schizophrenia (SC) and 12 healthy comparison (HC) subjects in a visual search paradigm in which the target could be easily located by virtue of its distinctive color (which is important for recording time-locked ERPs). Each stimulus array contained 24 outlined squares, each with one side missing. One square was red, one was green, and the others were white; the red and green squares were in opposite hemifields. Subjects were instructed to attend either to red or to green at the beginning of each trial block; for each stimulus array, they indicated whether the square drawn in the attended color had a missing top or a missing bottom. Target discrimination reaction times were significantly longer in the SC group (M = 977 ms) than in the HC group (M = 841 ms). However, a robust N2pc component was observed in both the SC and HC groups, and neither the onset time nor the amplitude of this component differed significantly between groups. Mean N2pc onset latency was 202 ms in both groups, and mean N2pc amplitude was –0.59 μV in the SC group and –0.57 μV in the SC group. These findings provide clear evidence that the operation of attention in this task is not impaired in SC patients, suggesting that the attentional deficit in these patients lies within a different variety or domain of attention. Supported by NIMH R01 MH65034.

SPECIFIC EFFECTS OF PARANOID-SPECTRUM PERSONALITY IN SOCIAL DECISION-MAKING

A. W. MacDonald,* M. K. Johnson, A. Rusticini
Psychology, University of Minnesota, Minneapolis, MN, USA

Paranoid ideation is associated with negative outcomes, including suicidality and violence, in many psychiatric disorders including schizophrenia-spectrum disorders. At the same time, there are no experimental or neuropsychological paradigms available that tap the specific affective networks underlying paranoia, thereby increasing the difficulty of studying this phenomenon. The current study was designed to validate a set of decision-making tasks that were 1) sensitive to variability in paranoia-spectrum personality; 2) capable of deconfounding from paranoia related constructs such as risk aversion and generalized deficits; 3) repeatable and conducive to functional imaging. We report on successive studies of undergraduates and the general population totaling over 100 subjects. The Alienation (AL) scale of the Multidimensional Personality Questionnaire, was used to divide the samples into paranoid (above 75%ile) and non-paranoid groups. These novel decision-making tasks, adapted from behavioral economics, involved a choice between a certain payoff ($5) or providing an anonymous partner a choice. In the Trust Game, the partner's choice is between a better payoff for both the partner and the subject ($9), or the best payoff for the partner ($11) and a "sucker's" payoff for the subject ($3). In line with predictions from game theory, most subjects choose the certain payoff with no difference between paranoid and non-paranoid subjects. The Paranoia Game is similar to the Trust Game, but the partner's alternatives are $9 each or a lower payoff for the partner ($6) paired with the sucker's payoff for the subject. Under these circumstances, non-paranoid subjects usually gave the partner a choice (56% of trials). In line with our prediction, paranoid subjects gave the partner a choice significantly less often (22% of trials). Thus, paranoid subjects failed to modulate their responses according to their partner's incentives. This may have occurred due to poor context processing, or because paranoia led to over-weighting the malevolent intentions of their partners. Other task conditions were included to control for risk aversion, motivation and task understanding. Thus, the current set of studies paves the way for understanding the cognitive basis and functional neuroanatomy of paranoia in both the general population as well as patient groups. Supported by the University of Minnesota.

RELATIONSHIP BETWEEN DURATION OF ILLNESS AND VERBAL INTELIGENCE QUOTIENT IN CHRONIC SCHIZOPHRENIA

K. Matsumoto,* T. Watanabe, Y. Nojima, N. Mori, N. Takei
Psychiatry and Neurology, Hamamatsu University School of Medicine, Hamamatsu, Japan

While it is believed that cognitive functions deteriorate in the course of illness among patients with schizophrenia, it is not clear whether intellectual ability in schizophrenia virtually declines over the lifetime course because there is paucity of longitudinal studies in which patients are individually followed up for decades. This study utilized a cross-sectional approach and examined the relationship between duration of illness (DOI) and intellectual ability in DSM-IV schizophrenia patients with a chronic course. We recruited 33 males and 31 females with schizophrenia, aged over 49, from three psychiatric hospitals. The mean DOI was 34.6 years (S.D. 9.6). Intellectual function was evaluated by Verbal Intelligence Quotient (VIQ) on the Wechsler Adult Intelligence Scale-Revised (WAIS-R). Although no relationship was found between the DOI and VIQ, there was a gender difference in the pattern of the relationship between the DOI and VIQ. The fitted regression models of the VIQ on the DOI revealed that VIQ prior to onset was 12 points lower in males (mean IQ = 91) than in females (mean IQ = 103). In addition, regression coefficients indicated that females showed a 3.3-point decrease in VIQ, whereas males had a 2.5-point increase in VIQ per duration of a decade. These results suggest that intellectual function in schizophrenia over the period of the illness development differs between the sexes, among patients with a chronic course.

SEARCH FOR VALID NEUROCOGNITIVE ENDOPHENOTYPES IN MULTIGENERATIONAL FAMILIES AFFECTED BY SZ AND BP: FROM OFFSPRING TO OLDER GENERATIONS

M. Maziade,* C. Merette, N. Rouleau, J. Boutin, M. C. Dore, C. Lehoux, A. A. Lefebvre, C. Cellard, K. Letourneau, M. A. Roy, N. Gingras
Psychiatry, Centre de recherche Universite Laval Robert-Giffard, 2061, de la Canardiere, Beauport, QC, Canada

We have gathered a unique sample of well-characterized multigenerational families of Eastern Quebec that are densely affected by schizophrenia (SZ) or by bipolar disorder (BP) or both. From the third, the fourth or the fifth generation of our multigenerational pedigrees, we selected 63 subjects in childhood or post-adolescence, at very high risk of schizophrenia (29 HRSZ) or bipolar disorder (34 HRBP). They were not affected by SZ or BP or spectrum disorders

and had no brain disorders. These offspring were all selected in the nuclear families having one parent affected by SZ or by BP that descended from our multigenerational pedigrees. The characteristics and ascertainment of the sample of the original multigenerational families have already been detailed (Maziade et al, 2001; Maziade et al, 2002). A direct interview K-SADS (Kaufman, 1997) was administered in addition to a complete WISC-III or WAIS-III, and a battery of neuropsychological tests. We observed no deficit in intelligence (global IQ) in HRSZ (average : 96.3, SD=8.4) and in HRBP (average : 99.6, SD=10,8) with no significant difference between the groups. Thus, global IQ could not account for the cognitive deficits observed. A Principal Component Analysis (PCA) with varimax rotation, using continuous variables, was performed on the tests that showed higher impairments in the sample. A factor structure was obtained and was composed of three clear octhogonal factors explaining 46% of the variance: 1) a verbal intelligence/motor/episodic memory deficit factor (factor 1; 16.1% of variance); 2) a second factor made of nonverbal intelligence/attention/planning deficit factor (factor 2, 15.1%) and 3) a third factor made of episodic memory (factor 3, 14.8%). Conclusion. HRSZ and HRBP are more likely to present serious cognitive problems with respect to normative values, whereas HRSZ and HRBP had similar average global IQ. HRBP subjects tended to present lower performance IQ, whereas HRSZ had lower verbal IQ. There were specific and shared neuropsychological deficits in HRSZ and HRBP which were also congruent with the differences on factor 1 and factor 2 from the factor analysis. In sum, in the offspring, a disease specificity appeared as likely to exist only for neurocognitive dysfunctions, but not for behavioural problems that showed only a difference of degree.

A MULTINOMIAL MODELLING ANALYSIS OF THE IMPACT OF DELUSION RELEVANT MATERIAL IN A MODIFIED DIRECTED FORGETTING PARADIGM IN SCHIZOPHRENIA

M. Menon,* T. S. Woodward, E. Pomarol-Clotet, P. J. McKenna, R. A. McCarthy
Department of Experimental Psychology, University of Cambridge, Cambridge, United Kingdom

Multinomial modelling represents a simple yet powerful method of separating 'true' item recognition from guessing biases. This paper reports the comparison of traditional methods and multinomial modelling using data from a modified directed forgetting paradigm. Groups of deluded schizophrenics, non-deluded schizophrenics and normal controls were shown lists containing a mixture of delusion relevant and non-delusion relevant words. The delusion relevant words were defined as words common in delusion related themes (e.g. conspiracy). After each word was presented, participants were instructed that the word was either 'to be remembered' (TBR) or 'to be forgotten' (TBF). In the test phase, participants carried out a recognition task, of discriminating previously seen words from novel distracters, and were asked to identify whether the words they recognised had been shown as TBR or TBF words. The raw data from the task was analysed using both traditional methods and Multinomial Modelling. The traditional (model free) analysis revealed no differences between groups on item recognition (old vs. new), but differences in their ability to identify the word category (TBR vs. TBF). This method failed to find any impact of material type. To explore this further, we reanalysed the data using a Multinomial Processing Tree that we created, and separated the stimuli into delusion relevant and non-delusion relevant words. This analysis replicated the findings of the traditional (model free) analysis, and also revealed that the schizophrenic groups (and particularly the deluded group) had greatest difficulties identifying the word category when the material was delusion relevant. This could be due to the relative 'salience' of the delusion relevant material to the patient group, which may dilute the impact of the inhibitory influence of the TBF instructions, thereby reducing the difference between the two types of stimuli in memory.

PSYCHOPHYSIOLOGIC MEASURES, ENCODING PERFORMANCE, AND BRAIN ACTIVATION DURING AFFECT- INDUCED MODULATION OF ASSOCIATIVE AND SPATIAL MEMORY

S. Milanovic,* S. Orr, M. Coleman, P. Holzman, D. Levy
Psychology Laboratory, McLean Hospital, Belmont, MA, USA

Although it has been established that different forms of working memory are impaired in schizophrenia, the mediating role of affect in memory processes is not well understood. We aim to caracterize the role of affect in memory by exploring: a) The modulation of cognitive networks by emotion and b) Communication between the periferal and central nervous systems during behavioral responses. Our pilot study established the paradigm that utilizes positive (funny), neutral (calm) and negative (sad) video clips to induce specific affective states. Positive affective states are associated with statistically significant increases in skin conductance (sc) and zygomaticus activity (emg2). Negative affective states result in statistically significant increases in skin conductance (sc) and corrugator activity (emg2). Level and valence of emotional arousal are measured by subjective report (Lickert scale). The core study includes NC (Normal controls) and SCH (Schizophrenic patients) as experimental groups. Subjects are randomized to the movie clip conditions on two experimental days. Half of the subjects from each experimental group are presented with the associative memory task on the first experimental day and with the spatial memory task on the second. The associative declarative memory task requires establishing an association between an emotionally neutral face and a name. The spatial working memory task explores different aspects of spatial recall, such as positional encoding and object-to-position assignment. Positive affect is hypothesized to facilitate and negative affect to attenuate, associative verbal encoding in normal controls and in high-arousal schizophrenic patients but to have no modulatory effect in the low-arousal schizophrenic group. fMRI is used to assess amygdaloid (AM), hippocampal (HIPP) and prefrontal cortical (PFC) activation during the affect induction, encoding and recall processes.

Skin Conductance (sc)—Repeated Measures Analysis of Variance

(a) Max_Diff = Max block value ± first block±s value (Group analysis done with 2 highest Max_Diff values for each subject from happy and sad clip states)

DEFICITS IN TIME PERCEPTION IN PATIENTS WITH SCHIZOPHRENIA ARE DUE TO DYSFUNCTIONAL MEMORY NOT A CLOCK MODULE

A. L. Mishara,* C. R. Gallistel
Psychiatry, Yale School of Medicine, New Haven, CT, USA

Clinical and experimental study have long suggested abnormalities of time-perception in schizophrenia. However, the nature of this dysfunction and its relation to higher cognitive deficits are not known. We tested the Scalar Expectancy Theory model in patients with schizophrenia. In animal studies, distortions of interval timing resulting from clock speed have been dissociated experimentally from distortions which result from memory-storage effects. Clock speed is linked to the nigro-striatal dopamine system, whereas memory storage is linked to acetylcholine function in the frontal cortex. Although this model has been tested in other putative DA-related disorders (PD, HD, ADHD), the crossover effect on the components of timing in schizophrenia patients taking or not taking antipsychotic medication has not been studied. 7 inpatients (2 females, 5 males) of the Clinical Brain Disorders Branch, NIMH with DSM-IV schizophrenia participated in a double-blind crossover, repeated measures study of time perception while taking and not taking antipsychotic medication (i.e., placebo). Patients were instructed to remember a pre-set duration in the seconds range indicated by a blue rectangle on a computer screen which changed color at the target duration. After subjects had been enrolled for at least two weeks of each arm in an 8-12 week protocol, sessions (with test, retraining and retest phases) were implemented every 7-10 days. The hypothesis that patients with schizophrenia would exhibit abnormalities in time-perception was supported. Paired comparison T-tests indicated that the mean latencies of the patients' responses deviated significantly from target in the placebo ($p = .025$) and drug ($p = .002$) conditions.The patients mean responses on and off drug were significantly longer than target. Without exception, the patients learned the interval quickly, were consistent in their responses despite days of non-exposure to the target and over-estimated the duration in both the medicated and non-medicated conditions. Since the abnormality persisted across conditions, the systematic error in overestimating the intervals did not result from an abnormal inner clock but from a disruption in temporal memory. These findings have relevance for our understanding of higher cognitive deficits and symptoms in schizophrenia. If events occur faster than anticipated, schizophrenia patients could easily feel overwhelmed and cognitively taxed when trying to interpret their meaning.

NEUROCOGNITION AND SUICIDAL BEHAVIOUR IN AN IRISH POPULATION WITH MAJOR PSYCHOTIC DISORDERS

J. E. Nangle,* S. Clarke, G. Donohoe, S. Schwaiger, D. Morris, K. McGee, M. Gill, A. Corvin
Neuropsychiatric Genetics Research Group, Institute of Molecular Medicine, Trinity College Dublin, Dublin, Ireland

Background: The relationship between suicidal behaviour, psychiatric symptomatology and sociodemographic factors in schizophrenia has been extensively investigated. Despite this, suicide attempts in this patient group remain high with over 50% making an attempt over their lifetime. The association between suicidality and neurocognition in the major psychotic disorders has received little attention to date. Our aim was to further elucidate the relationship between neurocognitive variables and suicidal behaviour in schizophrenia, schizoaffective and bipolar I disorders. Method: Ninety seven patients with DSM-IV diagnoses of schizophrenia, schizoaffective or bipolar I disorder were studied. Patients were categorised as either having attempted suicide or not having attempted suicide based on clinical interview and chart review. All subjects completed an extensive neuropsychological battery examining pre-morbid and current cognitive function (WTAR and WAIS subtests), episodic memory (CANTAB PAL, WMS Logical Memory), working memory (N-Back, CANTAB SWM), attention (CPT), and executive functioning (Trails A & B, FAS). Comparisons between suicide attempters and non attempters on neuropsychological scores were assessed using chi square and t-tests statistics as appropriate. Results: Suicide attempters displayed significantly higher functioning in working memory (N-Back:$t= -2.2$, $p=0.031$), CPT:$t =2.25$, $p=0.014$ and executive functioning (Trails: $t=2.1$, $p=0.038$ and FAS: $t= -2.2$, $p=0.03$) than non attempters in the sample. After controlling for age, gender, age of illness onset and diagnosis, the differences between attempter and non attempter groups remained significant on measures of psychomotor speed ($F=4.948$, $p=0.029$) and verbal fluency ($F=4.294$, $p=0.042$). Conclusions: Our findings provide evidence of subtle differences in neurocognitive performance between suicide attempters and non attempters in a patient group with major psychotic disorders. Specifically, suicide attempters displayed significantly better performance in some areas of cognitive function than non attempters. These findings will be discussed in terms of current hypotheses regarding suicidal behaviour in psychotic disorders.

TIMING DEFICITS IN SCHIZOPHRENIA

D. S. O'Leary,* B. M. Turner, C. L. Marvel, N. C. Andreasen
Psychiatry, University of Iowa College of Medicine, Iowa City, IA, USA

Timing is a function that is critical for a wide variety of cognitive abilities. Our group has suggested that dysfunctional timing is the basis of the cognitive impairment that characterizes schizophrenia. This study investigated the ability to tap at specific rates paced either by an external tone, or by an internal clock in the absence of a tone, in a large group of schizophrenic individuals and normal volunteers. Several tapping tasks were administered to 91 healthy volunteers and 164 patients with DSM-IV schizophrenia. The tasks involved tapping with the index finger to an isosynchronous tone for 50 sec and then continuing to tap at the same rate for 50 sec after the tone was turned off. In separate trials the tap-to-tap interval was 400 msec and 730 msec. Mean tap rates (standard deviations) are shown in the table. The patients were significantly more variable in all conditions. There were no significant differences either within- or between-groups at the 730 msec interval. At the 400 msec interval, compared to the tone-paced condition, controls slowed significantly in the self-paced condition, but patients increased their tapping rate (396.8 vs 391.2; $t = 2.03$, $p < .04$). The patient and control groups differed significantly only during the 400 msec self-paced condition ($t = 2.90$, $p < .004$). These data indicate that schizophrenia is characterized by an abnormality in an internally-paced motor behavior at a fast (400 msec) rate, but not at a slower rate. The fact that tapping rate was normal in the schizophrenic group during tone-paced tapping at both intervals and during self-paced tapping at the 730 msec interval indicates that this is not a basic sensory-motor deficit. It is interesting that the patient group tapped faster than normal, given that slowed reaction time is a common finding in schizophrenia. We are continuing to explore the relationship of this timing abnormality to cognitive dysfunction in other domains, to the clinical symptoms of schizophrenia, and its neural substrates.

EMOTION RECOGNITION IN STABLE SCHIZOPHRENIA AND ITS CORRELATION TO QUALITY OF LIFE

G. S. Paisley,* C. G. Kohler, E. A. Lallart, C. Brensinger, R. C. Gur, R. E. Gur
Neuropsychiatry Section, Dept. of Psychiatry, University of Pennsylvania Health System, Philadelphia, PA, USA

Schizophrenia is associated with impaired cognition, psychosocial functioning and quality of life. More recently, recognition of emotion, has also been shown to be impaired in schizophrenia. The purpose of this study was to investigate the association between quality of life and emotion recognition in stable, ambulatory patients, in comparison with associations between quality of life and other select areas of cognition. We hypothesized that quality of life in schizophrenia is more strongly correlated with emotion recognition than other areas of cognition, particularly because of the role that recognition of emotion plays in interpreting social cues and forming close relationships. 19 schizophrenia outpatients (12 males, 7 females) who were stable with respect to psychotic symptoms were assessed for quality of life and underwent computerized testing of emotion recognition of universal emotions and cognition, including tests of attention, verbal and spatial memory and spatial processing. Correlational analysis was performed between measures of quality of life, emotion recognition and cognition. We found correlations between quality of life and emotion recognition (r=0.74, p=0.003), and in particular recognition of the emotions angry (r=0.45, p=0.050), fear (r=0.55, p=0.014), happy (r=0.65, p=0.002), and neutral(r=0.46, p=0.048). Investigating select areas of cognition, no correlation was found with quality of life, with the exception of the category abstraction (r=0.52, p=0.034). Overall, the findings suggest that recognition of emotions in stable patients with schizophrenia may represent an important predictor of quality of life. Moreover, the findings elucidate the importance of emotion recognition remediation in schizophrenia, potentially resulting in improved reintegration and quality of life.

THE RELATIONSHIP OF SCHIZOTYPAL SYMPTOMS TO EMOTIONAL VALENCE IN VISUAL NEUROCOGNITIVE TASKS

V. B. Perez,* P. M. White, C. M. Yee
Psychology, University of Oregon, Eugene, OR, USA

Numerous studies report deficits in affect recognition in schizophrenia, but the mechanisms that generate these deficits remain unclear. In this study, P300 amplitudes were used to assess response to affective images in schizotypal subjects and to identify the relationship of these responses to schizotypal symptoms. The P300 component is an event-related potential sensitive to emotional responding. For example, the P300 area in a classic oddball task was found to be larger for happy faces while P300 amplitude was found to be larger for angry faces (Lang, Nelson, & Collins, 1990). Because P300 is sensitive to the meaning of a stimulus for an individual (Johnson, 1993), this effect may indicate that apparent valence differences are markers of perceived intensity or interest in the visual stimuli. In this study, electrodermal activity (EDA) and P300 to angry, happy, and neutral facial images were assessed in schizotypals (SZ, n=12), control subjects (C, n=12), and a patient control population with social anxiety, social phobics (SP, n=12). An oddball task was used with 4 combinations of angry, happy, and neutral faces in the following design: frequent or context stimuli (60%), infrequent nontarget stimuli (20%), and infrequent target stimuli requiring a button press (20%). Results indicate that when infrequent happy and angry images are assessed, SZ show parietal underactivation in response to happy but not angry images while SP showed a corresponding overactivation to angry images, $F(2,32)=4.38$, $p<.05$. Although the groups did not differ in P300 response to neutral targets in happy contexts, both SZ and SP showed lower EDA than C during this task. Also, with the 3 groups combined, symptoms of schizotypy (SPQ), trait anxiety (STAI), and social anxiety (LSDS) correlated with brainwave and electrodermal responding, e.g. SPQ sum score showed a negative correlation with frontal P300 amplitude in the neutral target/happy context ($r = -.526$, $p<.01$), while parietal P300 showed no such relation. If P300 is an index of stimulus salience, then SP may find angry images more salient than the other groups and SZ may find happy images less salient or arousing than other groups. Thus, these results support specific differences in emotional responding in schizotypals from both controls and socially phobic subjects, with symptom measures related to specific frontal underactivation and generally reduced arousal.

DO DELUDED INDIVIDUALS JUMP TO PERCEPTIONS, AS WELL AS TO CONCLUSIONS?

E. Peters,* N. Smedley, P. Tabraham
PO 77, Psychology, Institute of Psychiatry, Camberwell, London, United Kingdom

This study compared two theoretical models of delusion formation. The first suggests that delusions are caused by the application of normal reasoning to abnormal experiences (Maher, 1992). The second suggests that delusions are caused by an information-processing bias that results in both abnormal reasoning and abnormal experiences (Garety & Hemsley, 1994). The first model predicts that people with delusions who have perceptual anomalies (eg. hallucinations) will demonstrate fewer reasoning or information processing biases, while the second model predicts that they will show higher levels of both types of biases. The reasoning ('jumping to conclusions') and information processing ('jumping to perceptions') biases of fifty deluded individuals, with and without current hallucinations, were compared in order to determine which of the two models is the most accurate. Both groups jumped to conclusions on the Beads task, and showed high levels of need for closure and intolerance of uncertainty. The hallucinating group was significantly more likely to jump to perceptions than the non-hallucinating group, on both visual and auditory reality discrimination tasks. These findings do not provide full support for either model, but are more in line with Garety & Hemsley's proposition than Maher's.

PREMORBID ADJUSTMENT IN SCHIZOPHRENIA: HOW DOES IT RELATE TO NEUROCOGNITION, THEORY OF MIND (TOM), AND PSYCHOSOCIAL FUNCTIONING?

E. Pousa,* R. Duno, C. Domenech, C. Caceres, A. Ruiz, J. E. Obiols
Psychiatry, Parc Tauli Hospital, Sabadell, Barcelona, Spain

The study of Premorbid Adjustment (PA) in schizophrenia has gained considerable interest in recent years because of the proposed neurodevelopmental nature of the disorder. Research on the nature of PA has shown that it is a multidimensional concept, including two differenciated domains: academic and psychosocial (1,2). In turn, these domains have been found to be selectively related to clinical and epidemiological factors. However, with few exceptions (3), the relationship between PA dimensions and impairments after the illness onset has not been systematically approached. The aim of this study is to explore the relationship between PA dimensions and the following domains of current functioning: Neuropsychological performance, ToM -the ability to understand mental states of self and others-, and psychosocial functioning. Method: The sample consisted of 68 patients with DSM-IV diagnoses of schizophrenia, who were stabilized. Assessment:Premorbid Adjustment Scale,PANSS, BPRS, neuropsychological battery, ToM tests and psychosocial functioning.Results and discussion: A small but significant correlation was found between PAS-A and PAS-S. Different patterns of relationships were found between PAS dimensions and clinical and cognitive variables, these being in line with previous evidence supporting the dimensionality of PA. Results indicate that academic PA is associated to variables reflecting intellectual ability, whereas psychosocial PA relates to variables reflecting illness severity and current social functioning. Current neurocognitive difficulties and social cognition deficits seem to be related to overall PA rather than to a particular PA dimension. Conclusion: This study provides further support for the theoretical model of two PA domains in schizophrenia. Research on the selective association of PA domains to clinical, cognitive and psychosocial variables may help clarify potential developmental behavioural markers for schizophrenia risk. References: 1. Allen et al.Confirmation of a two factor model of premorbid adjustment in males with schizophrenia. *Schizophrenia Bulletin*, 2001; 27 (1): 39-46. 2.Cuesta et al. *Aula Medica Psiquiatria*, 2002; 4:247-268. 3.Silversteinet al.Premorbid adjustment and neuropsychological performance in schizophrenia. *Schizophrenia Bulletin*, 2002; 28 (1):157-165.

COGNITIVE PREDICTORS OF PSYCHOSOCIAL FUNCTIONING OUTCOME IN SCHIZOPHRENIA: A FOLLOW-UP STUDY OF SUBJECTS PARTICIPATING IN A REHABILITATION PROGRAM

A. Prouteau,* H. Verdoux, C. Briand, A. Lesage, P. Lalonde, L. Nicole, E. Stip
IFR of Public Health, University Victor Segalen Bordeaux 2, Bordeaux, France

The aims of this prospective study were to explore in subjects with psychosis participating in a rehabilitation program whether cognitive performances at baseline predicted (i) psychosocial functioning over a 15-16 months follow-up; (ii) improvement in psychosocial functioning over the rehabilitation program. Visuo-spatial tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) were administered to assess cognitive performance in 55 subjects with schizophrenia spectrum disorders who completed a rehabilitation program. The Multnomah Community Ability Scale (MCAS) was used to measure dimensions of community functioning. One subscale of the Client s Assessment of Strengths, Interests, and Goals (CASIG) provided a measure of subjective quality of life (QoL). Improvement was defined as a 15% or more increase in psychosocial scores between baseline and follow-up. Worse baseline sustained attention predicted better self-rated quality of life, and better baseline visual memory predicted better community functioning over the rehabilitation follow-up period, in particular, higher autonomy in activities of daily living, and less physical and psychiatric symptoms that could interfere with rehabilitation. Baseline cognitive performances predicted community functioning improvement during the follow-up period: visual memory predicted improvement in daily living autonomy and in social competence; sustained attention predicted improvement in behavioral problems (such as medication compliance, collaboration with treatment providers or impulse control) and social competence; planning performances predicted improvement in daily living autonomy. These cognitive functions could be specifically targeted in rehabilitation program aimed at enhancing functioning in those particular dimensions.

PERCEPTUAL, WORKING MEMORY, AND EXECUTIVE PROCESSES IN SCHIZOPHRENIA: RELATIONSHIP TO FLUID INTELLIGENCE

M. A. Rapp,* C. Schimming, A. Reichenberg
Dept. of Psychiatry, Mount Sinai School of Medicine, New York, NY, USA

Background: Several epidemiological studies suggest a premorbid decline in intellectual functioning in schizophrenia, particularly in processes related to fluid intelligence. This study is concerned with the role that specific perceptual, working memory, and executive control processes have in the fluid intelligence performance deficit in schizophrenia. Methods: The Raven Standard Progressive Matrices (RSPM) test was selected as a standard measure of fluid intelligence. We classified the items in this well-studied test according to their specific demands on perceptual, working memory, and executive processes. Items were presented in standard fashion. In addition, specific working memory and executive processes were studied using Verbal Span, Spatial Span, Visual Span, Set-Shifting, Inhibition, and Dual-Task performance measures. 30 schizophrenia patients and 30 age-, and gender-, and premorbid IQ-matched healthy controls participated in this study. Results: Compared to controls, schizophrenia patients were relatively unimpaired on RSPM items assessing perceptual processes ($p > .05$). However, with increasing working memory and executive control demands in the RSPM items, patients with schizophrenia exhibited performance impairments that exceeded error rates in controls ($p<.0001$). Schizophrenia patients also exhibited significant deficits in specific measures of working memory and executive processes. Controlling for these specific deficits attenuated the performance differences between patients and controls on the RSPM. Conclusions: The deficits in fluid intelligence in schizophrenia are dependent upon specific dysfunction in working memory processes and executive functions, supporting theories that suggest that working memory and executive functions may be the core neuropsychological dysfunction in this disorder.

ADVERSE EFFECTS OF THE ATYPICAL ANTIPSYCHOTIC RISPERIDONE ON WORKING MEMORY IN FIRST-EPISODE SCHIZOPHRENIA

J. L. Reilly,* M. S. Harris, R. Marvin, M. S. Keshavan, J. A. Sweeney
Psychiatry, University of Illinois Medical Center, Chicago, IL, USA

Impairments in working memory are a central neurocognitive deficit in schizophrenia and implicate dysfunction in dorsolateral prefrontal cortex (DLPFC). Studies with nonhuman primates have established a preferential role of dopamine D1 receptors in DLPFC in the modulation of working memory processes, and have also shown that administration of atypical antipsychotics results in a down regulation of these same receptors. These findings highlight the need to study the impact of atypical antipsychotics on working memory systems in schizophrenia. Thirty antipsychotic naive first-episode schizophrenia patients performed an oculomotor delayed response task, a widely used spatial working memory task translated into the clinic from laboratory studies with nonhuman primates. Patients were then retested after 6 weeks of low-dose treatment with the atypical antipsychotic risperidone (4.04 +/- 1.63 mg). Thirty-two age, IQ and parental SES matched healthy individuals were studied over a similar time period. Prior to treatment, patients demonstrated impairment in their ability to maintain spatial location information in working memory over time. This pretreatment impairment significantly worsened after 6 weeks of risperidone treatment despite substantial clinical improvement. At both time points, patients' ability to remember target locations declined more rapidly than healthy individuals as the delay period over which they were required to remember spatial information increased. Patients' impairment in maintaining spatial location information in working memory was not purely motor in nature, as the same pattern of effects was observed even after subjects were given the opportunity to correct for the error of their initial response. These findings with treatment-naive first-episode schizophrenia patients indicate that working memory deficits are present early in the course of illness and that these deficits are exacerbated by low-dose treatment with risperidone that effectively reduced clinical symptoms. As suggested by laboratory studies with nonhuman primates, the adverse medication effects on working memory reported here may be due to the robust down regulation of D1 receptors in prefrontal cortex that is a consequence of risperidone treatment. Support: MH01433, MH45156, MH62134, and RR00056.

CONTEXT AND SCHIZOPHREIC COGNITIVE PROCESSING

B. Roberts,* C. Schooler
National Institute of Mental Health, Bethesda, MD, USA

Braver, et al. (2001) developed a context model of selective attention, applied to young and old adults. The model modifies an earlier one based on schizophrenic individuals (Cohen et al. 1999). Braver et al. define context as "...any task-relevant information that is internally represented in such a form that it can bias processing in the pathways responsible for task performance." By this definition, context is not just a stimulus characteristic, but rather involves the entire process of generating responses. The definition is a bit problematic since relevance is defined, after the fact, by its effect; however, it provides an overarching conceptual framework for understanding a series of our experimental results on schizophrenic cognitive functioning. These include two previously reported studies and three as yet unreported studies. The first previous study, on the Stroop effect, suggested that for schizophrenic individuals out of sight is out of mind (Schooler et al. 1997). The second study (Zahn et al. 1998) showed that a pattern of differences between manual and ocular versions of the classic cross-over experiment (Shakow 1962) is explained by different demands made on working memory due to levels of stimulus-response compatibility. In the first new experiment a color signal indicated the location to which a saccade was to be made after a 1s.or 3s. interval. Intervals were blocked; context change was produced by order of interval blocks. Performance was worse when the 3s interval occurred first, cannot shift performance as task requiremnets change, Experiment 2 involved the reproduction of rhythms (duration) and patterns (stimulus position) by manual or ocular means. Performance of schizophrenic subjects was impaired when the ocular response was used. This suggests that dysfunctions in schizophrenics' memories lead to difficulties in maintaining the set necessary to respond using a novel response modality. Experiment 3 compared a saccade-antisaccade task using either visual or auditory stimuli. Task differences suggest a schizophrenic disability in maintaining the set necessary for a modality shift from stimulus reception to response. Our findings are congruent with Braver et al.'s definition of context. They suggest that, given this view of context, Cohen and his associates are correct in emphasizing the importance of context processing difficulties in the problematic information processing and response selection of schizophrenic individuals.

ARE SEMANTIC PROCESSING DEFICITS IN SCHIZOPHRENIA AN ACCESS OR STORAGE PROBLEM?

S. L. Rossell,* A. S. David
Cognitive Neuropsychiatry, Mental Health Research Institute, Melbourne, VIC, Australia

Semantic processing deficits are central to cognitive abnormalities in schizophrenia and have been inconsistently related to either poor access or poor storage of semantic information. 32 patients with schizophrenia and 32 matched normal controls performed a new word definition task, a categorisation task and a semantic priming task. The tasks compared high and low frequency stimuli and performance across three sessions. It is generally assumed that a storage deficit is signalled by item-specific consistent performance (i.e. consistent performance across independent sessions), an effect of word frequency (wherein items that are less frequently encountered engender poorer performance), and the occurrence of hyperpriming; an access deficit is signalled by the absence of these effects. On the word definition and categorisation tasks patients made multiple errors and had lower scores. Nevertheless, they showed consistent performance across the three sessions and significant effects of frequency. On the semantic priming task the patients also demonstrated consistent performance across sessions (i.e. errors to the same trials) and an effect of frequency. However, they additionally showed hyperpriming, especially of the high frequency stimuli, that is an exagerated facilitory priming effect compared to controls. The current data demonstrated item-specific consistency, a frequency effect and significant hyperpriming; this data is consistent with a storage deficit. We furthermore speculate that the data indicate a disorganised storage of semantic information is a primary deficit in schizophrenia. This disorganisation in turn interferes with efficient access when rapid processing is required (i.e. during semantic priming).

THE PERCEPTION OF EMOTIONAL POINTLIGHT DISPLAYS IN PARANOID SCHIZOPHRENIA

T. A. Russell,* A. B. Joiner, J. Carter, R. Gherling, A. Heberlein, M. L. Phillips
Section of Neuroscience and Emotion, Institute of Psychiatry, London, United Kingdom

Emotion processing abnormalities have been demonstrated by a number of studies in patients with schizophrenia. One aspect of emotional processing which has yet to be explored, and represents a novel avenue to probe emotion perception, is the recognition of emotion in full-body pointlight displays. Use of these impoverished displays prevents potential confounds from extraneous details in the stimuli and can provide a converging line of evidence for emotion processing abnormalities in this group. To control for symptom heterogeneity, a group of 20 patients with schizophrenia with paranoid symptoms were recruited and their performance on a new pointlight task was compared with 20 healthy comparison subjects. All subjects completed 8 trials of five emotions (fear, anger, happy, sad and neutral), watching each short video of the pointlight walker and responding by selecting the relevant emotion label (displayed throughout the task). Paranoid subjects were less accurate than comparison subjects in their identification on fearful, neutral and sad of fearful, sad and neutral stimuli. This deficit was not part of a general impairment as there was no difference in accuracy on happy or angry trials. Exploring the types of errors made on the neutral trials, it was revealed that paranoid subjects had a greater tendency to misinterpret the neutral stimuli as fearful, to a degree that a) differed from comparison subjects and b) was not evident for the other emotions. Accuracy on the neutral trails was significantly negatively correlated with SAPS scores, while accuracy on the happy trials was negatively correlated with SANS scores. Abnormalities in the perception of fear and sadness, and indeed, the tendency to misattribute fear to neutral stimuli, may be a consequence of abnormalities in brain regions responsible for the detection of these emotions and implicated in vigilance and threat-detection i.e.: the amgydala.

VOICES AND VIOLENCE: DIMENSIONS OF VOICES ASSOCIATED WITH AGGRESSION

A. J. Russell,* B. F. Frayne, T. Wykes
Psychology, Institute of Psychiatry, London, United Kingdom

The contribution of mental disorders such as schizophrenia to overall societal violence is relatively minor in comparison with risk factors such as substance misuse and antisocial personality characteristics. There is however evidence for an elevated risk of violent behaviour amongst some patients with psychotic symptoms. Previous symptom focused research in this area has found that patients who have been violent report less success in coping with auditory hallucinations, and report more negative emotions than non-violent patients. This study aims to investigate dimensions of auditory hallucinations in voice-hearers, with and without, a history of violent behaviour. A between-group comparison of violent (n=16) and non-violent (n=16) voice-hearers was carried out investigating participants' responses on a number of clinical severity and symptom rating scales including the Beliefs about Voices Questionnaire. The results were not in the direction expected. Non-violent voice hearers were more likely to attribute negative characteristics and emotions to their voices when compared with violent voice-hearers. The non-violent group also reported higher levels of distress and greater attemmpts to resist engagement with their voices than the violent group. Beliefs about the omniscience of the voices, as well as overall psychpathology ratings and depression explained a significant proportion of the variance in violence severity scores. In line with previous findings, a higher proportion of the violent group had a history of substance misuse. Interpreting the results within social ranking theory suggests that a struggle to resist a powerful and dominant other, whether real or perceived, is a means of inhibiting aggression. Appropriate means of assertion may assist voice hearers with high levels of distress and depression. With the exception of substance misuse, the findings do not provide any clues for factors significant in precipitating acts of aggression. Future research might consider the role of social rank more experimentally.

HOW SPECIFIC ARE COGNITIVE AND EMOTION RECOGNITION DEFICITS FOR SCHIZOPHRENIA? A COMPARISON OF OCD AND SCHIZOPHRENIA PATIENTS

G. Sachs,* M. Aigner, E. Bruckmueller, D. Steger-Wuchse, I. Kryspin-Exner, R. Gur, H. Katschnig
Department of Psychiatry, Medical University Vienna, Vienna, Austria

Previous investigations have demonstrated impaired recognition of facial affect and cognitive dysfunction in schizophrenia. The specificity of these deficits is still under debate. The aim of this study was to invastigate the disease specificity of deficits in emotion recognition and cognition. Fourty patients with schizophrenia (DSM-IV, SCID-P, 15 females, 25 males, mean age: 30.4 SD 8,1) were compared with 40 OCD patients (SCID-IV, SCID-P, 16 females, 24 males, mean age: 34.7 SD 10.4) and 40 healthy volunteers (DSM-IV, SCID-NP, 15 females, 25 males, mean age: 34.7 SD 8.7). All participants underwent a computerized neuropsychological test battery (CNP, Gur et al 1992). A German version of the PENN Facial Discrimination, the Facial Differentiation and the Facial Memory Test, including happy, sad and neutral faces was administered. Executive functions were assessed by a computerized version of the Wisconsin Card Sorting Test (WCST) and attention was evaluated using the Continuous Performance Test (CPT). Patients with schizophrenia and OCD patients performed worse than control subjects in the discrimination of happy faces ($p<0.001$), in facial memory ($p=0.04$), in the WCST ($p=0.01$) and in the CPT ($p<0.001$). There were no significant differences in the Facial Memory Test or in the WCST between schizophrenia and OCD patients. Whereas, in the facial discrimination ($p<0.001$), facial differentiation ($p<0.01$) and in the CPT ($p<0.001$), schizophrenic patients showed a significantly greater impairment than the OCD patients. Dysfunctions in the domains of executive function and facial memory were not confined to one of OCD or schizophrenia. However, schizophrenic patients were found to have a greater attention defict than OCD patients. This may be due to the fact, that in schizophrenia the fronto-dorso-lateral limbic networks are affected and in OCD patients the orbito-frontal-limbic networks seem to be dysfunctional. References: Sachs et al. Facial recognition deficit and cognition in schizophrenia. *Schizophr Res*. 2004; 68: 27-35. Parker et al. No disgust recognition deficit in obsessive - compulsive disorder. *J Beh Ther Exp Psychiatry* 2004; 35: 183-192. Kohler et al. Recognition of facial emotions in neuropsychiatric disorders. *CNS Spectr* 2004; 9: 267-274.

INVESTIGATING SPATIAL WORKING MEMORY AS A COGNITIVE ENDOPHENOTYPE OF SCHIZOPHRENIA: ASSESSING RISK FOR PATHOPHYSIOLOGICAL DYSFUNCTION

A. Saperstein,* R. L. Fuller, M. T. Avila, H. Adami, G. K. Thaker, J. M. Gold
Psychology, University of Maryland, College Park, College Park, MD, USA

This study proposed to examine visuospatial working memory (SWM) as a cognitive endophenotype of schizophrenia (Sz) by expanding the concept of risk for pathophysiological dysfunction beyond overt psychosis. Due to the variability in the genetic liability for Sz, first degree relatives and individuals with schizophrenia spectrum personality disorders (SSPD) may be non-penetrant carriers of the genetic diathesis. SWM was assessed using a computer task, modeled after work by Jonides et al. (1993), which tested memory for dots at a cued spatial location. We hypothesized that SWM performance would decrease as a latent genetic liability for Sz increased, where liability was defined by familial status and the presence of SSPD. Participants were recruited from inpatient and outpatient facilities at the Maryland Psychiatric Research Center and from the Baltimore/Washington D.C. community. SWM performance was assessed in the following groups, in order of decreasing likelihood of genetic vulnerability: patients with schizophrenia (23), relatives of patients with schizophrenia with SSPD (17), relatives of patients with schizophrenia without SSPD (23), community members with SSPD without a family history of psychosis (14), and community members without SSPD (36). SWM performance was quantified by A Prime. Relative risk ratios were calculated for each group as the percentage of participants "affected" by SWM deficits relative to the percentage of healthy community members "affected" by deficits on the SWM task. An A Prime value of 1 SD below the mean of the healthy community group defined the cutoff for "affected" status. Magnitude of relative risk for SWM deficits reflected the proposed model of varying genetic liability. In a chi square analysis, patients with Sz demonstrated moderate to high risk for SWM deficits (3.76; p=0.002), while family SSPD participants demonstrated moderate risk (2.97; p=0.027). Family members without SSPD exhibited higher relative risk (1.88) than the community members diagnosed with SSPD (1.03), although these ratios were not significantly different from the healthy community group (p=0.241 and p=0.971 respectively). The differential risk for SWM deficits suggests the existence of a cognitive phenotype that varies in its expression with respect to the degree of vulnerability. This study thus upholds spatial working memory as a viable cognitive endophenotype of schizophrenia.

DEFICITS IN CLOSURE FLEXIBILITY ARE RELATED TO IMPAIRMENTS OF PERCEPTUAL ORGANIZATION AND EARLY STAGE VISUAL PROCESSING

I. Schechter,* P. D. Butler, V. Zemon, M. Jalbrzikowski, D. Kim, D. C. Javitt
Program in Cognitive Neuroscience and Schizophrenia, Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, USA

Schizophrenia is a complex neurocognitive disorder. Patients with schizophrenia demonstrate a range of information processing deficits. Prominent among them are deficits of early visual processing. In this study, we investigated visual perceptual and organization functioning in patients with schizophrenia using the Closure Flexibilty Test (CFT) a task of organizing and or structuring visual percepts despite distractions. In order to study underlying mechanisms and contributions to higher order deficits, patients also received transient visual evoked potentials (tVEP) using contrast reversing checkerboards, known to be impaired in schizophrenia, as well as several neuropsychological tests. Neuropsychological measures reflected general visual spatial functioning (Perceptual Organization Index (POI) of the Wechsler Adult Intelligence Scale-III), executive function (the Wisconsin Card Sorting Test (WCST)) and memory (Logical Memory Recall (LMR) of the Wechsler Memory Scale-III). Patients showed a significantly greater number of incorrect responses ($p<.001$) but no difference in correct responses as compared with controls on the CFT. CFT (# correct and # incorrect) showed a significant correlation with the P1 and N1 amplitudes of the tVEP. As expected, CFT (# incorrect) correlated significantly with the POI but showed no correlation with the WCST or LMR. These findings demonstrate that patients with schizophrenia have difficulty in maintaining visual organization in the face of irrelevant information. This deficit is related to neurophysiologically-assessed dysfunction of early stages of visual processing. Furthermore, this deficit relates to impairments of visual spatial functioning but appears to be independent of executive or memory dysfunction. This supports the hypothesis that lower-level visual processing deficits are related to higher order dysfunction.

EFFECTS OF INCIDENTAL PROCESSING OF EYE GAZE AND FACIAL EXPRESSION ON CONTROLLED ATTENTION IN SCHIZOPHRENIA

B. L. Schwartz,* M. T. Rowan, C. J. Vaidya, J. H. Howard, S. I. Deutsch
Psychiatry, Veterans Affairs Medical Center, Washington, DC, USA

Overwhelming evidence indicates a deficit in face expression identification in schizophrenia. Much of this evidence, however, is derived from research that asks subjects to make intentional evaluations about a facial expression. Implicit or incidental paradigms provide a more realistic way to study how people read and respond to emotional signals in the environment, as people are often unaware of emotional expressions during social encounters. This study aimed to examine how incidental processing of facial expression and eye gaze affected attentional control processes in schizophrenia. We used a Stroop-like interference task to determine whether facial expression and eye gaze moderated interference effects. Two types of conditions were used: arrow condition and face condition. In the arrow condition, the word right or left was presented above an arrow pointing to the right or left, or a box with no directional information. The task was to read the word and press the right key if the word was right or the left key if the word was left. As expected, response times (RT) in incongruent conditions (e.g., word is right, arrow points to left) were slower than RT in congruent conditions (e.g., word is right, arrow points to right), hence demonstrating interference effects. In the new face condition, subjects see facial expressions (happy, fear, anger, and neutral) with eyes in one of three gaze positions: eyes averted to the right, eyes averted to the left, or direct gaze (no directional information). The word right or left is shown on the face. Again, the task is to press a response key that corresponds to the word. Results from the face condition showed a) interference from direction of eye gaze in that RT were slower in incongruent conditions (word is right, eye gaze is left) compared with RT in congruent conditions (word is right, eye gaze is right); b) interference varied as a function of facial expression; and c) interference differed between the groups as a function of

expression: fear, relative to other expressions, was most disruptive to patients, whereas negative expressions (fear and anger), relative to positive ones (happy), disrupted performance for controls. The results show that incidental processing of facial expression and eye gaze modulate attention, with fear expressions exerting a unique influence on controlled attentional processing in schizophrenia. Supported by NARSAD & The Essel Foundation.

EMOTIONAL PROSODIC PROCESSING IN AUDITORY HALLUCINATIONS

T. L. Shea,* A. A. Sergejew, G. F. Egan, D. Burnham, D. L. Copolov
Mental Health Research Institute of Victoria, Parkville, VIC, Australia

The aim of the present study was investigate emotional prosodic processing deficits in hallucinating and non-hallucinating patients with schizophrenia. Prosodic processing deficits have long been described in the literature on acquired brain damage, and this deficit has also been reported in patients with schizophrenia. This patient group has difficulty not only in comprehending emotional prosody but also expressing it. These deficits occur in the presence of intact linguistic prosody (Murphy & Cutting, 1990) and largely intact auditory processing (McKay et al, 2000). Cutting (1994) proposed that prosodic deficits may be directly related to auditory hallucinations, however no study to date has directly compared emotional prosodic processing between hallucinators and non-hallucinators. The present study compared hallucinators, non-hallucinators and normal controls on an emotional prosodic processing task. After Cutting, it was hypothesised that hallucinators would demonstrate greater deficits in emotional prosodic processing (both expressive and receptive) than non-hallucinators who in turn would show deficits compared to normal controls. Participants listened to a series of neutral sentences that were expressed in happy, sad and neutral voices and rated them on a 7-point likert scale from sad (-3) through neutral (0) to happy (+3). A mood scale (PANAS) was also administered. Preliminary results for receptive prosody indicate deficits for hallucinators compared to non-hallucinating patients and normal controls. A trend was observed for hallucinators to rate all sentences as more positive compared to ratings from hallucinators and normal controls. These results are the first to lend support to Cuttings hypothesis.

SCHIZOPHRENIA, QUESTION COMPLEXITY, AND RESPONSE BIAS IN SELF-REPORT MEASUREMENT

M. Shumway,* G. J. Unick, T. L. Sentell, W. Bamberg
Psychiatry Department, University of California, San Francisco, San Francisco, CA, USA

Research on standardized questions in opinion surveys documents that question complexity is associated with response biases. Regardless of question content, complexity increases response bias and persons with limited cognitive capacities are particularly sensitive to question complexity. This study tested the hypotheses that a diagnosis of schizophrenia, which is associated with a variety of cognitive deficits, would increase sensitivity to question complexity and increase response biases in standardized self-report mental health measures. Community mental health clients' responses to the 32-item BASIS-32 Behavior and Symptom Identification Scale (complete by 1,324 clients) and the 26-item MHSIP Consumer Survey (completed by 2,501 clients) were examined using general estimating question (GEE) and mixed regression methods. Dependent variables were question response and objectively identifiable "response effects" associated with comprehension difficulties (choosing the first response, last response, a neutral response or repeating the previous response). Independent variables were indicators of question cognitive complexity (length, position, readability, linguistic problems), client characteristics (age, gender, education, ethnicity, language ability), and diagnosis (schizophrenia, mood disorder, anxiety disorder). Analyses of the BASIS-32 showed that question complexity and diagnosis had a statistically and practically significant impact on responses ($p<.01$) and hypothesized response effects ($p<.05$). Persons with schizophrenia were more prone to response effects ($p<.01$) and selectively sensitive to question complexity ($p<.01$). Resulting response biases shifted response distributions enough to compromise comparison of diagnostic groups. Analyses of the MHSIP Survey, which has fewer, less complex questions than the BASIS-32, showed a similar pattern of statistically significant effects, but the effects were too small to be of practical significance or to alter response distributions. Together, these results suggest that question complexity increases response bias in self-report mental health measures and that a diagnosis of schizophrenia increases sensitivity to cognitive complexity. However, using measures with lower levels of cognitive complexity appears to reduce response bias and enhance measurement equivalence across diagnostic subgroups. Supported by NIMH grant K01MH64073.

PERCEPTUAL ORGANIZATION DEFICITS IN THE COURSE OF SCHIZOPHRENIA: IMPLICATIONS FOR A THEORY OF COGNITIVE COORDINATION FAILURE

S. M. Silverstein,* P. J. Uhlhaas, B. Essex, U. Schall, S. Halpin, V. Carr
Psychiatry, University of Illinois at Chicago, Chicago, IL, USA

Deficits in perceptual organization have been consistently reported in schizophrenia, as has an association between these deficits and disorganized symptoms. This presentation reports data from two recent studies which clarify the relationship between perceptual organization deficits and illness course. The first study focuses on young people considered to be at ultra high risk for schizophrenia, defined by the close-in strategy (Yung et al., 1996). The high-risk group (n=70) was compared to first-episode patients (n=54), and nonpatients (n=24) using a task with known sensitivity to perceptual organization deficits in schizophrenia, and whose scores have predicted long-term outcome and disorganized symptomatology in past studies (Knight & Silverstein, 1998; Silverstein et al., 1996, 1998). There were no differences between groups, and the high-risk group demonstrated nonsignificantly more sensitivity to stimulus organization than the other groups. When the high-risk group was broken down into its 3 subgroups (A-family history of psychotic illness and recent onset of general symptoms; B-history of attenuated psychotic symptoms; C-brief limited intermittent psychotic symptoms), only group A demonstrated evidence of impairment, but this group differed significantly only from first- and young later-episode schizophrenia patients (who had increased grouping), not from nonpatients. These findings are consistent with recent data on pre-attentive processes in schizophrenia which indicate that performance is not impaired, and may even be enhanced, early in the illness. The second study tested hospitalized patients at admission and discharge to a short-term unit. Disorganized schizophrenia patients (n=14) were

compared to nondisorganized (n=33) patients, patients with other psychotic disorders (n=19) and nonpsychotic controls (n=25). Only the disorganized patients demonstrated abnormal perceptual organization on the two tasks, and normalization of performance over the course of the admission was linked to a reduction in disorganized symptoms. Taken together, and in the context of past studies, these data suggest that abnormal perceptual organization is not a feature of early-stage schizophrenia, but develops as the illness progresses, where it is linked to chronic disability, reduced coordination of contextually-related representations within multiple cognitive domains, and the expression of disorganized symptoms.

SCHIZOPHRENIA SYMPTOMS, SCHIZOTYPY, VULNERABILITY FACTORS AND COGNITIVE EFFICACY IN FIRST ONSET SCHIZOPHRENIA PATIENTS AND HEALTHY CONTROLS

H. G. Smid,* R. Bruggeman, H. Knegtering, J. van Burgel, R. J. van den Bosch
Psychiatry, Univerisity Hospital Groningen, Groningen, Netherlands

We investigated the relationships between type/severity of clinical symptoms and cognitive impairment and the modulating effect of the vulnerability factors schizotypy, neuroticism, intelligence and coping style on cognitive deficits in first onset schizophrenia patients. We further investigated the relation between subjective cognitive failure and objective cognitive failure. We administered questionnaires for measuring schizotypy, neuroticism, coping behavior and subjective cognitive complaints. In addition we applied standard (Trail-making, Stroop, CVLT, WAIS) and non-standard (Simon-, Eriksen- and Stroop interference; attention switching, divided attention cost) cognitive tests to patients and healthy controls. In patients PANSS scores were obtained. The results showed that schizotypy, neuroticism, coping and intelligence modulate cognitive performance in both patients and controls. Avoident coping styles in patients were associated with high vulnerability, high subjective cognitive failure, but smaller objective cognitive deficits. They further showed that different clinical symptoms are related to different cognitive profiles. We conclude that vulnerability factors differentially modulate cognitive deficits in different clinical symptom dimensions and that avoident coping styles in patients may actually protect them for cognitive deficits.

DOMAINS OF AFFECT IN SCHIZOPHRENIA

J. Snyder,* R. Moorehead
Psychology, Univ. of N. Carolina at Chapel Hill, Chapel Hill, NC, USA

The symptoms of schizophrenia vary greatly from person to person, making it difficult to identify and understand the disorder's common causes. Among these symptoms are affective deficits, or problems with expressing and understanding emotion. Affective deficits are of significant interest to psychologists because they complicate rehabilitation. The goal of our study is to better understand how deficits in certain domains of affect are manifested, as well as related to each other. We administered a battery of three tests to fifty-two patients on the acute admissions ward of John Umstead Hospital, in Butner, North Carolina. To measure levels of experienced emotions, subjects completed self-report measures of experienced emotions (the PANAS) after watching emotionally stimulating video clips. To measure ability to perceive the emotions they experience, subjects completed a self-report measure tapping difficulty identifying feelings (a subscale of the TAS-20). To measure capacity for perception of others' emotion, subjects completed two sections of an emotional intelligence test (the MSCEIT): the first involving recognition of emotions in faces, and the second involving recognition of emotions in nature scenery and abstract art. Subjects that had difficulty understanding their own emotions experienced significantly higher levels of negative emotion, and somewhat lower levels of positive emotion, in response to emotional video clips. Equally interesting was the absence of a relationship between subjects' abilities to perceive their own and others' emotions. Both subjects that reported difficulty understanding their own emotions and those that did not report such difficulty had external emotion perception scores below those of a normative sample. It appears that the deficit underlying subjects' difficulty understanding their own emotions may not be related to the deficit underlying subjects' difficulty understanding others' emotions.

MEASURING MULTI-MODAL INTEGRATION IN SCHIZOPHRENIC PATIENTS WITH VIRTUAL REALITY TECHNOLOGY

A. Sorkin,* A. Peled, D. Weinshall
Interdisciplinary Center for Neural Computation, Hebrew University, Jerusalem, Israel

Our goal was to study brain functions in parallel, and the integration among them, in schizophrenic patients, using virtual reality technology (VRT). We studied sensory integration within working memory. Subjects were asked to navigate through a VRT maze, passing through multiple rooms with 3 doors each. Each door was characterized by three features: color, shape and sound. At any given moment there was a rule controlling door opening based on a certain combination of these features (or part of them). The rule changed over time. The subject needed to learn the rule and to use it for successful navigation through the maze. 39 schizophrenic patients and 21 healthy controls participated in the study. Upon completion, each subject was characterized by a vector of 26 measurements, measuring various errors scores, response time, navigation ability and strategy. In addition, we monitored the improvement of subjects with time. Generally, the patients group showed a very large variance in all measurements. The biggest difference between the patients and control groups was manifested in increased errors rate, and a much larger number of consecutive errors. Approximately half of the patients showed one (or more) of the following deficits: "distractor effect" (indicating patients' decreased ability to ignore irrelevant information), increased errors rate when learning the rule, poorer navigation ability and elevated RT. Generally, the patients were significantly slower than the controls, but didn't show marked difference in game strategy. Surprisingly, patients didn't differ from controls on perseveration errors. Though no single parameter can separate the patients and controls groups, a classification procedure based on all the measurements achieves 88% prediction accuracy. We also tested the correlation between our measurements and the subjects' PANSS scores, revealing a number of significant correlations ($p<0.01$): error rates were significantly correlated with 5 positive and 4 negative symptoms; recovery errors rates were correlated with 6 negative symptoms; slow RT was correlated with 6 negative symptoms; and poor selection strategy was correlated with 6 positive symptoms. We conclude that the ability to study multi-modal performance simultaneously using VRT opens new possibilities for the diagnosis of schizophrenia in an objective setup.

COGNITIVE INHIBITION OF THE PUPILLARY LIGHT REACTION IN SCHIZOPHRENIA AND ALCOHOLISM: PHYSIOLOGICAL EVIDENCE FOR EFFORTFUL PROCESSING

S. R. Steinhauer,* R. Condray, G. J. Siegle, J. A. Gurklis
Biometrics Research, VA Pittsburgh Healthcare System, Pittsburgh, PA, USA

A generalized deficit has often been assumed to underlie the failure of information processing operations in schizophrenia patients. This assumption was challenged by evaluating physiological reactivity while subjects were engaged in tasks varying in relative cognitive demand. The pupillary reaction to light is quantitatively sensitive to both effortful and cognitive influences. Moreover, functional anatomical pathways that control direct stimulation of the light reaction as well as inhibition associated with reticular and cortical activity have been identified. We hypothesized that measures of effortful processing should be intact in patients when actively attending to task requirements. This should be revealed in activation of parasympathetic activity from central sources, having the effect of inhibiting activity at the Edinger-Westphal nucleus. Method: Pupil diameter was recorded in 15 schizophrenia patients, 23 alcoholic patients, and 12 healthy control subjects. Averaged light reactions to 11 stimuli were assessed under three conditions: no task, during an easy verbalization task (Add 1), and during a difficult serial subtraction condition (Subtract 7). Results: Prestimulus pupil diameter increased linearly with increasing task demand for all groups (No Task < Add 1 < Subtract 7; $p < 0.001$). Light reaction amplitude did not differ for No Task and Add 1, but was reduced by the Subtract 7 operation for all groups ($p = 0.001$). Conclusions: Findings of increased overall diameter with increasing task demand, but decreased light reaction only for a high demand task, suggest two pathways of inhibitiory activity in all three groups. Increased diameter with greater demand has been linked to reticular activation. Reduction of the light reaction only under the demanding cognitive task appears indicative of cortical activation. Both physiological pathways inhibit central parasympathetic activity. This is consistent with the hypothesis that effortful processing reflected in the parasympathetic pathway is intact in schizophrenia patients. The findings are incompatible with a generalized deficit, but do provide evidence of appropriate physiological reactivity to task demands. Supported by USPHS MH-55762, and the Medical Research Service and VISN 4 MIRECC of the Dept. of Veterans Affairs.

ASSESSMENT MODE: A CRITICAL CONSIDERATION IN OBTAINING VALID SELF-REPORT DATA FROM SCHIZOPHRENIA PATIENTS

J. E. Strong Kinnaman,* A. S. Bellack
Psychology, VA Maryland Health Care System, VISN 5 Mental Illness Research, Education, and Clinical Center (MIRECC), Baltimore, MD, USA

Several instruments have been developed to assess attitudes about drug use and motivation to reduce use among people with drug problems. Accurate assessment of these dimensions can be very helpful in predicting treatment readiness and treatment outcome. However, the cognitive deficits endemic to schizophrenia can interfere with introspection, complex problem solving, and abstract reasoning, making the utility of such instruments doubtful for this population. The purpose of this investigation was to evaluate the validity of several instruments that have proved to be useful for less impaired populations. Schizophrenia patients with either concurrent cocaine dependence (n = 68) or dependence in remission (n = 51) were assessed at Baseline and at 6-months follow-up regarding their drug use and motivation to change. Subjects completed the University of Rhode Island Change Assessment (URICA), a widely used self-report inventory that assesses subjective judgment and motivation to change that is based on Prochaska and DiClemente's Transtheoretical Model (TTM). Subjects also completed the Wells Cartoon Stage of Change Measure. The Wells measure is analogous to the URICA, but requires subjects to rate their motivation to change by selecting cartoons that most resemble their attitudes about drugs, rather than answering hypothetical questions about themselves. Relationships between recent drug use and the Readiness to Change scores (the main index of motivation to change on the TTM) on the URICA and the Wells assessment were examined at Baseline and 6-months. Increased motivation to change on both measures was related to fewer days of cocaine use in the past month. However, the correlation between drug use and the (more concrete) cartoon assessment ($r = -.35$, $p = .0001$) was substantially higher than with the (more abstract) URICA ($r = -.18$, $p < .05$). The relationship between these measures and recent treatment utilization revealed a similar pattern. Results demonstrated stability of these patterns at 6-month follow-up (e.g., URICA and drug use: $r = -.15$, $p = .16$; Wells and drug use: $r = -.42$, $p < .0001$). These results suggest that people with schizophrenia can provide valid information about their motivation to reduce drug use, but that the mode of assessment is critical. These findings are pertinent to assessment of attitudes, affect, and motivation in other domains as well as for assessing subjective phenomena about drug use. Supported by NIDA grant DA09406 to ASB.

MEMORY TESTS IN FIRST DEGREE RELATIVES OF SCHIZOPHRENIC PATIENTS—A META-ANALYSIS

A. Szoke,* A. Trandafir, F. Schurhoff, A. Meary, M. Leboyer
Psychiatry, "Albert Chenevier" Hospital, Creteil, France

The existence of memory deficits has been clearly demonstrated in schizophrenic patients. However, studies of memory performances in their relatives compared to normal controls provide conflicting results. To synthesize all published data a meta-analyses was needed. As most used memory tests differ according to stimulus type (verbal, nonverbal), retrieval condition (free and cued recall, recognition) or retention interval (immediate, delayed) we decided, in contrast with previously published studies, to realise separate analyses for each memory test for which enough data (i.e. at least three separate reports) were available. We identified 82 potentially relevant articles, from which we retained 15 articles that met the inclusion criteria. Those articles provided data on 8 different tasks, from 5 memory tests: 4 tests derived from the Wechsler Memory Scale (WMS) and the California Verbal Learning Test (CVLT). For each task, after assessing the homogeneity of the data, effect sizes were estimated and publication bias was tested using funnel plots. Relatives of schizophrenic patients performed significantly less well on most, but not all, tasks. Most important deficits were observed for Verbal Paired Associates (estimated effect [EE] = 0.53 [0.32-0.74]), Digit Span Forward (EE=0.48 [0.32-0.64]) and Digit Span backward (EE = 0.46 [0.28-0.64]). In contrast, no significant differences were observed in tasks of delayed recall, when deficits in immediate conditions (reflecting encoding) were taken into account. For Visual Reproduction, in the immediate recall task,

differences between relatives and controls were influenced by the type of relatives included, i.e. for the younger samples that included only siblings of schizophrenic patients no deficit was observed (EE = -0.03 [-0.31-0.24]) although a significant deficit was observed in samples including siblings and parents (EE = 0.50 [0.32-0.68]). In conclusion, relatives of schizophrenic patients appear to have wide but not severe memory impairments. The magnitude of estimated effects observed suggests that the encoding processes are impaired although the maintaining of successfully encoded material is relatively spared. For Visual Reproduction–immediate recall, data suggest that performances deteriorate with age. Because of relatively small number of studies, those conclusions are provisional, needing more research to validate or invalidate them.

DOUBLE-BLIND COMPARISON OF QUETIAPINE AND HALOPERIDOL ON COGNITIVE FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA

A. Tapp,* A. E. Wood, N. Kilzieh, A. Kennedy
VA Puget Sound Health Care System, Tacoma, WA, USA

With the emergence of second generation antipsychotic medications came the hypothesis that these new medications could improve the cognitive dysfunction associated with schizophrenia. Although initial reports were promising, subsequent studies raised doubts about the potential of atypical antipsychotics to improve cognitive function. In this study, patients with schizophrenia or schizoaffective disorder who had been stable on a conventional antipsychotic for at least one month, were randomized, double-blind, to either haloperidol or quetiapine. Dosing was flexible based on a medication algorithm from 5-20mg/day of haloperidol or 300-600mg/day of quetiapine, in order to find the optimal dose of medication for each subject. Subjects were given a battery of cognitive tests at baseline and 12 weeks, including measures of attention, memory, and executive function. The measures of attention included a computerized continuous performance test and trail-making. Measures of memory included list learning, paragraph recall, and letter-number sequencing, a measure of working memory. Measures of executive functioning included a card sorting task and verbal fluency. Additional testing consisted of the Positive and Negative Syndrome Scale (PANSS) and measures of common side effects associated with antipsychotic medications. Subjects were all veterans being treated for chronic psychiatric symptoms related to schizophrenia or schizoaffective disorder. Average age was 45.5 years and average number of years since first diagnosis was 20.75. Neither the haloperidol group (N=9) nor the quetiapine group (N=11) demonstrated any significant improvements on the battery of cognitive tests between baseline and 12 weeks. Both groups had modest improvements on the PANSS; the haloperidol group showed significant improvements on the positive subscale ($p<.05$) and the quetiapine group showed significant improvements on the general psychopathology subscale ($p=.05$). The quetiapine group showed additional improvements on a measure of akathisia ($p<.01$). The results support the conclusion that quetiapine does not improve cognitive function in schizophrenia. However, the significant chronicity of this sample may make the population tested less able to experience improvements in cognitive domains. In conclusion, while quetiapine may be able to improve psychiatric symptoms without the same risk of side effects as haloperidol, it did not improve cognition in this sample.

EXPERT PERFORMANCE AND THE WISCONSIN CARD SORTING TEST: IMPLICATIONS FOR THE ROLE OF EXCUTIVE FUNCTION IN SCHIZOPHRENIA

B. Thurston-Snoha,* R. Lewine
Clinical Psychology, University of Louisville, Louisville, KY, USA

The literature on schizophrenia is primarily concerned with the deficits associated with the illness and thus focuses on those individuals who are more negatively affected by the disorder. The research fails to examine those individuals who retain significant function and may therefore be able to cope successfully with the disorder. Sternberg (as cited in Bellack, Gold, and Buchanan, 1999) used the term "expert" to connote "targets" of study. That is, according to Bellack et al. (1999), rehabilitation in schizophrenia can be studied by focusing on "expert" performers. Using the data obtained from an earlier database of people with schizophrenia-related disorders, scores on the Wisconsin Card Sorting Test (WCST) were examined to find those subjects who performed poorly (nonexpert) and those subjects who performed well ("expert"). "Expert" peformers ($n = 43$) were those who made less than ten percent perserverative errors on the WCST while "nonexpert" was operationalized to refer to those individuals ($n = 141$) who made ten percent or more perseverative errors. To control for aging effects, patients over the age of 55 were excluded. The two groups ("expert" performers versus nonexpert performers) were then compared on various clinical and sociodemographic variables in order to ascertain the differences that may account for more successful performance on the WCST. The results indicate that the "expert" performers were more similar than different from the nonexpert performers. The relationship between level of expertise and age at first hospitalization was significant ($p = .032$). Specifically, the "expert" performers were approximately two years older on age at first hospitalization. A subsequent analysis revealed that differences in age at first hospitalization were not accounted for by sex. Based on MMPI scores, it was also inferred that later age at first hospitalization cannot be accounted for by severity of illness since both groups showed similar illness severity. WCST performance is thought to be a measure of executive function. Thus, there seems to be a relationship between executive function and later age of hospitalization. Perhaps higher executive functioning prevents patients from earlier hospitalization. Since these analyses did not yield many significant differences between "expert" performers and nonexpert performers, these results suggest that the role of executive function in schizophrenia may need to be reexamined.

RECOGNISING FACIAL EXPRESSIONS FROM MOVING AND STATIC IMAGES IN SCHIZOPHRENIA

E. Tomlinson,* R. Johnston, C. A. Jones, A. Meaden
Psychology, University of Birmingham, Birmingham, United Kingdom

Background: It is well established that schizophrenia is associated with difficulty interpreting facial emotion. However, the specificity of this deficit remains uncertain. Archer et al., (1992; 1994) found a generalised face-processing deficit when testing with static images but a specific emotion recognition deficit with moving images. In contrast, we recently found a generalised deficit with both moving and static images, when comparing emotion recognition with facial speech (Tomlinson et al., 2004). The present study investigates this further using Johansson point-light images to isolate pure movement

information. Method: All participants (14 schizophrenic and 24 controls) completed 4 emotion recognition tasks (2 moving and 2 static) with Johansson point-light images. Results: Overall moving images were significantly better recognised than still images ($F(1,28) = 295.2$, $p < 0.0001$) and controls were significantly more accurate than schizophrenics ($F(1,28) = 20.155$, $p < 0.001$). These effects were modified by a significant interaction between Image type and Group ($F(1,28) = 25.3$, $p < 0.0001$). Analysis of the simple main effects revealed the control group performed significantly better than schizophrenics with the moving images ($F(1,58) = 2.27$, $p < 0.001$) but there was no difference between groups for static images ($F(1,58) = 1.18$, $p = 0.37$). No other interactions were significant. Conclusions: People with schizophrenia are able to use pure movement information to judge emotion from moving images, but are less efficient at this than controls. It is proposed that depending on the way in which this emotion deficit is tested different levels of impairment will be found.

JUMPING TO CONCLUSIONS: STATE OR TRAIT?

F. Van Dael,* L. Krabbendam, J. van Os
Department of Psychiatry and Neuropsychology, South Limburg Mental Health Research and Teaching Network, EURON, Maastricht, Netherlands

Objective Patients with delusions have been found to show a tendency to jump to conclusions. The present study examined whether this reasoning bias reflects a state that is associated with delusions, or rather a trait that can also be detected in non-delusional schizophrenia patients, relatives and subjects with a high level of schizotypy. Method Four groups of participants with increasing schizophrenia risk (SR) were included (yielding an SR variable with 4 values): 54 subjects from the general population with an average level of schizotypy (control group, coded 0); 41 subjects from the general population with a high level of schizotypy (coded 1); 47 first-degree relatives of patients (coded 2), and 45 patients with schizophrenia or a schizo-affective disorder (coded 3). "Jumping-to-conclusions" (JTC) bias was assessed using the beads task and level of delusions was represented as a 4 level variable. Results There was a dose-response relationship in the association between level of schizophrenia risk and JTC (defined as needing only a single bead to complete the beads task; high schizotypy score relative to controls: OR=1,34; p=0,63; relatives: OR=2,61; p=0,09; patients: OR=3,51; p=0,022). However, this association was generally much stronger in those with delusional ideation than in those without (compared to those without delusions (level 0): level1: OR=1,43; p=0,560; level 2: OR=2,86; p=0,116; level 3: OR=5; p=0,010). Conclusion JTC-style of reasoning is associated with liability to schizophrenia (trait), in particular if the psychosis phenotype is characterised by delusional ideation (state).

OPTIMIZATION OF A MULTINOMIAL MODEL FOR INVESTIGATIONS OF HALLUCINATIONS AND DELUSIONS WITH SOURCE MONITORING

T. S. Woodward,* M. Menon, X. Hu
Research and Quality Management, Riverview Hospital, Coquitlam, BC, Canada

Hallucinations and delusions in schizophrenia partially reflect inner/outer confusions in cognition. Thus, source monitoring has proven an important cognitive paradigm for investigating psychosis. We propose a new statistical/cognitive model for the study of hallucination and delusions, using multinomial modelling. In general, multinomial modelling allows guessing strategies to be estimated separately from source-discrimination processes. Importantly, it also allows source misattributions to be separately estimated for when (1) items are recognized, but source information is not accurately remembered, and (2) items are not recognized, but a source is guessed based on a metacognitive strategy. Our new model was optimized for the study of schizophrenia, and allows estimation of independent externalization and internalization bias parameters, as well as the likelihood of external source confusion. This was achieved by allowing parameter estimates of biases to vary with the originating source instead of the response type. Multinomial modelling of responses suggested that patients with schizophrenia as a group were impaired on item recognition for all sources, but were mostly spared on source discrimination for recognized items. However, within the patient group, the results provided support for a double dissociation: hallucinating patients displayed evidence for an externalization bias but not an internalization bias, whereas delusional patients displayed evidence for an internalization bias but not an externalization bias. Neither symptom group displayed an increased likelihood of external source confusion.

NEUROPSYCHOLOGICAL PERFORMANCE IN SCHIZOTYPAL PERSONALITY DISORDER: IMPORTANCE OF WORKING MEMORY

G. L. Zegarelli,* P. D. Harvey, V. Mitropoulou, A. S. New, J. M. Silverman, L. J. Siever
Psychiatry, Mount Sinai School of Medicine, New York, NY, USA

Background: Cognitive deficits have been reported consistently in schizophrenic patients and in patients with schizotypal personality disorder (SPD). For this study, we wanted to identify which of the domains of cognitive impairment represent core deficits in the schizophrenia spectrum comparing SPD subjects to two control groups: healthy volunteers and patients with personality disorders unrelated to the schizophrenia spectrum. Method: 82 DSM-III-R SPD patients, 44 patients who met DSM-III-R criteria for another non-schizophrenia spectrum personality disorder (OPD), and 63 healthy volunteers (HV) were tested on a neuropsychological battery that included the California Verbal Learning Test (CVLT), Trailmaking parts A & B, the DOT test of working memory, the Stroop Color-Word interference, the Paced Auditory Serial Addition Test (PASAT), the Wechsler Memory Scale Visual Reproduction Test (WMSVR), and the WAIS-R vocabulary and block design. Results: Normative standards for performance (controlling for age, gender and education) were created utilizing the HV group. Overall, SPD patients performed significantly worse compared to HV and the non-schizophrenia spectrum group: specifically, SPD patients demonstrated impaired performance on the PASAT, WMSVR immediate and delayed recall, DOT test, CVLT word list learning total and delayed recall. Additionally, in a stepwise regression analysis, the PASAT accounted for more of the variance than all other measures combined, consequently controlling for PASAT performance abolished group differences across all measures. Conclusions: SPD patients demonstrate modest cognitive impairment compared to HV (significant for seven out of eleven measures). These differences reached statistical significance for working memory tasks, episodic memory, and delayed recall tasks. Controlling for working memory (ie auditory) performance accounted for the group differences. This study sup-

ports the view that working memory represents a core deficit of the schizophrenia spectrum disorders.

TESTING DRUGS WITH RELEVANCE TO SCHIZOPHRENIA IN MICE: CAN EFFECTS ON COGNITION BE DISSOCIATED FROM NON-SPECIFIC BEHAVIORAL EFFECTS?

N. M. de Bruin,* M. Mahieu, T. Patel, D. Ashton
CNS Discovery Research, Johnson & Johnson/Pharmaceutical Research & Development (J&J PRD), Beerse, Belgium

Patients with schizophrenia demonstrate deficits in certain domains of cognitive functioning. In the present study, drugs with relevance to schizophrenia were tested in order to investigate whether they would affect cognitive processes in mice and to determine whether these effects could be dissociated from motor effects. Male B6129SVF2 mice were tested in the Morris water maze, a test for spatial learning and memory. Several drugs were tested: MK-801, scopolamine, haloperidol, clozapine and nicotine. MK-801 increased latency to platform during acquisition and impaired performance in the probe trial. However, MK-801 caused a profound decrease in swim speed at the same doses. Scopolamine impaired acquisition and reduced time in target quadrant and number of platform crossings at all doses tested without effects on swim speed. Haloperidol increased latency to platform during acquisition and impaired probe trial performance, but swim speed was also significantly reduced at the same doses. The highest dose of clozapine reduced swim speed during the first 2 days of acquisition, while impairing platform finding on day 4. Clozapine also significantly reduced the number of platform crossings during the probe trial and the swim speed. Finally, the middle dose of nicotine significantly enhanced time in target quadrant and number of platform crossings without displaying effects on swim speed. In contrast, the highest dose of nicotine decreased swim speed in the probe trial. It is concluded that there is no dose of MK-801 that selectively affects learning and memory processes. In contrast, with scopolamine, impairments in learning/memory can be dissociated from motor effects. Therefore, disruption with scopolamine is suggested to be a better model for cognitive deficits in comparison to MK-801. The highest doses of both haloperidol and clozapine impaired spatial performance and in addition also lowered the swimming speed. With both antipsychotic drugs, effects on learning/memory in the Morris water maze cannot be dissociated from nonspecific behavioral effects. Finally, the relatively low dose of 0.16 mg/kg of nicotine proved to be beneficial for performance in the probe trial without effects on motor activity. These results show that it is important that factors that contribute to the reduction in swim speed such as loss of balance, ataxia and sedation are taken into consideration in order to determine effects of drugs on learning and memory capabilities.

LONGITUDINAL STUDY OF IQ ON THE WECHSLER ADULT INTELLIGENCE SCALE IN SCHIZOPHRENIA

Y. Takai,* T. Toyoda, N. Mori, N. Takei
Hamamatsu University School of Medicine, Hamamatsu, Japan

Schizophrenia patients have long been believed to deteriorate over the course of the illness; that is, intellectual deterioration. There is, however, paucity of longitudinal studies in which patients are individually followed up over decades. Therefore, it is not clear whether intelligence in schizophrenia virtually declines over long-term course. This study attempted to reassess IQ with an interval of more than a decade in patients with DSM-IV schizophrenia using the WAIS, and also examined any relationship between intellectual changes, and symptom severity and neurocognitive performance as evaluated at the time of the follow-up. We recruited 15 schizophrenia patients whose IQ had been previously assessed with WAIS within one year of the first contact with psychiatric services and who maintained psychiatric care and provided agreement to participate into the study. The mean interval of IQ assessment was 18 years (range 12 to 27 years). The patients underwent reassessment with WAIS and comprehensive neuropsychological evaluations. Symptom severity was evaluated with PANSS. There was no significant overall change in full-scale IQ. However, verbal IQ significantly decreased over the period by an average of 7.9 points (95% Cl, -12.7 to -3.1 points: p=0.003), whereas performance IQ increased by an average of 6.3 points (95% Cl, 0.2 to 12.5 points: p=0.044). When correlational analysis was made between changes in IQ and neuropsychological measures, decreases in VIQ were found to be significantly related to poor visual memory (p=0.047). There was no correlation of the symptom severity with changes in IQ over time. These findings suggest that there may be a different process in the change of cognitive performance over the course of the disorder. In particular, linguistic ability may deteriorate more over the illness development than performance ability. Memory deficits may also concur with verbal intellectual changes in schizophrenia in the long-term course.

13. Neuroimaging, Structural

RELATIONSHIPS BETWEEN BDNF AND NTF3 GENE VARIANTS AND BRAIN VOLUMES ASSESSED BY MAGNETIC RESONANCE IMAGING

I. K. Agartz,* E. G. Jonsson, A. Sillen, B. Edman-Ahlbom, A. Gunnar, G. Okugawa, C. Tamagaki, B. Ekholm, H. Hall, G. C. Sedvall, L. Terenius
Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

Genetic factors have been shown to be of importance in schizophrenia. Disturbances in neurodevelopment have been suggested as a putative pathologic mechanism of the disorder. Brain derived neurotrophic factor (BDNF) and neurotrophin-3 (NTF3) belong to the neurotrophins, a family of growth factors promoting neuronal survival and differentiation. The purpose of the study was to investigate associations between BDNF and NTF3 gene variants and brain morphology in chronic schizophrenic patients and healthy subjects. Segmented grey, white, and cerebrospinal fluid (CSF) tissue class volumes of frontal, occipital, temporal, and parietal regions and total brain volume were obtained using 1.5 Tesla magnetic resonance (MR) imaging and image analysis methods (BRAINS). MR volume data from parcellated cerebellar vermis subregions and hemispheres was investigated. BDNF and NTF3 genotyping was performed using PCR and pyrosequencing techniques. In 109 schizophrenic patients, compared with 106 control subjects, CSF of total brain, frontal lobe, and ventricular volumes were increased ($p<.001$). Bilateral frontal white and temporal grey matter were reduced ($p<.002$). Cerebellar vermis and tonsil volumes were highly significantly reduced ($p<.006$ and $p<.0000$) in a randomly selected subset of 61 chronic schizophrenic patients compared with 56 control subjects. There were no significant differences in BDNF or NTF3 polymorphism variation between 200 schizophrenic patients and 240 control subjects. In preliminary analyses of 150-200 subjects, BDNF polymorphisms 758 G/A and 11757 G/C were associated ($p<.01$) with frontal and cerebellar grey matter and BDNF -633 T/A with occipital grey matter variation. NTF3 295 A/G showed an association with occipital grey matter. No significant associations were found between the gene variants and white matter or CSF tissue volumes. Among 117 individuals there were significant associations between BDNF 758 G/A and 11757 G/C polymorphisms and the cerebellar vermis. BDNF or NTF3 gene variants may influence brain morphology. Supported by the Swedish Research Council, the Wallenberg Foundation and Sanofi-Synthelabo.

COMPOUNDED WHITE MATTER ABNORMALITIES IN ADOLESCENTS WITH SCHIZOPHRENIA-CANNABIS COMORBIDITY

M. Ashtari,* S. Kumra, K. Cervellione, S. Sevy, E. Thaden, H. Kester, D. Roofeh, J. Rhinewine, J. Wu, T. Clarke, G. Fisch, J. Kane, T. Lencz, B. Ardekani, P. Szeszko
Radiology, North Shore Long Island Jewish Health System, New Hyde Park, NY, USA

Abnormalities in white matter have now been reported in a number of diffusion tensor imaging studies in patients with schizophrenia. In a previous study, we reported decreased fractional anisotropy (FA) in patients with early-onset schizophrenia (EOS) (onset of psychotic symptoms by age 18), relative to healthy volunteers, in six regions of left hemisphere white matter: anterior cingulate, parahippocampal gyrus, amygdala, superior temporal gyrus, precuneus, and medial frontal gyrus. The etiology of these abnormalities in adolescents with EOS remains unclear, although environmental factors are thought to play an important role. In this report, the authors investigated whether recurrent exposure to cannabis was associated with reduced fractional anisotropy levels in white matter in the medial-frontal gyrus (Broadmann's Area 6) in patients with EOS. Prior developmental studies in healthy volunteers using diffusion tensor imaging have suggested that there is ongoing development of white matter in this area (Schmithoorst et al 2002). We hypothesized that areas of the brain where there is ongoing development might be particularly susceptible to the neurotoxic effects of cannabis. Thirty-six EOS patients (including 10 patients with cannabis misuse) and 34 age-, gender- and handedness matched healthy volunteers were studied with diffusion tensor imaging (DTI) using a voxelwise method. Using linear regression methods, we found a significant group-by-age interaction ($p=.03$) for FA in the medial frontal gyrus in subjects between the ages of 14 and 19 years. Cannabis misuse also significantly predicted FA values ($p=.003$) in patients when controlling for age and premorbid social functioning. These preliminary data suggest that some feature of cannabis abuse is associated with abnormal developmental trajectories in subcortical white matter of the supplementary motor area in adolescents with EOS. References Schmithorst VJ, Wilke M, Dardzinski BJ, Holland SK (2002): Correlation of white matter diffusivity and anisotropy with age during childhood and adolescence: a cross-sectional diffusion-tensor MR imaging study. *Radiology* 222: 212-218. Supported by NIMH grants MH-60221 to Dr. Kane; MH-64556 to Dr. Kumra; MH-01990 to Dr. Szeszko; and a grant from the North Shore-Long Island Jewish Hospital Research Institute. Presented at the 43rd American College of Neuropsychopharmacology Annual Meeting, San Juan, Puerto Rico, 2004.

BRAIN VOLUMES IN PARENTS OF PATIENTS WITH SCHIZOPHRENIA

H. B. Boos,* W. Cahn, M. C. Appels, M. M. Sitskoorn, H. E. Hulshoff Pol, H. G. Schnack, S. J. Palmen, R. S. Kahn
Department of Psychiatry, University Medical Center, Utrecht, Utrecht, Netherlands

Imaging studies have consistently demonstrated structural brain abnormalities in patients with schizophrenia. These brain abnormalities include reduced total brain volumes and have also been found to a lesser extent in healthy offspring or siblings of patients with schizophrenia. However, structural brain volumes have not been studied in parents of patients with schizophrenia. The present study was designed to examine the contribution of genetic factors to structural brain abnormalities. 1.5 T Structural MRI brain scans were obtained from both biological parents of 33 patients with schizophrenia (N=66) and from 26 control couples (N=52), matched for age, ethnicity, IQ, length, weight and handedness. The parents of patients with schizophrenia had at least one child who met the DSM-IV criteria for schizophrenia. They were physically healthy and did not have a history of psychotic disorder, nor drug or alcohol abuse. Control couples had no history of psychotic disorder, no family history of psychotic disorder, nor did they have any psychiatric disorder according to DSM-IV. They were physically healthy and did not have a history of drug or alcohol abuse. Volumes of total brain, cerebrum, cerebellum, lateral ventricles, third ventricle, gray matter, and white matter, were

analyzed using analyses of variance (ANOVA), adjusted for intracranium volume and corrected for age. Parents of patients with schizophrenia had significantly smaller total brain volumes (98.12%, F=4.968; df=1; p=0.028), cerebrum volumes (98.15%, F=4.019; df=1; p=0.047), and cerebellum volumes (96.99%, F=5.410; df=1; p=0.022), compared to the control couples. However, volumes of the lateral ventricles, third ventricle, and gray and white matter did not differ significantly between the two groups. The findings indicate that parents of patients with schizophrenia have smaller brains than control subjects. This is in agreement with our findings of earlier twin studies and studies in siblings of patients with schizophrenia. However, brain volumes have never been explored in parents. As the parents in our study had no history of psychosis, we suggest that reduced total brain volume is not illness-related but an expression of the genetic proneness to schizophrenia.

MORPHOMETRIC EVIDENCE TOWARDS A DYSFUNCTION OF CORTICO-CEREBELLAR-THALAMIC-CORTICAL CIRCUITRY (CCTCC) IN FIRST-EPISODE SCHIZOPHRENIA

C. Bottmer,* S. Bachmann, V. Magnotta, J. Pantel, F. Giesel, M. Essig, J. Schroeder
Dept. of Psychiatry, University of Heidelberg, Heidelberg, Germany

"Cognitive Dysmetria" refers to the hypothesis of a dysfunctional cortico-cerebellar-thalamic-cortical circuitry in schizophrenia which manifests itself as positive and negative symptoms (Andreasen et al, 1996). Our study compared volumes of frontal cortex and cerebellum of 71 patients with DSM-IV diagnoses of first-episode schizophrenia, schizophreniform and schizoaffective disorder, respectively, to 41 healthy age- and gender-matched controls. MRIs were obtained with a 1.5 T Siemens Magnetom, for volumetric assessment the software BRAINS was used. Patients' psychopathological symptoms were rated with the Positive and Negative Syndrome Scale (PANSS). ANCOVAs with intracranial volume serving as a covariate revealed significantly reduced cerebellar volumes in patients compared to controls (left hemisphere: 63.07±8.55 vs. 67.16±9.34, $p<0.05$; right hemisphere: 63.57±8.89 vs. 67.45±8.12, $p<0.05$), whereas frontal lobe gray matter volumes were larger in patients than in controls (left hemisphere: 139.35±17.67 vs. 134.28±13.86, $p<0.01$; right hemisphere: 143.85±17.85 vs. 141.56±14.81, $p=0.06$). Frontal lobe white matter volume was reduced in patients compared to controls (left hemisphere: 78.74±14.17 vs. 88.52±15.53, $p<0.001$; right hemisphere: 81.28±15.27 vs. 92.72±15.98, $p<0.001$). For temporal, occipital, parietal and ventricular volumes no significant differences emerged between patients and controls with the exception of parietal lobe white matter being reduced in the patients′ group bilaterally. There were no significant correlations between volumetric measurements and psychopathological symptoms on admission or remission of acute symptoms. Cerebellar changes have previously been described (Bottmer et al, in press) and support the concept of "cognitive dysmetria." Our findings regarding the frontal lobes are in line with Garver et al (2000) who found discrete volumetric alterations in the course of the disease with enlarged structures during the acute phase. Andreasen, NC et al, 1996. PNAS 93, 9985-9990 Bottmer, C et al. *Psychiatry Res: Neuroimaging*, in press Garver DL et al, 2000. *Schizophr Res* 44, 11-23 The study was supported by the Th. and V. Stanley Foundation.

STRUCTURAL BRAIN CHANGES IN PATIENTS WITH SCHIZOPHRENIA AND THEIR HEALTHY SIBLINGS: A 5-YEAR FOLLOW-UP MRI STUDY

R. Brans,* N. van Haren, W. Staal, H. Schnack, R. Kahn, H. Hulshoff Pol
Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Centre, Utrecht, Netherlands

Sibling and twin studies have revealed that genetic factors play an important role in the risk to develop schizophrenia, and are related to the brain abnormalities found in patients with this disease. Earlier we found that genetic risk factors in schizophrenia are related to decreased cerebral volume1, white matter volume2, and increased third ventricular volume1, whereas environmental risk factors may be reflected in (additional) cerebral decrease, decreased gray matter2 and increased lateral ventricular volume. Recent evidence suggests that some of the brain morphological changes in schizophrenia are progressive during the entire course of the ilness3. However, whether genetic or environmental (disease-related) factors mediate this progress, is unknown. For this purpose, we measured the extent of brain volume change in sibling-pairs discordant for schizophrenia1. Two MRI scans of the brains were obtained from eleven patients with schizophrenia, 10 same-sex siblings of patients and 22 matched healthy comparison subjects in a longitudinal study with a scan-interval of 5 years. Differences between the groups in volumes change over time, were analyzed using t-tests with a two-tailed ?-significance level. Cerebral volume decreased progressively in patients (-15.6 ml) and not in siblings (-0.8 ml) compared to healthy comparison subjects (+1.7 ml) ($t(31) = -2.05$, $p = 0.049$; $t(29) = -0.25$, p = ns). Lateral and third ventricle enlargements were found in the patients in both scans compared to their siblings and healthy comparison subjects. No significant differences or changes in time were found between the groups for any of the other brain volumes. The observed progressive decrease in cerebral volume in patients but not in their siblings, suggests that a disease related, non-genetic risk factor is involved in the progressive brain changes with age in schizophrenia. The study has limitations. The number of subjects was small and only healthy siblings were involved. Therefore, findings have to be considered preliminary and more final conclusions await larger follow-up studies in mono- and dizygotic twins discordant for schizophrenia. 1. Staal et al. *Am.J.Psychiatry*. 2000;157:416-421. 2. Hulshoff Pol, Brans et al. *Biol.Psychiatry*. 2004;55:126-130. 3. Haren van et al. 2004. This conference.

IMPROVED MR-MORPHOMETRY ANALYSIS TECHNIQUES SHOW LONGITUDINALLY NO DECREASE IN NEURONAL TISSUE IN FIRST-EPISODE SCHIZOPHRENIC PATIENTS

D. F. Braus,* W. Weber-Fahr, S. Brassen
Psychiatry, NeuroImage Nord, University of Hamburg, Hamburg, Germany

Introduction: Recent series of MRI studies revealed changes of brain structures in schizophrenic patients even over short periods. These studies have generated the discussion for a "neurodegenerative hypothesis" proclaiming a decrease in neural tissue associated with psychosis, that may be more favourably influenced by atypical antipsychotics than typical neuroleptics. Variations in MRI measurements can, however, also reflect alterations in neuronal and non-neuronal tissue compartments or physiological alterations in brain tissue (e.g. changes in tissue perfusion). Recent MRI findings that

ventricular size can alternatively increase, decrease, and then increase again in the same patients scanned repeatedly over a few months suggest that such changes may reflect physiological variations. Furthermore, based on PET-data, neuroleptics may rapidly change brain volume via changes in tissue perfusion (hyperperfusion in psychotic state, hypoperfusion under therapy). In the present longitudinal study, we focused on this question in well characterized samples using two different (both highly sensitive) types of analysis techniques: Voxel-based morphometry (VBM) (sensitive to small changes in grey matter concentration), and tensor-based morphometry (TBM) (sensitive to changes on a mesoscopic scale). Methods: Using 3D-MRI, we studied a group of 10 first-episode neuroleptic-naive schizophrenic patients (paranoid subtype) before and after at least 12 months of olanzapine treatment and 10 controls. For VBM, data were affine transformed to Talairach space and segmented using SPM02. For TBM, a highly non-linear warping algorithm was used and Jacobian images computed. Results/Discussion: In cross-section, patients differed significantly from controls before treatment with an increase in the frontal cortex and a decrease in the parietal cortex. Longitudinally, using VBM, as expected, no volume change was observed for healthy control subjects with either method. In patients, however, a significant ($p<0.05$) decrease in cortical grey matter concentration was found, most pronounced in the frontal cortex; the preexisting decrease in the parietal cortex remained stable. On the mesoscopic level, TBM showed comparable volume reduction in the frontal lobe as well as a ventricular enlargement. The normalization of a VBM increase in frontal volume in the acute state with therapy may reflect more likely changes in tissue perfusion than a neurodegenerative process.

INTERNAL CAPSULE SIZE IN GOOD AND POOR OUTCOME SCHIZOPHRENIA

A. M. Brickman,* M. S. Buchsbaum, Z. Ivanov, E. Hahn, S. A. Mitelman, E. A. Hazlett, R. E. Newmark, S. J. Lincoln, L. Shihabuddin
Taub Institute for Research on Alzheimer, Columbia University, New York, NY, USA

There has been a recent focus on defective white matter as central to the pathophysiology of schizophrenia. Reduction in the size of the anterior limb of the internal capsules (ALIC) in schizophrenia patients would suggest diminished corticothalamic and corticostriatal connectivity and would be consistent with reports of abnormalities in the striatum, thalamus, and cortex. The purpose of this study was to examine ALIC size in controls and good- and poor-outcome schizophrenia patients. Distinguishing patients by functional status has been one strategy of reducing clinical heterogeneity. A secondary goal was to examine the size of the ALIC compared to surrounding ventricular volume. 106 patients with schizophrenia or schizoaffective disorder comprised the patient group. There were 42 matched normal controls. Patients were divided into either good- (n=52) or poor-outcome (n=54) based on longitudinal analysis of self-care deficits. Participants received high resolution structural MRI with a 1.5 T Signa 5x system. The left and right ALIC were manually traced in the axial plane on 5 equidistant dorsal-to-ventral slices by placing 4 landmarks defined by striatal anatomy. The volumes of the anterior and temporal horns and lateral ventricles were determined by manual tracing. Data were analyzed with mixed-model repeated-measures ANOVA (Group x Slice Level x Hemisphere) and correlations. Controlling for total brain volume, no statistically significant effects emerged when the patient groups were considered together and compared to controls. When the patient groups were divided by outcome, the dorsal internal capsule was significantly smaller in poor-outcome patients than in good-outcome patients and controls (Group x Level, $F(2, 144)=3.15$, $p=0.046$). In controls, there were several significant negative correlations between ALIC size and volume of the anterior, temporal, and lateral ventricles. In the good outcome group, dorsal ALIC was negatively associated with anterior and lateral ventricular volume. No significant correlations with the ventricles emerged for the poor outcome group. The findings implicate abnormalities in cortical-thalamic and intrastriatal pathways particularly in poor-outcome schizophrenia. The relationship between ALIC size and ventricular volume was weaker in good-outcome patients and non-existent in poor-outcome patients, suggesting that reductions in ventricular size are independent of surrounding tissue reduction.

DIFFUSION TENSOR AND REGIONAL WHITE MATTER VOLUME IN SCHIZOPHRENIA

M. S. Buchsbaum,* A. Brickman, M. Haznedar, S. Mitelman, J. Schneiderman, L. Shihabuddin
Psychiatry, Mount Sinai School of Medicine, New York, NY, USA

We examined the structural correlates of schizophrenia in two cohorts. High-resolution anatomical and diffusion tensor MR images were acquired in adult patients with schizophrenia (n=106) and normal adult comparison subjects (n=42). Patients were divided into good-outcome (n=52) and poor-outcome (Kraepelinian, n=54) subtypes based on their ability for self-care. We also examined a subset of 37 schizophrenic adults and an additional 29 adolescents (15m, 14f, mean age=16.07, SD=2.00, range=13-21) experiencing their first psychotic episode and age and sex-matched normal adolescents (10m, 11f, mean age 16.3). Brain images were stereotaxically divided into 39 Brodmann areas and gray and white matter segmented and volumetrically quantified. Both early and late onset patients had volumetric reductions in the frontal and temporal lobe in comparison with age-matched normal volunteers. Patients with early onset schizophrenia had more marked volumetric deficits than older patients and these were most marked in the gray matter of the left temporal lobe. White matter was most decreased in the medial frontal lobe, cingulate gyrus, and frontal pole and relatively increased in other frontal and temporal areas. Diffusion tensor analysis showed lower than normal cingulate anisotropy in adults with schizophrenia but higher values than normal in adolescents with schizophrenia. A similar pattern was seen in the anterior thalamic radiations. Statistical analysis of tracts from the internal capsule to frontal regions will be presented. These data suggest that gray matter volume decrease in schizophrenia is more marked than white matter volume decrease but the white matter is more disorganized as assessed by anisotropy measures.

SCHIZOPHRENIA AND PROGRESSIVE GRAY MATTER VOLUME DECREASE DURING THE FIRST FIVE YEARS OF ILLNESS

W. Cahn,* H. E. Hulshoff Pol, N. E. van Haren, H. G. Schnack, E. Caspers, D. Laponder, R. S. Kahn
Psychiatry, UMC Utrecht, Utrecht, Netherlands

Introduction: Progressive gray matter volume decrease occurs in the (very) early course of schizophrenia. Whether this progressive decrease continues in schizophrenia is not yet known. This longitudinal MRI study examined gray matter volume changes over the first

five years of the illness. Method: Patients with first-episode schizophrenia who had taken antipsychotic medication for 0-16 weeks (n=25) and matched healthy comparison subjects (n=29) were included in the study. For all subjects MRI scans of the whole brain were obtained at inclusion (T0), after one (T1) and five years (T5). To compare between groups gray matter volume over time, multiple-repeated measures analyses of (co)variance were conducted with intracranial volume and age as covariates. In addition clinical symptoms, need of care and cumulative antipsychotic medication were related to changes in patients' gray matter volumes (T0-T5). Results: Gray matter volume progressively decreased during the first five years of schizophrenia (F=8.14, df=1,51, p=.006). This progressive decrease was mainly due to gray matter volume changes occurring between T0-T1. More negative symptoms (r=.48, df=21, p=.02), greater need of care (r=.45, df=21, p=.03) and greater amounts of antipsychotic medication taken (r=.49, df=21, p=.02) correlated with the progressive gray matter decrease. Conclusion: This suggests that progressive gray matter volume decrease occurs during the first five years of schizophrenia and is related to the illness process and to antipsychotic medication. The importance of intervening early on in the illness is underlined by our finding that the rate of gray matter decrease is the greatest in the first year.

THE EFFECT OF DELETION 22Q11 ON BRAIN ANATOMY AND BEHAVIOUR: A STRUCTURAL IMAGING STUDY OF CHILDREN WITH VELO-CARDIO-FACIAL SYNDROME (VCFS)

L. E. Campbell,* A. F. Stevens, E. M. Daly, X. Chitnis, M. Catani, R. Azuma, R. Morris, A. Karmiloff-Smith, E. Simonoff, M. J. Owen, D. G. Murphy, K. C. Murphy
Institute of Psychiatry, London, United Kingdom

Background: VCFS is a genetic disorder characterised by borderline learning disability and psychosis, and associated with variably sized deletions of 22q11.2. VCFS individuals have high rates of learning disability and psychiatric disorder e.g., schizophrenia. However, there have been few large quantitative studies of the effects of the deletion on brain anatomy and the relationship between brain and behaviour. Method: Magnetic resonance imaging of the brain was performed on a GE Signa 1.5 Tesla system to study 39 children (6-16 years) and 26 non-VCFS siblings. Pre-statistical image processing was carried out with Statistical Parametric Mapping (SPM99) software using study specific customised prior probability maps. Between-group statistical inferences of grey and white matter differences was performed using Brain Activation and Morphological Mapping (XBAMM), with an analysis of variance modelling at each intracerebral voxel. A manual tracing method (MEASURE) was used to calculate lobar and regional volumes. Post-hoc within-group correlational analyses were utilised to identify any brain-behaviour relationships. Results: Subjects with VCFS had significantly more midline abnormalities such as cavum septum pellucidum/vergae and peripheral white matter hyperintensities. In addition, they had decreased volume of posterior grey matter and indeed smaller volume of white matter in the brainstem, and bilaterally in the cerebellum, temporal, occipital and parietal lobes. The VCFS group also had increased grey matter in regions centred in the insula (bilateral) and the thalamus (bilateral). Schizotypy scores were found to have a positive association with regional grey matter volume in the temporal lobe and the basal ganglia. Conclusions: A deletion at chromosome 22q11.2 is associated with brain abnormalities, most likely neurodevelopmental in origin, which may partially explain the high prevalence of learning disability and psychiatric disorders in VCFS. In particular, a preliminary link between grey matter in the temporal lobe and the basal ganglia with schizotypy was identified. The individuals in this study are part of a longitudinal study to identify early indicators of mental health problems which may lead to early intervention and therefore (hopefully) a better outcome.

MORPHOMETRY AND THOUGHT DISORDER IN PEDIATRIC EPILEPSY

R. Caplan,* P. Siddarth, D. Ott, J. Levitt, R. Tenorio, S. Gurbani, R. Sankar
Child Psychiatry, UCLA NPI, Los Angeles, CA, USA

This study examined morphometric measures associated with thought disorder in children with epilepsy and normal childrenand the relationship with seizure, cognitive, linguistic, and demographic variables in the epilepsy group. A structured psychiatric interview, as wll as cognitive, linguistic, and thought disorder testing were administered to 32 complex partial seizures, 11 childhood absence epilepsy, and 21 normal children, aged 6.6-14.0 years. Parents provided demographic and seizure information. Frontal and temporal lobe volumes were measured in both hemispheres using high-resolution magnetic resonance imaging. Controlling for differences in IQ, language, and demographic variables, the epilepsy group had significantly smaller anterior hippocampus ($p<.0001$), but no significant differences in total brain, frontal lobe parcellations, superior temporal gyrus (STG), and Heschl's gyrus volumes than the normal group. ANCOVA of fronto-temporal volumes demonstrated a diagnosis x thought disorder interaction with a negative and significant relationship in the normal but not the epilepsy group between left inferior frontal gyrus (IFG) gray and white matter volumes, anterior hippocampus volumes, and formal thought disorder ($p<.04$); bilateral IFG and DLPFC gray and white matter volumes and impaired repair of errors in organizing thoughts ($p<.04$); left IFG, DLPFC, and STG gray matter volumes and poor revision of linguistic errors ($p<.003$); and a trend between bilateral IFG and DLPFC volumes and under use of cohesive ties to connect ideas across sentences ($p< .1$). A principal components analysis of seizure variables yielded four components. An onset/duration component was significantly associated with smaller total brain, white matter, and posterior hippocampus volumes ($p<.01$); an EEG component with reduced total brain, gray and white matter, STG, and anterior hippocampus volumes ($p<.05$); a seizure frequency/antiepileptic drugs component with decreased DLPFC gray and white and STG gray matter volume ($p<.02$); and a status epilepticus/febrile convulsions component with decreased IFG volumes ($p<.02$). Ethnicity ($p<.04$) and socioeconomic status ($p<.04$) were significantly related to volumes of total brain, gray and white matter, and DLPFC. These findings imply direct and cumulative effects of seizures on the development of brain regions involved in organizing and processing thoughts. NIMH R01 MH067187.

STRUCTURAL MRI BRAIN FINDINGS IN A GENETIC SUBTYPE OF SCHIZOPHRENIA

E. W. Chow,* J. Logan, R. B. Zipursky, D. J. Mikulis, A. S. Bassett
Clinical Genetics Research Program, Centre for Addiction and Mental Health, Toronto, ON, Canada

Background: In schizophrenia, common brain findings include ventricular enlargement and decreased gray matter volumes. Schizophrenia associated with 22q deletion syndrome (22qDS-SZ) is a

genetic subtype of schizophrenia which may be a good neurodevelopmental model for the psychotic illness. We have previously reported on significantly increased lateral ventricular volumes and decreased grey matter volumes in 22qDS-SZ compared to healthy controls (Chow et al., 2002) Objective: To assess brain volumes in adult patients with 22q deletion syndrome (22qDS) using magnetic resonance imaging (MRI). Method: 19 adults with 22qDS-SZ (mean age=28.1 y, SD=5.9; 9 male, 10 female), 19 adults (mean age=25.1 y, SD=9.8; 8 male, 11 female) with 22qDS and no history of psychosis had MRI scans of the brain according to a research protocol. Scans were analysed quantitatively using Brain Image (Reiss et al., 1995) software to derive ventricular volumes, whole brain and lobar cerebrospinal fluid (CSF), gray matter(GM), and white matter (WM) volumes. Results: The two groups did not differ in sex, age, IQ, height, and total intracranial volumes(ICV). The groups, however, differed significantly ($p<0.05$) in total and left lateral ventricular volumes and on all whole brain and regional CSF volumes. Significant differences in GM volumes were also found in whole brain, left brain, right brain, frontal and temporal lobes. There were no group differences in whole brain, right brain, left brain, frontal and temporal lobe WM volumes, but significant differences were detected in parietal and occipital lobe WM volumes. Conclusion: The differences in brain volumes on MRI in 22qDS adults with and without schizophrenia share similarities with reported differences between patients with schizophrenia and healthy controls in the general population. These MRI findings support 22qDS-schizophrenia as an etiologic subtype of schizophrenia and as an appropriate model for a neurodevelopmental hypothesis of schizophrenia.

HIPPOCAMPAL VOLUME AND SHAPE IN SCHIZOPHRENIA SUBJECTS AND THEIR UNAFFECTED SIBLINGS

J. G. Csernansky,* L. Wang, P. A. Thompson, M. I. Miller
Psychiatry, Washington University School of Medicine, St. Louis, MO, USA

Structural features of the hippocampus appear to be heritable and abnormal in schizophrenia. In the present study, we used high-resolution magnetic resonance imaging and large-deformation high-dimensional brain mapping to quantify the volume and shape of the hippocampus in 21 subjects with schizophrenia, 18 of their unaffected siblings, 21 healthy controls and 20 of their siblings. The effect of diagnosis on hippocampal volume was significant ($F = 3.59$, $df = 3,76$, $p = .018$) and the ordering of groups was schizophrenia subject < unaffected sibling of schizophrenia subject < sibling of control subject = control subject. A post-hoc, between-group comparison of the unaffected siblings of the schizophrenia subjects and the siblings of the controls ($p=.048$) was significant. To compare hippocampal shape across the four groups, we applied a statistical model developed to discriminate schizophrenia subjects and healthy controls in a prior study (Csernansky, et al, 2002) (i.e., coefficients associated with shape eigenvectors in the prior study were used to compute log-likelihood ratios for the subjects in this study). Schizophrenia subjects ($p<.0001$) and the unaffected siblings of schizophrenia subjects ($p<.0001$) were discriminated from the controls, but there was no difference between the current samples of schizophrenia subjects and their unaffected siblings ($p=.84$). A discriminant function solution using the same eigenvector coefficients ordered the groups as follows: schizophrenia subjects = -.20; unaffected siblings of the schizophrenia subjects = .39; siblings of the controls = .58; controls = .72). Thus, the unaffected siblings of the schizophrenia subjects had shape values there were intermediate between the schizophrenia subjects and the two control groups. For left hippocampal volume, the between-sibling correlation was .02 (pNS) in the schizophrenia sibling pairs and .44 ($p=.10$) in the control sibling pairs. For right hippocampal volume, the between-sibling correlation was .38 ($p=.13$) in the schizophrenia sibling pairs and .55 ($p=.03$) in the control sibling pairs. Among the first ten eigenvectors representing hippocampal shape in the four groups of subjects, eigenvector 7 was nearly correlated in the control sibling pairs ($r=.43$, $p=.10$), but not in the schizophrenia siblings pairs. Thus, the presence of schizophrenia as a disease disturbed normative correlations in measures of hippocampal structure between related individuals.

PROGRESSIVE STRUCTURAL BRAIN CHANGE IN THE 10 YEARS SUBSEQUENT TO A FIRST EPISODE OF SCHIZOPRENIA: CORE PATHOLOGY OR EPIPHENOMENON?

L. E. DeLisi,* A. L. Hoff
Psychiatry, New York University, New York, NY, USA

Ventricular enlargement, presumably indicative of cortical tissue reduction, has been reported in patients with chronic schizophrenia since the early pneumoencephalographic literature, then later by CT and MRI. Currently results from several MRI longitudinal follow-up studies have been reported. While ventricular enlargement appears to be present at the first episode, ventricles also continue to enlarge after the 1st episode as well as after chronicity has set in. Regardless of when in the course of illness patients are examined, it is detected during relatively short time intervals. Similarly, decreases in frontal and temporal lobe, hippocampus and STG volumes have been reported over short time intervals, but these data are so far not consistently replicated across studies. The project reported here was a much longer follow-up study of patients and controls for 10 years subsequent to a first episode of schizophrenia. 50 patients and 20 controls were available for a 5 year follow-up, while 27 of the patients and 10 of the controls were available at 10 years for complete evaluations. All, however, were available for clinical follow-up at 10 years. 4 of the 50 had suicided. Ventricular enlargement continued throughout the 10 year period in approximately 1/3 of the patients while no indication of temporal lobe changes occurred. Verbal and non-verbal memory also declined over that time period in comparison to controls. However, there was no correlation of cognitive decline with structural brain change and no correlations to clinical status. We conclude that these structural changes seen in chronic patients are likely due to a progressive process that varies in timing among individuals, but is not likely to be neurodevelopmental, although other signs of early brain developmental anomalies can be detected, such as reduced brain lateralization. The lack of clinical correlation suggests that many of the changes seen may be epiphenomenon due to physiological changes unrelated to the psychotic illness or perhaps due to medication. Future genetic examinations, however, may implicate a phenotype with progressive brain structural change.

ALTERATIONS IN THE BALANCE OF GRAY AND WHITE MATTER IN THE BRAINS OF YOUNG FIRST-EPISODE SCHIZOPHRENIA PATIENTS

V. A. Diwadkar,* M. Vemulapalli, D. M. Montrose, M. S. Keshavan
Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

Brain organization results from a complex schedule of genetically programmed neurodevelopment and environmental interaction.

Healthy development results in an "optimal" balance in gray and whilte matter designed to minimize energy consumption and maximize connective efficiency. A characteristic of development is programmed loss of cortical gray matter (synaptic pruning) during adolescence in conjunction with an expansion of white matter enhancing inter-regional connectivity. The global organization of the cortical neural network is reflected in measures such as the ratio of brain gray matter to white matter (GM/WM) which can be estimated using *in vivo* high-resolution MRI images. Abnormal neurodevelopment associated with neuropsychiatric illnesses such as schizophrenia is likely to alter GM/WM. This study assessed possible changes in GM/WM in the brains of first-episode schizophrenia patients. In order to capture abnormal neurodevelopment, as opposed to neurodegenerative processes that might be associated with the illness, the analysis was restricted to young (age≦25) first-episode schizophrenia patients with little or no neuroleptic exposure. We analyzed *in vivo* structural MRIs of healthy controls (HC; n=79, mean age=18.5 yrs, 43 males) and first-episode schizophrenia patients (FE; n=61, mean age=19.4 years, 42 males) (all subjects aged 8-25). Total brain gray and white matter was estimated following segmentation using SPM2b. An analysis of covariance (with age and gender as covariates) revealed a significant reduction in GM/WM in FE subjects (1.80 < 1.89), $F_{1,136}$=5.30, p<.02, MSerror=.019. Trend analyses were conducted to explore non-linear relationships between age and GM/WM in each group separately. In HC, a decrease in GM/WM in HC in childhood and adolescence was observed, followed by a plateauing in young adulthood. An articulated developmental trend was absent in FE. The results suggest schizophrenia is marked by a significant reduction in GM/WM, consistent with documented reductions in heteromodal GM in the illness. These results expand upon previous findings in older, chronic male schizophrenia samples. They suggest that the alterations in the balance of brain organization may be present at the earliest stages of the illness, consistent with neurodevelopmental hypotheses of schizophrenia. They also suggest that schizophrenia may be expressed as a disorganization of the global brain network as opposed to abnormalities in focal cortical regions.

VOLUME OF THE THALAMUS IN MONOZYGOTIC TWINS WITH SCHIZOPHRENIA: A MAGNETIC RESONANCE IMAGING STUDY

U. Ettinger,* M. Picchioni, M. H. Hall, K. Matsumoto, T. Toulopoulou, N. Davies, R. M. Murray
Division of Psychological Medicine, Institute of Psychiatry, London, United Kingdom

Abnormalities of the thalamus have been proposed to underlie the pathophysiology of schizophrenia. A number of structural magnetic resonance imaging (MRI) studies have demonstrated thalamic volume reductions in schizophrenia patients as well as their biological first-degree relatives. Here we report results from an ongoing structural MRI investigation of thalamic volumes in monozygotic (MZ) twins with schizophrenia. Participants include 18 pairs (15 male, 3 female) of MZ twins concordant for a DSM-IV diagnosis of schizophrenia (age mean=36.04 years, SD=9.20) and 5 pairs (3 male, 2 female) of MZ control twins without a diagnosis of schizophrenia (age mean=30.37 years, SD=6.57). All participants underwent structural MRI at 1.5T. Thalamic volumes were calculated based on stereological principles using semi-automated techniques. Preliminary analyses indicate that MZ concordant twins had reduced thalamic volume (all volumes in cm3) (mean=9.85; SD=1.09) when compared to non-schizophrenic MZ control twins (mean=10.77; SD=1.22), with a large effect size (Cohen's d=0.82). Intraclass correlation (ICC) coefficients for thalamic volume were ICC=0.29 for concordant pairs and ICC=0.85 for control pairs. These findings are compatible with previous reports of thalamic volume reductions in patients with schizophrenia. Twin pair correlations suggest an erosion of phenotypic similarity amongst schizophrenic twins.

IS FRONTAL HYPERGYRIFICATION SPECIFIC TO SCHIZOPHRENIA? A COMPARISON BETWEEN BIPOLAR DISORDER, OBSESSIVE COMPULSIVE DISORDER, AND SCHIZOPHRENIA

P. Falkai,* W. G. Honer, T. Schneider-Axmann, T. Wobrock, S. Denter, S. Kraft, H. Scherk, T. Kamer, O. Gruber, M. Backens, W. Reith
Psychiatry and Psychotherapy, Saarland University Hospital, Homburg/Saar, Germany

Introduction: Recently several groups including ourselves revealed dysgyrification in schizophrenia. More specifically we were able to find frontal hypergyrification in a post-mortem and a large family-based MRI sample. In order to examine whether these changes are specific to schizophrenia, we have determined the Gyrification Index (GI) in the MRI scans in a cohort of 69 subjects including three different disorders. Sample description: The sample consisted of 22 control subject (9 males, 13 females, mean age 30 years), 12 first break schizophrenic patients (7 males, 5 females, mean age 34 years), 14 patients with bipolar disorder (6 males, 8 females, mean age 44 years) and 21 patients with obsessive compulsive disorder (OCD) (6 males, 15 females, mean age 32 years). Methods: Analysis of covariance (ANCOVA) was used to compare GIs between the diagnostic groups. The model was adjusted for factors sex and hand preference and covariates age, height and years of education. The frontal gyrification index (GI), the ratio of inner and outer surface contours, was measured bilaterally in three different slices from each brain. An asymmetry coefficient of the GIs ((right - left) / (right + left)) was calculated. Results: There was a bilateral GI increase in schizophrenic patients compared to controls (6 - 7%, p<0.046), patients with bipolar disorder (5 - 6%, p<0.036) and patients with obsessive compulsive disorder (OCD) (5 - 6%, p<0.007). There were no significant differences between the non-schizophrenic diagnostic groups, showing mean GI values that were nearly on the same level. Between all diagnostic groups there were no significant differences for the GI asymmetry coefficient. Discussion: Taking the limitations of the sample, especially size, into account the data seems to demonstrate that frontal hypergyrification is specific to schizophrenia and can not be found in bipolar or obsessive compulsive disorder. This is further evidence for a neurodevelopmentally acquired lesion in the frontal lobe in schizophrenia.

MANCOVA (Diagnosis Group x Sex x Hand Preference; Covariates Age, Height, Education)

LEFT TEMPORAL LOBE ABNORMALITIES IN PATIENTS WITH SCHIZOPHRENIAL-LIKE PSYCHOSIS AND TEMPORAL LOBE EPILEPSY USING MAGNETIZATION TRANSFER IMAGING

D. Fluegel,* M. Cercignani, M. Symms, M. J. Koepp, J. Foong
Experimental and Clinical Epilepsy, The National Hospital of Neurology and Neurosurgery, Queen Square, London, United Kingdom

Chronic interictal psychosis has been reported in 4-10% in patients with epilepsy and appear to be more often associated with temporal lobe epilepsy. The clinical symptoms of interictal psychosis closely resemble those in primary schizophrenia. However, the underlying pathological mechanisms in schizophrenia-like psychosis have not been fully determined and both focal or widespread brain changes have been reported. Magnetization transfer imaging (MTI) is known to be more sensitive than conventional MRI in detecting subtle structural brain abnormalities. This technique provides a measure of the macromolecular structural integrity in tissue which is represented by the Magnetization Transfer Ratio (MTR). In a previous MTI investigation of patients with chronic schizophrenia, widespread cortical MTR reductions, predominantly in the fronto-temporal regions were detected (Foong et al, 2001). Our current study sought to determine whether subtle structural brain abnormalities in patients with schizophrenia-like psychosis and temporal lobe epilepsy are similar to those reported in patients with chronic schizophrenia. We compared 20 patients with temporal lobe epilepsy and schizophrenia-like psychosis to 20 age-matched patients with temporal lobe epilepsy and no psychosis. In each group of patients, there were 10 with no focal lesions, 6 with left hippocampal sclerosis and 4 with right hippocampal sclerosis on conventional MRI. A voxel-based analysis revealed significant reductions of MTR in the left superior and middle temporal gyrus in the subgroup of 10 psychotic patients without focal lesions when compared to the non-psychotic patients. The MTR reductions could not be attributed to volume reductions. There were no significant MTR changes between the psychotic and non-psychotic patients with hippocampal sclerosis. This study has demonstrated that focal MTR abnormalities can be detected in the left temporal lobe in some patients with schizophrenia-like psychosis and temporal lobe epilepsy. Our findings are in contrast to the widespread cortical MTR reductions previously reported in patients with chronic schizophrenia which suggests that the underlying neuropathological abnormalities in interictal psychosis may differ from those in chronic schizophrenia.

PROGRESSIVE CHANGES IN THE CORTICO-CEREBELLUM-THALAMIC-CORTICAL CIRCUITRY IN EARLY-ONSET SCHIZOPHRENIA

S. Frangou,* M. Hadjulis, J. Suckling, J. Jogia, E. Bullmore
Section of Neurobiology of Psychosis, Institute of Psychiatry, London, United Kingdom

AIMS: As part of the Maudsley Early Onset Schizophrenia (EOS) study we examined longitudinal changes in the brain of individuals with EOS (onset before the age of 17) patients. A previous longitudinal study of a similar cohort examined cortical gray matter only and showed volume loss in prefrontal and temporal regions. Our aim was to confirm these findings and extend them to subcortical regions. METHODS: Three-dimensional T1-weighted high-resolution, whole brain scans were acquired twice separated by a mean period of years 3.85 (1.4) years from 21 EOS patients and 21 yoked healthy volunteers on a 1.5T Signa Scanner. Data were segmented into component tissues with SPM2. Differences were located using both image data and regional volumes measured relative to a parcellation of standard space. RESULTS: Patients' mean age at baseline was 15.7 (1.3) and 19.8 (1.5) at follow-up. Both patients and controls showed changes over time. Compared to controls, significant reduction over time was observed in patients bilaterally in the dorsal and ventral prefrontal cortex, the superior parietal cortex, the middle and inferior temporal gyrus as well as the thalamus and cerebellum. Left-sided reductions were observed in the anterior cingulate and paracingulate gyrus, cuneus and pre-cuneus and the superior temporal gyrus. CONCLUSIONS: Our results confirm progressive gray matter loss in EOS in prefrontal and temporal regions and further indicate that subcortical regions including the thalamus and cerebellum are also implicated. Our results also suggest that there are progressive changes in the cortico-cerebellum-thalamic-cortical circuitry during the early phases of schizophrenia that could contribute to cognitive and psychosocial deficits.

A MAGNETIZATION TRANSFER IMAGING STUDY OF SCHIZOPHRENIA

J. I. Friedman,* C. Y. Tang, J. Celestin, D. G. Stewart, M. Buchsbaum, P. D. Harvey, J. G. Gorman, K. L. Davis
Psychiatry, Mt. Sinai School of Medicine, New York, NY, USA

Introduction: Convential MRI studies have demonstrated modest reductions of white matter volume in the brains of schizophrenic patients. Newer techniques such as magnetization transfer imaging (MTI) extends our understanding of these white matter deficits from merely assessing volumetric loss to providing evidence for reductions in myelin content/integrity. However, studies employing this technique in schizophrenia are lacking. Methods: 60 schizophrenic patients between the ages of 20-80, equally represented across this age span, were compared to 60 age and gender matched healthy comparison subjects on measures of regional magnetization transfer ratio (MTR) measures. First, structural scans for morphological analysis were acquired. Then, magnetization transfer imaging was performed using a turbo spin echo sequence (TR=700ms, TE=12ms, FOV=21cm, Matrix=256x256, 28 slices, thickness=3mm skip 1mm). Results: To date, imaging data has been processed for 30 schizophrenic patients (mean age = 43 years, 77% male) and 21 healthy comparison subjects (mean age = 49 years, 57% male). The schizophrenic subjects demonstrated significantly lower MTR in the left frontal ROI ($p = .03$) and trend decreases in the left occipital ROI ($p = .07$). Further, there were significant age related correlations with MTR in the healthy controls in the left medial temporal ($r=-.54$), left frontal ($r=-.40$), left occipital ($r=-.40$), and right occipital($r=-.44$) ROIs. However, schizophrenic subjects demonstrated no such correlations. Conclusions: These prelimary data are suggestive of decreased myelin content/integrity in the brains of schizophrenic patients. Moreover, the negative linear relationship between age and MTR appears disturbed in schizophrenic patients.

AUTOMATIC PIPELINE FOR QUANTITATIVE BRAIN TISSUE SEGMENTATION AND PARCELLATION: EXPERIENCE WITH A LARGE LONGITUDINAL SCHIZOPHRENIA MRI STUDY

G. Gerig,* S. Joshi, D. Perkins, R. Steen, R. Hamer, J. Lieberman
Computer Science, UNC Chapel Hill, Chapel Hill, NC, USA

Introduction: Quantitative large-scale imaging studies require processing pipelines that are mostly automatic, reliable, generic in regard to differences in imaging protocols, and rigorously tested for reproducibility. Such software, if distributed to other sites, could help with cross-validation of results obtained at other various sites and thus meet concerns in regard to processing-specific results. We have developed software within the open-source Insight Toolkit (ITK, National Library of Medicine), that includes registration to standard coordinates, brain tissue segmentation, inhomogeneity correction, brain stripping, and brain lobe parcellation. Methods: An ITK implementation of automatic brain segmentation from multi-modal MRI has been combined with a brain parcellation based on template deformation. This results in an automatic pipeline for efficient processing of large image databases to provide reliable estimates of gray matter, white matter and cerebrospinal fluid. A parcellation template is obtained by an expert's parcellation of an average MRI image. This template is deformed to each subject's MRI by diffeomorphic large scale registration. We applied this new method to a large first-episode longitudinal schizophrenia study with 91 FE patients and 37 controls at baseline and 48 patients and 26 controls at 6 month follow-up. All MRI was performed on a 1.5T GE Signa, using T1-w gradient echo and dual-echo T2w/PDw spin-echo protocols. Results: Reliability of tissue segmentation was tested on data from a multi-site reliability study with the same subject imaged at 5 sites two times. Reproducibility of full brain tissue volumes were below 1%, demonstrating the excellent stability of segmentation. Reliability of the parcellation was tested with two cross-validation studies using two manually parcellated templates and qualitative assessment by three experts. Conclusions: Validation of the automatic brain processing pipeline demonstrated its excellent reproducibility and performance. The resulting gray, white matter and cerebrospinal fluid volumes for each sub-parcellation extends statistical analysis of a single tissue class to explaining local loss and growth in relationship to the changes of other tissue classes, a property that is essential for follow-up studies. Standardization of software and potential for distribution to other sites will be valuable to confirm results and to do cross-center validation.

SHORT-TERM EFFECTS OF TYPICAL AND ATYPICAL ANTIPSYCHOTIC MEDICATION ON CAUDATE NUCLEUS VOLUME IN FIRST-EPISODE SCHIZOPHRENIC PATIENTS: RELATION TO DOPAMINE D2/3 RECEPTOR OCCUPANCY PSYCHOPATHOLOGY AND EXTRAPYRAMIDAL SIDE-EFFECTS

B. Y. Glenthoj,* K. Pagsberg, A. Glenthoj, E. Jagersma, R. Hemmingsen, C. Videbaek, C. Svarer, W. Baare
Center for Neuropsychiatric Schizophrenia Research, Dept. of Psychiatry E, University of Copenhagen, Bispebjerg Hospital, Copenhagen, Denmark

Objective: Caudate nucleus enlargement has been consistently observed in schizophrenic patients treated with typical antipsychotics whereas the results following treatment with atypical compounds are equivocal. The differential responses have been ascribed to differences in D2 receptor blockade. Longitudinal studies directly comparing the effects of specific typical and atypical antipsychotics on caudate volume in the initial treatment phase of randomized drug-naive patients are lacking and so are studies relating volume changes to D2 receptor occupancy. Hypotheses: 1. Brief exposure to a typical, but not an atypical compound leads to increased caudate nucleus volume in drug-naive first-episode patients. 2. Increases are related to D2/3 receptor occupancy. Method: Nineteen drug-naive first-episode schizophrenia patients were randomly allocated to treatment with either low doses of the typical drug zuclopenthixol or the atypical compound risperidone. SPECT scans were performed using a Tomomatic 232 scanner and the D2/D3-receptor ligand 123I-epidepride. Occupancy was calculated from scans of patients after 3 months of treatment. Caudate nucleus was manually traced on high resolution MRI-scans before and after 12 weeks of exposure to medication by a single rater blind to subject identification, time of scan and brain hemisphere. Results: Mean daily dose of zuclopenthixol was 10.3 mg/day (comparable to haloperidol 3.4 mg/day) and mean daily dose of risperidone was 3.4 mg/day. A significant main effect for Time ($F1,17 = 4.39$; $p < 0.05$) and Time x Group interaction ($F1,17 = 4.95$; $p < 0.04$) was evident, with caudate nucleus volume being larger at follow-up compared to baseline only in the zuclopenthixol treated group. Data on caudate D2/3 receptor occupancy will be presented at the meeting. No differences were observed between groups in extrastriatal areas. Conclusions: The main finding was the demonstration of changes in caudate nucleus volume in drug-naive first-episode schizophrenia patients after only three months of treatment with low doses of the typical antipsychotic compound zuclopenthixol, whereas no volume change was found after treatment with the atypical drug risperidone. The relation of volume changes following antipsychotic treatment to D2/3 receptor occupancy is currently being investigated and will be presented at the meeting.

MRI OF PREFRONTAL CORTEX IN THE HEALTHY RELATIVES OF SCHIZOPHRENIA PATIENTS AND CONTROLS

V. Goghari,* K. Rehm, C. S. Carter, A. W. MacDonald
Psychology, University of Minnesota, Minneapolis, MN, USA

Schizophrenia is hypothesized to be associated with functional and structural abnormalities of the prefrontal cortex. We have previously reported dysfunctional prefrontal cortex activation in never medicated first-episode schizophrenia patients (MacDonald et al., in press, *Am J Psychiatry*) and their healthy relatives (MacDonald et al., 2003, *Schiz Res*, 60 (Supplement): 228). This study attempted to expand those findings by investigating prefrontal cortical structure in healthy relatives of schizophrenia patients. Measurements were acquired from SPGR structural scans (3T, 1.5 mm thickness) for healthy relatives (n=16) and demographically similar healthy comparison subjects (n=14). Gray matter, white matter, and cerebrospinal fluid volumes were acquired for the total brain and prefrontal cortex. Preliminary analyses were restricted to total brain gray, white, and cerebrospinal fluid volumes. A MANCOVA revealed no significant effect of group, covarying for age and gender. Individual ANCOVAs revealed no significant effect of group on gray matter ($F(1, 25)=1.76$, $p=0.20$; Cohen's $d=0.18$), white matter ($F=(1,25)=0.36$, $p=0.55$; Cohen's $d=0.06$), and cerebrospinal fluid ($F(1,25)=0.63$, $p=0.43$; Cohen's

d=0.20) covarying for age, gender, and total brain volume. However, structural abnormalities associated with the general liability to schizophrenia may be specific rather than global. This suggests further analysis of the prefrontal cortex may show larger effects, and may allow for replication of previous findings of reduced gray matter and increased cerebrospinal fluid in healthy siblings of schizophrenia patients (Cannon, et. al., 1998, *Arch Gen Psychiatry*, 55: 1084-91). We gratefully acknowledge the support of University of Minnesota Graduate Research Partnership Grant and NIMH. We thank Eric Peterson, David Rottenberg, Stephen Malone, Kristi Boesen, and Kirt Schaper for their technical assistance.

DYNAMIC MAPPING OF CORTICAL BRAIN DEVELOPMENT IN PEDIATRIC BIPOLAR ILLNESS

N. Gogtay,* A. E. Ordonez, D. H. Herman, J. N. Gied, K. M. Hayashi, D. Greenstein, C. Vaitiuzis, T. F. Nugent, L. Clasen, P. M. Thompson, J. L. Rapoport
Child Psychiatry, NIMH, Bethesda, MD, USA

We report the first quantitative time-lapse movie of cortical development in pediatric bipolar illness, reconstructed from serial brain MRI scans of children with psychosis NOS who became bipolar I at 2-8 year prospective follow up. Prior MRI studies of gray matter (GM) changes in Bipolar Illness have shown inconsistent results with side to side differences although majority point to the abnormalities in fronto-striato-limbic circuitry. There are no longitudinal studies in pediatric mood disorders. Applying novel cortical pattern matching algorithms to longitudinal brain MRI scans obtained before and after the onset of Bipolar I illness, we have created 3-D time lapse sequence of cortical development in the Bipolar I Illness. Twenty-four 3D (1mm isotropic) T1-weighted fast SPGR MRI scans were acquired from 7 children and adolescents, scanned repeatedly every 2 years, before and after the onset of bipolar illness, and compared with 42 scans from 14 age and sex matched healthy controls prospectively scanned at same time points. 3D cortical surface models were extracted from spatially registered, tissue-classified scans and 38 sulcal curve landmarks were delineated on each brain hemisphere. For both groups, 3D maps localizing brain changes were derived using high-dimensional elastic deformation mappings to match gyral anatomy across subjects and time. A quadratic statistical model, with random effects, was fit to the profile of gray matter density against time, at each of 65,536 cortical points. Ratio maps of GM density of bipolar subjects over healthy controls were created and animated to create a time-lapse movie. This revealed significant regional GM change across the brain surface in bipolar subjects with side to side differences. The prefrontal cortical regions, temporal poles and inferior parietal cortex on the left side appeared to enlarge with the onset of bipolar illness, while these regions on the right side showed reduction in GM volume. The anterior and subgenual cingulate cortices also showed GM loss prominently on the right side. These heterochronous GM changes in bipolar illness may be attributable to disease pathology and/or medication effect.

HYPOTHALAMIC ABNORMALITIES IN SCHIZOPHRENIA: SEX EFFECTS AND GENETIC VULNERABILITY

J. Goldstein,* L. J. Seidman, N. Makris, T. Ahern, L. M. O'Brien, V. S. Caviness, D. N. Kennedy, S. V. Faraone, M. T. Tsuang
Harvard Medical School Department of Psychiatry at Massachusetts Mental Health Center, Massachusetts General Hospital (MGH), Athinoula Martinos Center for Biomedical Imaging at MGH, Boston, MA, USA

There is little current work examining the hypothalamus in schizophrenia. However, the hypothalamus is a critical brain region in the control of appetitive drives, affect, the reward system, and endocrine control, functions that go awry in schizophrenia. Further, studies have shown that particular hypothalamic nuclei are the most highly sexually dimorphic in the brain, primarily significantly larger in males. To our knowledge, this is the first MRI-based study that tested the hypothesis that there were hypothalamic volumetric abnormalities in schizophrenia. As we demonstrated with other normally sexually dimorphic brain regions, we predicted abnormal sexual dimorphism in the hypothalamus. We further tested the hypothesis that abnormalities would be more severe in multiplex (i.e. cases with more than one family member with schizophrenia) than in simplex cases, in which there is only one ill family member. Finally, we hypothesized these abnormalities were not due to medication use, but were part of the vulnerability to schizophrenia, thus present in nonpsychotic first-degree relatives of patients. A general linear model for correlated data (GLM-CD) and generalized estimating equations (GEE) were used to compare groups and sex on right and left hypothalamus, controlled for age and total cerebral volume. Structural MR images from which the hypothalamus was segmented came from 88 DSM-III-R schizophrenia cases (40 simplex and 48 multiplex), 43 first degree nonpsychotic relatives of cases, and 48 normal comparisons. Findings demonstrated significantly increased hypothalamic volume in cases and nonpsychotic relatives, particularly arising from paraventricular (PVN) and mammillary body (MB) nuclei, respectively, increases that were linear from simplex to multiplex family subjects, positively correlated with anxiety, and had a greater propensity in female cases. Our findings of increased hypothalamic volume, particularly around the PVN and MBs, in cases and relatives, have important implications for understanding the genetic vulnerability and the high rate of endocrine disorders in schizophrenia, given the critical roles of the PVN & MB in the HPA axis, stress response and endocrine function. Findings from our fMRI study of aversive affective arousal in normals, demonstrating increased activity in PVN with arousal, illustrate one of the functional roles of the PVN and suggest implications for dysregulation of arousal in schizophrenia.

PHYSIOLOGICAL CORRELATES OF BRAIN MORPHOLOGY IN PATIENTS WITH SCHIZOPHRENIA AND HEALTHY COMPARISON SUBJECTS

H. Gunduz-Bruce,* K. L. Narr, R. L. Gueorguieva, A. W. Toga, P. R. Szeszko, M. Ashtari, D. G. Robinson, J. M. Kane, R. M. Bilder
Psychiatry, Yale University School of Medicine, New Haven, CT, USA

Background: Serum Na level and osmolality may have acute effects on brain morphology, such as the lateral ventricle size; the most replicated structural abnormality in schizophrenia. Because patients with

schizophrenia often suffer from poor hydration, we investigated the relationship between serum Na level, osmolality and brain morphology in patients with first episode schizophrenia and healthy controls. Methods: Twenty nine patients and 28 healthy controls completed a baseline MRI session and gave blood sample. High-resolution 3D SPGR images were obtained on a GE 1.5 Tesla scanner as a series of 124 contiguous 1.5 mm coronal brain slices. Scalp-edited MRI volumes were used for estimates of intracranial gray, white matter and sulcal CSF. Results: Patients had significantly higher serum Na levels (t=5.11, df=53, p<0.0001), and osmolality (t=2.36, df=28, p=0.025) compared to healthy controls. CSF volumes did not differ between groups when intracranial content, age and sex were used as covariates (F=1.02, df=1, 52, p=0.31). No differences were found between groups in gray matter volumes. There were no significant correlations between Na or osmolality and the brain volume measures. However, by using voxel based morphometry, localized differences in sulcal CSF bilaterally around the temporal lobes and inferior frontal areas were detected. Moreover, these increases were associated with serum Na levels in the patient group. Conclusions: Patients presented with increased Na and serum osmolality. These increases were associated with localized volumetric differences bilaterally around the temporal and frontal lobes. Further analyses will extend these investigations to other compartments of CSF. These results may indicate a need for controlling for serum Na levels in brain morphology studies.

ANTERIOR AND POSTERIOR CINGULATE GRAY MATTER VOLUME IN SCHIZOTYPAL AND BORDERLINE PERSONALITY DISORDERS

E. Hazlett,* M. S. Buchsbaum, A. S. New, L. J. Siever
Neuroscience P.E.T. Laboratory, Mount Sinai School of Medicine, New York, NY, USA

Structural abnormalities in prefrontal and cingulate gyrus regions-important in affective processing and cognition may contribute to pathology in cognitive and affective evaluation, implicated in the psychopathology of schizotypal personality disorder (SPD) and borderline personality disorder (BPD) respectively. Previous MRI studies from our laboratory examing volume have demonstrated that compared with healthy controls, temporal volume is reduced in both SPD and schizophrenia patients while frontal lobe volume is reduced in schizophrenia, but not SPD. We extended this investigation by examining gray and white matter volume of frontal and cingulate gyrus Brodmann areas (BAs) in 3 groups of age- and sex-matched participants: patients comorbid for BPD and SPD, patients with BPD but not SPD, and healthy controls. MRI scans were acquired and gray/white matter volume in individual BAs within the cingulate gyrus, anterior, medial, dorsolateral, and orbital frontal lobe were assessed. The BPD without SPD subgroup had isolated gray matter volume loss in BA 24 in comparison with controls, but were spared for BA 31 in contrast to the BPD subgroup with SPD, suggesting anterior cingulate involvement in the affective dysregulation of BPD and posterior involvement with the additional cognitive impairment of SPD. There were no significant group differences in total frontal lobe volume. The finding of more pervasive cingulate shrinkage (BA 24 and 31) in the patients with a comorbid diagnosis of BPD and SPD resembles recent observations with the same methods in patients with schizophrenia. The pattern of reduced anterior and posterior cingulate gray matter volume in BPD patients, in particular those comorbid for SPD is consistent with the affective and attentional deficits observed in these personality disorders. Data for a group of patients with SPD, but not BPD will also be presented.

3 DIMENSIONAL MORPHOMETRIC STUDY OF CRANIOFACIAL DYSMORPHOLOGY IN SCHIZOPHRENIA: ANALYSIS OF THE FACIAL SURFACE

R. J. Hennessy,* A. Kinsella, P. Baldwin, J. L. Waddington
Department of Clinical Pharmacology, Royal College of Surgeons in Ireland, Dublin, Ireland

Craniofacial dysmorphology has been proposed as a marker of cerebro-craniofacial dysmorphogenesis in psychotic illness. Geometric morphometrics applied to 3D data allows patient-control differences to be tested with robust statistical analysis and visualised with dynamic 3D graphics. For optimal biological interpretation, dysmorphology over the entire facial surface should be interrogated. Described here are analyses of high resolution facial surface scans, consisting of ~100,000 3D coordinates, recorded with a handheld laser scanner. The sample was 69 patients with DSM-IV schizophrenia or schizoaffective disorder (37 male, 32 female; mean age 47.9, SD 11.5) and 92 controls (58 male, 34 female; mean age 43.9, SD 9.0). The facial surfaces were warped onto a lower resolution target mesh. Points of correspondence (pseudo-landmarks) were located on the facial surface for each point of the target mesh and their 3D coordinates were analysed by geometric morphometrics. Principal component [PC] analysis was used to reduce the dimensionality of the shape space and analyses were carried out on PCs with eigenvalues greater than the mean (14 PCs for males and 12 PCs for females). Overall differences in facial shape were tested by Hotelling's T^2 test. Shape differed for both males [$T^2 = 31.2$, $P < .05$] and females [$T^2 = 76.0$, $P < .001$]. Parsimonious statistical models of shape difference were produced by logistic regression and visualised by multivariate regression of shape PCs onto predicted group membership and warping mean facial surfaces along discriminant axes. Colour coding was added to aid the location of the regions of the surface most important for the patient-control differences and also to indicate whether the transformation from patient to control faces involved convex or concave surface displacement, the contraction or expansion of the surface area and other geometric features. This produced a detailed description of the facial dysmorphology for both males and females. The male schizophrenia face was characterised by receding mouth and chin, narrow mouth and protrusive cheeks and orbits. The female schizophrenia face was characterised by receding midface, small nose, narrow mouth and wide jaw and lateral margins. The findings are interpreted with reference to cerebrocraniofacial developmental biology. These studies were supported by the Stanley Medical Research Institute.

A CONTROLLED STUDY OF MEMORY FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA

R. Hijman,* N. van Haren, H. E. Hulshoff Pol, H. G. Schnack, R. Janssens, R. S. Kahn
Psychiatry of University Medical Center Utrecht, Rudolf Magnus Institute of Neuroscience, Utrecht, Netherlands

Memory impairment is often described as being the key cognitive deficit in schizophrenia. The abnormalities in patients with schizophrenia as compared to control subjects seem to be especially prominent in the verbal domain. Whether abnormalities in brain volumes

is associated with memory impairment remains unclear. A total of 69 patients with schizophrenia and 80 healthy control subjects between 16 and 56 years of age were included. The groups were matched on age, height, handedness and parental level of education. The California Verbal Learning Test (CVLT), a digit span task, the visual memory and logical memory subscales of the Wechsler Memory Scale-Revised, and a verbal fluency task were assessed. High resolution Magnetic Resonance Imaging brain scans were obtained for all subjects and volumes of the whole brain, cerebral gray and white matter, third and lateral venticles were measured. On the CVLT patients with schizophrenia performed significantly worse on total immediate recall (b=-6.23, SE=1.85, t=-3.37, p<0.001), delayed free recall (b=-1.67, SE=0.53, t=-3.16, p<0.002) and recognition (b=-0.68, SE=0.30, t=-2.33, p<0.025) than the healthy control subjects. Furthermore a significant decrease in word fluency performance (b+-3.33, SE=0.97, t=-3.44, p<0.001) was found in the patients compared to the control subjects. No significant interaction group-by-age effects were found. In the control subjects significant negative partial correlations (corrected for intracranium, age, sex and IQ) were found between cerebral volume(r=-0.31, p<0.08), especially white matter (r=-0.41, p<0.001) and the total recall of the CVLT. No significant correlations were found in the patient group. Using the Fishers's r-to-z transformations these correlations were significantly different between groups. It was confirmed that verbal memory functions in patients with schizophrenia are impaired. The findings indicate that these memory abnormalities are stable during development. In the patients the negative relationship between memory performance and cerebral (white matter) volume, that was found in the healthy control subjects, no longer exists. This could indicate that in schizophrenia normal brain-behavior relationships may be disrupted.

WHITE MATTER INTEGRITY VARIES WITH COMT GENOTYPE

M. J. Hoptman,* K. O. Lim, B. A. Ardekani,
H. M. Lachman, K. A. Nolan
Clinical Research, Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, USA

Using diffusion tensor imaging (DTI), white matter integrity has been found to be reduced in patients with schizophrenia. However, genetic variants within schizophrenia have been poorly studied. COMT val158met is a functional polymorphism that is associated with cognitive and behavioral alterations in schizophrenia. The L allele is associated with higher levels of aggression and better performance on certain cognitive tasks than is the H allele. We studied COMT-related variations in white matter integrity by conducting DTI scans in 26 patients. Of these, 9 had the HH genotype and 17 had either LL (n=5) or LH (n=12) genotype. Because of the low number of subjects with the LL genotype, LL and LH groups were combined. DTI scans were placed in standardized space using previously published methods. Group differences between the HH group and the other two groups combined were examined using t-tests. A threshold of $p < .05$ and an extent (cluster) threshold of 100 cubic mm was used, and at least one voxel in the cluster had to be significant at the $p < .005$ level. The HH group had higher fractional anisotropy (FA) in the lateral aspects of the right middle frontal gyrus, right Brodmann Area (BA) 6, the left cingulate, and bilaterally in the medial temporal gyrus and inferior parietal lobule (IPL). The HH group had lower FA in right thalamus and putamen, left IPL, and bilaterally in the precuneus, the pre- and postcentral gyri, the superior, middle, and inferior frontal gyri, and the anterior cingulate in regions different from those in which increases were found. These results may have relevance for the functional roles of the COMT genotype in schizophrenia.

HYPOTHALAMUS VOLUME IN SCHIZOPHRENIA USING MAGNETIC RESONANCE BRAIN IMAGING

H. Hulshoff Pol,* E. de Jong, W. Staal, R. Kahn
Psychiatry, Rudolf Magnus Institute of Neuroscience, Utrecht, Netherlands

The distribution of ages at onset in schizophrenia closely parallels the ages at onset and decline of the reproductive period.1 Moreover, in schizophenia significant brain volumetric changes have been reported, including increases in third ventricle volume,2 associated with poor outcome of the disease.3 These findings are suggestive for decreases in surrounding brain tissue of the anterior forebrain nuclei. Hypothalamus volume was measured in high resolution magnetic resonance brain images of 20 poor outcome and 24 good outcome chronically ill patients with schizophrenia and compared to 24 healthy comparison subjects. The intrarater reliability determined by the intraclass coefficient was 0.81. Poor outcome patients had been hospitalized for more than 50% of their total duration of illness. Good outcome patients had been hospitalized for less than 10% of their total duration of illness, and were not hospitalized during during the past year. Mean (sd) hypothalamus volume was 0.91 (0.15) in poor outcome patients; 0.96 (0.12) in good outcome patients; and 1.01 (0.14) in comparison subjects. General linear modelling with hypothalamus volume as dependent variable, groups (poor outcome, good outcome, controls) as between subjects factor, and total brain volume as covariate revealed a significant difference between groups ($F(2,65)=3.20$, $p=0.047$). The effect was mostly due to a decrease in the poor outcome patients as compared to the controls ($t(42)=2.37$, $p=0.022$) and less so to a decrease in the good outcome patients as compared to the controls ($t(47)=1.46$, $p=0.15$). The decreased hypothalamus volume in patients with schizophrenia, in excess to the overall brain volume decrease, and its association with poor outcome of the disease, suggest involvement of this forebrain structure in psychosis. Whether the changes in hypothalamus volume in schizophrenia are directly related to changes in gonadal hormone levels or indirectly through inhibitory transmitters such as dopamine, serotonin and gamma-aminobutyric acid as discussed in 4 remains to be investigated. 1. Hafner H, et al. *Psychol Med* 1993; 23:925-940. 2. Hulshoff Pol HE, et al. *Am J Psychiatry*. 2002; 159:244-250 3. Staal WG, et al. *Am J Psychiatry*. 2001;158: 1120-1122. 4. Stevens JR. *Am J Psychiatry*, 2002;159:713-719.

GREY MATTER REDUCTIONS OVER TIME AS AN EARLY DIAGNOSTIC TEST IN SUBJECTS AT HIGH RISK OF SCHIZOPHRENIA

D. Job,* H. C. Whaley, E. C. Johnstone, S. M. Lawrie
Psychiatry, Edinburgh University, Edinburgh, United Kingdom

Introduction: The aim of this study was to see if changes in structural MR images over 18 months could distinguish 8 subjects at high risk of schizophrenia who developed schizophrenia 2 to 3 years later, from 10 subjects at high risk of schizophrenia who had had transient or isolated psychotic symptoms but did not develop schizophrenia, with a view towards using this as a diagnostic test. Methods: We used voxel based morphometry[1] to perform this analysis. T1 data were acquired on a 1T Siemens machine. All images were correct-

ed for inhomogeneity using a phantom, spatially normalised and segmented using study specific templates, and smoothed at 12 mm FWHM. The resulting grey matter segments for each individual were then entered into a paired t-test, supported by SPM99[2]. A contrast was constructed to examine changes in grey matter over time in those 8 subjects that later developed schizophrenia (PSE[5], ICD-10[6]), excluding any areas of change in high risk subjects who had had transient or isolated psychotic symptoms (PSE[5]) (p-uncorrected = 0.05). The resulting statistical maps were thresholded at a significance level of $p<0.05$ corrected. We further restricted the analyses to the temporal lobe and amygdalo-hippocampal complex using a small volume correction, based on apriori hypotheses from previous studies[3,4]. Results: The high risk subjects who developed schizophrenia had reduced grey matter in the left uncus, left inferior temporal gyrus and right cerebellum. No regions with an increase were seen. Using the sum of changes over time in grey matter density in all three of these regions, for each subject, a ROC curve was plotted. A threshold of 0.095, gives the highest Positive Predictive Value (PPV) of 0.83, and a Negative Predictive Value of 0.75. This cut off gives 5 true positives, 1 false positive, 3 false negatives and 9 true negatives. Discussion: This PPV shows that structural MR imaging could be used as part of a positive predictive test for schizophrenia. Further work would be required to show repeatability of this test and to examine the value of such a test in non-familial schizophrenia. (1) Wright et al., 1995. *Neuroimage* 2:244-252 (2) Ashburner et al., 2000. *Neuroimage* 11:805-821 (3) Lawrie et al., 2001. *Biol. Psych*. Vol. 49 No. 10:811-823 (4) Lawrie et al., 2002. *Brit. J. Psych*. 181, 138-143 (5) Wing et al., 1974. Cambridge, UK: Cambridge University Press. (6) WHO: World Health Organisation. (1992) (ICD-10). Geneva: WHO.

INTER-RATER RELIABILITY OF MANUAL SEGMENTATION OF THE MIDDLE FRONTAL GYRUS

J. P. John,* L. Wang, A. J. Moffitt, H. Singh, M. H. Gado, J. G. Csernansky

Psychiatry, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, Karnataka, India

Previous studies using structural and functional imaging, EEG, autopsy as well as neurobehavioral assessments have implicated frontal lobe dysfunction in the pathophysiology of schizophrenia. Structural MRI findings in schizophrenia however are equivocal (review, Shenton et al., 2001). Perhaps the most important limitation that has dogged research in this area is the failure to compartmentalize the frontal cortex into anatomically and functionally homogenous areas. The use of reference planes in parcellation of cortical regions introduces a certain amount of arbitrariness in the definition of the brain sub-regions as well as ambiguity and inaccuracies in measurements that are based on these planes. We describe a reliable method for parcellation of the middle frontal gyrus based on the surface sulcal-gyral patterns, with minimal dependence on arbitrary landmarks that in turn would afford greater anatomical precision to measurements in structural and functional imaging research on the frontal cortex. We have based our method on a thorough examination and understanding of the normal sulcal variations of the frontal lobe (Ono et al., 1991) as well as the existing knowledge about cytoarchitectonic divisions within this area. Manual segmentation was carried out by two researchers independently on 10 high resolution subvolumes acquired using MPRAGE sequence. Good inter-rater reliability was obtained between the two sets of manual segmentation. Thus it may be inferred that the middle frontal gyrus may be reliably parcelled on the basis of the surface sulcal-gyral patterns without reliance on arbitrary reference planes.

THE CORPUS CALLOSUM IN SCHIZOPHRENIA EXAMINED WITH DTI TRACTOGRAPHY

R. A. Kanaan,* S. S. Shergill, G. J. Barker, P. K. McGuire, V. W. Ng, D. K. Jones

Psychological Medicine, Institute of Psychiatry, London, United Kingdom

Introduction: Diffusion Tensor Magnetic Resonance Imaging (DTI) has been applied to schizophrenia with conflicting results. We previously used DTI to examine a large group of schizophrenic patients and controls using a voxel-based group method, finding reduced fractional anisotropy (FA) in the genu of the corpus callosum of the patient group[1]. As doubts remain over the use of voxel-based analyses in DTI, we sought to validate our result using both a novel approach which employs tractography to define the region-of-interest (ROI) for FA comparisons[2] and a conventional manually-defined ROI-based approach. Methods: 33 schizophrenic (DSM-IV) patients and 40 age- and IQ-matched controls were scanned with an optimized DTI sequence on a 1.5T GE MR system. After correction for eddy-current distortions, the diffusion tensor and FA were calculated at each voxel. An ROI was devised, with the help of an experienced tractographer, such that tracking from this region defined the genu of the corpus callosum. After training (intra-rater reliability α=0.86), this ROI was defined on the individual subject FA maps. Tracking was initiated from this ROI and the mean FA obtained from samples at 0.5 mm intervals along each tract in the reconstructed genu computed, which was then compared between groups (independent samples t-tests). Similar comparisons were performed for FA values from the conventional ROI approach. Results: The tractographic FAs had a group mean (s.d.) which was significantly lower (p=0.005) in the patients (0.499 (0.028)) than controls (0.516 (0.017)). There was no group difference in either mean length of tracts or in variances of group length around this mean. Though some aberrant trajectories were identified (average 3% of fibers), there was no significant group difference in their number (p=0.9). The conventional ROI approach suggested a trend for reduced FA in patients, but this was not significant. Conclusion: Tractographic ROIs confirm our earlier finding of reduced FA in the genu of the corpus callosum in schizophrenia. The lack of significance using the conventional ROI-based approach suggests superior sensitivity of the tractographic method. References 1 Kanaan RAA et al. A Diffusion Tensor Imaging Study of Schizophrenia, Schizophrenia Research, Vol 67 (1), Suppl 1, 2004 2 Jones DK et al. White Matter Fasciculi in Schizophrenia Studied by Diffusion Tensor MR Tractography, in *Organization for Human Brain Mapping* (New York, NY, 2003).

DIFFUSION TENSOR IMAGING OF FRONTAL LOBE WHITE MATTER IN PATIENTS WITH SCHIZOPHRENIA, THEIR HEALTHY TWINS, AND CONTROL SUBJECTS

K. H. Karlsgodt,* T. van Erp, S. Therman, J. Hiltunen, R. Hari, M. Manninen, M. O. Huttunen, J. Lonnqvist, J. Kaprio, T. D. Cannon

Department of Psychology, UCLA, Los Angeles, CA, USA

Previous research has suggested that the symptoms and cognitive deficits associated with schizophrenia might arise a result of a disconnection syndrome in which either functional coordination

between regions, or the integrity of the structural connections between them, is compromised. Indeed, in recent work diffusion tensor imaging (DTI) has shown differences in white matter structure and organization between patients with schizophrenia and control subjects. Often the difference takes the form of lower fractional anisotropy (FA), an index of the organization of the white matter tracts, in the patient group. This measure may reflect axonal size and integrity, myelination, and overall structural organization of the tract. However, the etiology of this change, in particular, whether it is a genetically based or disease-specific abnormality, has yet to be determined. This study employed a twin design to assess whether the differences in FA seen in patients with schizophrenia are shared by their healthy co-twins. In a preliminary analysis, 5 dizygotic twin pairs discordant for schizophrenia and 5 dizygotic control pairs (n=20) were compared. DTI scans of the whole brain in 3.5mm slices were taken on a 3T GE scanner in six directions. FA images were first warped into standard space, and then masked with a region of interest (ROI) comprising the prefrontal cortex of each hemisphere. The ROI analysis indicated that in the frontal lobe the difference of FA between members of discordant pairs was greater than the difference in healthy pairs, and this difference was more pronounced in the right than left hemisphere. In the discordant pairs, healthy subjects had higher FA than their schizophrenic co-twins on average. These findings may indicate that there is an environmental as well as a genetic influence on white matter anisotropy and provide a basis for future investigations into the heritability of white matter structure in schizophrenia.

FRONTAL AND TEMPORAL SYSTEMS ARE LINKED WITH ACUTE AND ONE-YEAR TREATMENT OF FIRST SCHIZOPHRENIA EPISODE

T. Kasparek,* H. Kucerova, R. Prikryl, E. Ceskova, B. Prokes, J. Spacek, M. Ondrusova, M. Mechl
Psychiatry, Masaryk University, Brno, Czech Republic

(a) To analyze relationship of the medial temporal, prefrontal systems and symptomatology during one-year treatment of the first schizophrenia episode; (b) 50 men suffering from first schizophrenia episode were included. They underwent MRI examination with hippocampal volume measurement (anterior, posterior and total volume) during the first episode, neuropsychological assessment of the prefrontal cortex by Wisconsin Card Sorting Test and clinical evaluation by Positive and Negative Syndrome Scale during the first episode at admission and at discharge and after one year. The analysis of covariance was used for the calculations of additive impact of hippocampal volume (covariate) and neuropsychological parameters of frontal cortex (scaled scores of the Wisconsin Card Sorting Test) on the clinical picture assessed by PANSS scale. The impact of body size differences on results was corrected by body height calculations; (c) There were no significant correlations of hippocampal volume with PANSS scores or neuropsychological test scores as assessed during the first episode and after one year. According to the analysis of covariance left anterior hippocampal volume with the conceptual level responses (WCST, during the first episode) predicted endpoint PANSS scores, total right hippocampal volume with the conceptual level responses (WCST, during the first episode) predicted PANSS scores after one year, and both left and right total hippocampal volume with the perseverative errors CST, after one year) predicted PANSS scores after one year, all results indicated that patients with normal ability to solve WCST had lower PANSS scores than those with failure to solve the test appropriately, but only after computing for the hippocampal volume. The results remained significant after the correction for the body height; (d) Severity of the residual symptoms after acute and one-year treatment is associated with the prefrontal functioning together with hippocampal structure which implies the importance of front-temporal interplay. This study failed to find any significant relationship between separate parameters of prefrontal and medial temporal systems and clinical picture of schizophrenia. Only when computing with parameters of both systems we can get significant results. Thus multifactor approaches seem to be more appropriate for the assessment of clinical-CNS relationship.

LONGITUDINAL ASSESSMENT OF THE EFFECTS OF NEUROLEPTIC MEDICATIONS ON THE SUPERIOR TEMPORAL PLANE STRUCTURES IN SUBJECTS WITH SCHIZOPHRENIA

J. K. Kemp,* P. C. Nopoulos, B. C. Ho, N. C. Andreasen
University of Iowa Carver College of Medicine, Iowa City, IA, USA

Previous studies from our lab have shown that neuroleptic medications directly affect the volume of cortical regions with the "typical" antipsychotic medications causing an increase in volume and the "atypical" antipsychotic medications cause a decrease in volume over time. The current study was designed to evaluate the volume of the superior temporal plane (STP) over time, assessing whether change in volume is related to antipsychotic medication exposure, and if this volume change is associated with symptom improvement. A sample of 41 patients with schizophrenia participated in a symptom assessment and an MRI scan before treatment and again two to five years later, and were compared to healthy controls (N=35) evaluated in the same manner. The patient group was divided into those exposed to mostly atypical medications (n=29) and those exposed to mostly typical medications (n=12), with the amount of medication exposure calculated for each class (dose-years). Measurements of the planum polare (PP), Heschl's gyrus (HG) and planum temporale (PT) were obtained by manual tracing, and measurements of clinical symptom severity were assessed using the SANS/SAPS. Cortical volume was measured for both scans, and difference scores were calculated to determine the change in these measurements over time. Correlations were run both between volume and dose-years for each class of medication, and between measures of symptom improvement and change in volume. No significant difference was seen in volume change of any of the STP regions between patients and controls. However within the patient group, there were significant findings: the greater the atypical neuroleptic exposure, the greater the decrease in PP volume (r=-0.544, p=0.0028) and overall STP volume (r=-0.4475, p=0.0169); and the greater the typical neuroleptic exposure, the greater the increase in PT volume (r=0.8279, p=0.0017). All symptoms improved similarly over time in both patient subgroups. Improvements in global symptoms of patients on typical neuroleptics showed a significant positive relationship with increased PT volume (r=0.604, p=0.049). While both classes of medications treat the symptoms of schizophrenia effectively, their effects on the morphology of specific regions of the cortex are diametrically opposed. Moreover, the structural changes associated with typical neuroleptic exposure are directly related to clinical outcome.

SULCAL VARIABILITY: AN INVESTIGATION OF THE VENTRAL STREAM IN SCHIZOPHRENIA

N. Keren,* D. Hwang, B. P. Mahoney, M. A. Eckert, J. M. Kuldau, C. M. Leonard
Neuroscience, University of Florida, Gainesville, FL, USA

The neurodevelopmental hypothesis of schizophrenia predicts that cortical morphology should be perturbed in schizophrenia. The most popular method of testing this idea has been to compare manually segmented gray matter volumes. Effect sizes are usually small and details of results and methodology in attempted replications frequently differ. In a previous study we were able to replicate a loss of fusiform gyrus (FG) volume in right handed male patients with schizophrenia (n=12) compared to matched controls (n=12). The FG was visualized in three planes using MEASURE© and manually segmented using published rules. Unlike the original report, however, the gray matter reduction we found was in the posterior, not the anterior segment of the gyrus, and the ratios between the size of anterior and posterior portions of the gyri were reversed between the two studies. The striking variation in size and number of sulci in the FG was not captured by the volumetric measures, leading us to suspect that other measures more sensitive to possible neurodevelopmental differences in cortical formation should be used to investigate ventral stream structures. To test this idea, we analyzed a subset of 12 brain scans from six patients and six controls from the sample above using BrainVisa©, a freely available automated sulcal labeling program that uses knowledge of developmental growth patterns to identify and quantitatively characterize all sulci on the cortical surface. Advantages of the software also include the elimination of human error and the need for arbitrary decisions required in manual gyral tracing. There were moderate correlations between the manual measures of the fusiform gyrus and the automatically derived surface area of the occipitotemporal but not the collateral sulcus. Consistent with our prediction, the coefficients of variation were larger for the sulcal than the gyral measures (.35 - 1.07 vs .17-.31). We will investigate whether disruptions of ventral stream sulci are associated with information processing deficits in patients with schizophrenia. The availability of this software should make it possible for many groups to apply the same techniques to their data in order to identify specific sulcal patterns that are altered in schizophrenia. To our knowledge this is the first such investigation of ventral stream neuroanatomy utilizing this method. Supported by the Research Service of the Veterans Administration.

A LONGITUDINAL STUDY ON THE AFFECTS OF TYPICAL VERSUS ATYPICAL ANTIPSYCHOTIC DRUGS ON THALAMIC VOLUME IN SCHIZOPHRENIA

B. Khorram,* D. J. Lang, L. C. Kopala, R. A. Vandorpe, Q. Rui, G. N. Smith, V. M. Goghari, W. G. Honer
Centre for Complex Disorders, Psychiatry, University of British Columbia, Vancouver, BC, Canada

The thalamus acts as the functional gateway to the cerebral cortex. Some but not all studies have shown that thalamic volume is lower in patients with schizophrenia relative to healthy comparison subjects. The possibility of antipsychotic drug effects is not well studied. We performed a longitudinal study on the affects of switching from typical to atypical antipsychotic drugs on thalamic volume in schizophrenia. Coronal IR sequence MRI scans (4 mm slice thickness, 1 mm interslice gap) were acquired from chronic schizophrenia patients (n=10). At baseline, patients were treated with various typical antipsychotics for a continuous duration of at least 1 year. Patients were switched to olanzapine, and rescanned, approximately 1 year later. Thalamic volume was measured in a group of healthy comparison subjects (n=20) for comparison. An ANCOVA at baseline showed a significant group effect for total thalamic volume ($F(1, 26)=4.16$, $p=0.04$), with chronic schizophrenia patients being 5.8% larger than healthy comparison subjects. Additional analysis revealed a significant positive correlation between baseline thalamic volume and dosage of typical antipsychotic drug (mg/day of chlorpromazine equivalents) ($r=0.768$, $p=0.007$). An ANCOVA at follow-up showed no significant group effect for total thalamic volume ($F(1, 26)=0.77$, $p=0.39$), with chronic schizophrenia patients being slightly smaller than healthy comparison subjects. A repeated measures ANOVA was used to investigate the effects of group, time (baseline or follow-up), and group by time interaction. The analysis showed significant effects of time ($F(1, 28)=35.20$, $p=0.0001$) and group by time interaction ($F(1, 28)=26.57$, $p=0.0001$). Switching to olanzapine resulted in a significant reduction of thalamic volume in chronic schizophrenia patients. Higher doses of antipsychotic drug at baseline were correlated with larger reductions in volume following switch to olanzapine ($r=0.80$, $p=0.004$). Antipsychotic drug effects may be a factor in the wide range of thalamic volume differences reported between patients with schizophrenia and controls.

A VOXEL-BASED MORPHOMETRIC STUDY OF THE CORRELATION BETWEEN GRAY MATTER CONCENTRATION AND SYMPTOM SEVERITY IN SCHIZOPHRENIA

L. Kingery,* N. G. Cascella, S. M. Meyer, G. D. Pearlson, D. J. Schretlen
Psychiatry and Behavioral Science, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

Although numerous studies have documented brain abnormalities in schizophrenia, especially in ventricular, frontal, and temporal lobe regions, fewer of these examined the relationship between clinical symptom severity and brain structural features. Using the Scale for Assessment of Negative Symptoms (SANS), Baare et al. (1999) found a significant negative correlation between orbito-frontal brain volume and negative symptoms. Positive symptoms, as measured by the Scale for Assessment of Positive Symptoms (SAPS), did not correlate with frontal lobe volume in dorsolateral, medial, or orbitofrontal areas. The aim of our study was to examine the relationship between symptom severity and regional gray matter concentration using voxel-based morphometry (VBM) in schizophrenia. The sample included 33 outpatients with schizophrenia (mean age = 38 ±11 years; 75‰ male; 25 male; 64‰ African American, 36‰ Caucasian) diagnosed according to DSM-IV criteria. All patients were administered the SANS (average score = 12.7, SD=6.4) and SAPS (average score = 4.8, SD=3.7) and underwent magnetic resonance brain imaging (1.5 Tesla GE Signa scanner) with identical image acquisition parameters (124 contiguous, T1-weighted, 1.5mm coronal slices). MRI image preprocessing and VBM analyses were conducted with Statistical Parametric Mapping (SPM2) software, using the Good et al. (2001) optimized method to preprocess the brain scans and construct gray matter brain segments. After normalization to the SPM T1-weighted template, images were re-sliced as 1.5mm isotropic voxels and smoothed using a 12mm FWHM kernel. Correlations were computed between gray matter concentration and total

SANS scores and total SAPS scores. The results showed that SANS scores correlated negatively (p≤.005, uncorrected) with voxels in the left orbito-frontal region, left middle frontal gyrus, and bilateral cerebellar posterior lobe. No correlations between SAPS scores and gray matter concentration were obtained. These results are consistent with those reported by Baare et al. (1999), who used manual tracing of regions of interest. Both studies appear to implicate the structural integrity of orbito-frontal cortex in the severity of negative, but not positive symptoms of schizophrenia.

SMALLER NEOCORTICAL GRAY MATTER AND LARGER CSF VOLUMES IN FEMALE NEUROLEPTIC-NAIVE SUBJECTS WITH SCHIZOTYPAL PERSONALITY DISORDER

M. Koo,* C. C. Dickey, M. E. Shenton, N. Y. Ji, S. Bouix, N. Kuroki, M. M. Voglmaier, L. J. Seidman, M. Nakamura, R. W. McCarley

Department of Psychiatry, Harvard Medical School at Brockton/West Roxbury VA Medical Center, Brockton, MA, USA

Structural brain differences including increased cerebrospinal fluid volumes have been observed in our previous findings of male subjects with schizotypal personality disorder (SPD), which has the same genetic diathesis as schizophrenia. We developed a new segmentation method that, according to our data, has substantial advantages in terms of accuracy, and applied it to female subjects with SPD. We hypothesized that this new method would show deficits in neocortical gray volume in female subjects with SPD. MRI scans were obtained on a 1.5 T magnet with 1.5-mm contiguous slices in 30 right-handed, neuroleptic-naive female subjects with SPD and in 29 female healthy comparison subjects. Subjects were group matched for age, parental socioeconomic status and IQ. MRI scans obtained from the subjects were automatically parcellated into CSF, gray matter, and white matter. Subsequent manual editing separated neocortical from subcortical and non-cortical structures (hippocampus). We found significantly reduced left (4.3%) and right (3.2%) relative and left (6.1%) and right (5.0%) absolute neocortical gray matter volumes and increased CSF relative volumes (9.9%) in female subjects with SPD compared with female healthy comparison subjects. However, there was no difference in white matter volume between groups. These data are consistent with our previous findings of increased CSF volume and trend level reduction in neocortical (p=0.07) gray matter in 16 males with SPD. It is likely that the increased sensitivity of the new segmentation method and the larger sample size revealed this statistical significant decrease of neocortical and increase of CSF volumes in female SPDs.

EVIDENCE OF EXECUTIVE ATTENTIONAL NETWORK ABNORMALITIES IN SCHIZOPHRENIA

M. Kubicki,* P. G. Nestor, E. Connor, L. Ungar, M. Niznikiewicz, R. Kikinis, R. W. McCarley, M. E. Shenton

Psychiatry, Boston VA Health Care System-Brockton Division, Harvard Medical School, Brockton, MA, USA

The executive attentional network, which includes dorsolateral prefrontal cortex (DLPC), anterior cingulate cortex (ACC) and the supplementary motor area have been demonstrated to be abnormal in schizophrenia. These abnormalities are believed to underlie many of the cognitive disturbances observed in schizophrenia, especially those related to attentional control and conflict monitoring. It has been further suggested that a disruption of connectivity between structures forming the executive attentional network, provided by the cingulum bundle (CB), might be the source of these observed abnormalities. Diffusion Tensor Imaging (DTI) is a magnetic resonance technique that can detect white matter tract disruptions by assessing the integrity of directionally organized fibers. This new imaging tool, as well as the Stroop/Negative Priming paradigm, which is sensitive to both control and conflict monitoring, are used in this study to asses the neuroanatomical substrates of executive attentional network abnormalities in schizophrenia. Fourteen chronic schizophrenic patients and 14 healthy controls were scanned using a Line Scan Diffusion Tensor protocol, and the anterior CB was extracted using a segmentation procedure based on directional diffusion information. Fractional Anisotropy, a measure of white matter integrity, and volume were calculated for the anterior portion of the CB. All subjects completed the Stroop negative-priming task, where both Stroop interference effect (reflecting attentional control), as well as negative priming effect (believed to reflect conflict monitoring), were assessed and correlated with the CB diffusion measures. Schizophrenics demonstrated decreased mean fractional anisotropy (FA) within the left CB, as compared with controls (p=0.025). Control subjects showed both the Stroop interference (P=0.004), as well as negative priming (P=0.001). Patients showed a significant Stroop interference effect (P<0.001), but no significant negative priming effect (P=0.71). For patients only, negative priming correlated positively with left cingulum volume (rho=0.67, p=0.017). These findings indicate that disease related abnormalities of executive attention may be related to reduced left CB volume. In addition, within the patient group, higher levels of negative priming, a presumed indicator of monitoring and inhibitory attentional functions, corresponded to stronger CB-DLPC connectivity.

WHITE MATTER ABNORMALITIES IN EARLY-ONSET SCHIZOPHRENIA: A VOXEL-BASED DIFFUSION TENSOR IMAGING STUDY

S. Kumra,* M. Ashtari, K. L. Cervellione, I. Schvartz, H. Kester, D. Roofeh, J. Wu, T. Clarke, E. Thaden, J. M. Kane, G. Fisch, A. Diamond, B. A. Ardekani, P. R. Szeszko

Psychiatry Research, Hillside Hospital, North Shore-LIJ HS, Glen Oaks, NY, USA

The objective of this study was to investigate abnormalities in the structural integrity of brain white matter as inferred by diffusion tensor imaging (DTI) in adolescents with early-onset schizophrenia (onset of psychosis by age 18). Twenty-six patients with schizophrenia and 34 age- and gender-matched healthy volunteers received DTI and structural magnetic resonance imaging exams. Fractional anisotropy (FA) maps were compared between groups in the white matter (WM) using a voxelwise analysis following inter-subject registration to Talairach space. The methods of the voxelwise analysis have been detailed previously (Ardekani et al., 2003; Ashtari et al., in press; Szeszko et al., in press). Compared to healthy volunteers, patients demonstrated lower FA values in the left anterior cingulate region in close proximity to the caudate nucleus (p<.001, uncorrected). In this region, a cross-sectional analysis revealed that the rate of change in FA differed significantly between groups across the age span examined (10.2 to 19.9 years). At a lower threshold (p<.01, uncorrected), patients demonstrated lower FA values in the left

amygdala and parahippocampal regions. There were no areas of significantly higher FA in patients compared to healthy volunteers. These findings suggest a disruption in the structural integrity of prefrontal WM in adolescents with schizophrenia compared to healthy volunteers. These data also provide support for a hypothesis of abnormalities in fiber pathways connecting cortico-limbic regions in adolescents with early-onset schizophrenia. This work was supported in part by grants from NARSAD (SK, as a Lieber Investigator), The Whitaker Foundation (BA; RG-00-0350) and the National Institute of Mental Health to Dr. Kumra (MH01990), and Dr. Kane (MH60575, MH60004, MH41960).

STRUCTURAL CHANGES IN EMOTION-RELATED BRAIN AREA AND ITS RELATIONSHIP TO PSYCHOPATHOLOGY IN SCHIZOPHRENIA: 3T MRI VOLUMETRIC STUDY

G. Lee,* J. J. Kim, J. H. Seok, S. H. Park, J. H. Jeon, T. S. Chung, H. S. Lee
Department of Psychiatry, Yonsei University College of Medicine, Seoul, South Korea

Introduction: Patients with schizophrenia has been known to have impairments in emotional information processing. This study aims to investigate whether or not there is a structural abnormality in the emotion-related brain areas. Methods: High resolution 3D T1-weighted images with 0.5mm slice thickness were obtained from twenty three patients with schizophrenia (14 men, 9 women) and 23 healthy volunteers using 3T MR scanner. Both sides of five regions of interest such as the hippocampus, the amygdala, the nucleus accumbens, the ventromedial prefrontal cortex and the orbitofrontal cortex were manually traced. Severity of schizophrenic symptoms was assessed with PANSS. Results: There were no significant volumetric differences in any regions between patient and control groups. However, asymmetry index of the amygdala - right to left - was significantly increased in the patient group compared with the control group. Furthermore, when the correlations of volumes and symptom severities were examined in the patient group, the volumes of both sides of the nucleus accumbens were found to inversely correlate with negative symptom severity. Conclusion: In this study, we suggest that the structural abnormality of amygdala observed in the patient group might play an important role in impairments of schizophrenia in emotional information processing. Inverse relationship between volume of the nucleus accumbens and negative symptom severity may reflect involvement of the brain reward circuit in volitional impairment of schizophrenia.

THE LIMBIC STRIATUM IN SCHIZOPHRENIA: AN MRI STUDY

J. J. Levitt,* E. E. Connor, S. L. Woolston, L. P. Ungar, N. Kuroki, R. Kikinis, F. A. Jolesz, R. W. McCarley, M. E. Shenton
Psychiatry, VA Boston Healthcare System, Brockton Campus, Harvard Medical School, Brockton, MA, USA

The ventromedial striatum (VMS), or the limbic striatum, includes the nucleus accumbens, and the rostral, ventral caudate and putamen. It is an important component in frontal subcortical circuitry. It receives afferent innervation from medial orbital and anterior cingulate prefrontal cortex and it, in turn, sends efferents back to these structures via the thalamus. Additionally, the VMS is further modulated by input from amygdala and hippocampus limbic structures and midbrain DA neurons. It is believed that these brain structures, which are linked via the frontal striatal thalamocortical circuits, are relevant both for reward-guided behaviors, and for the expression of psychosis. We, thus, hypothesized that the VMS may be abnormal in schizophrenia. Hence, using MRI, we assessed the volume of the VMS in schizophrenia and NCLs. We measured the VMS, using 1.5 Tesla MRI scans in 7 right-handed male, chronic, medicated schizophrenic subjects, and in 7 NCLs. We used 1.5 mm SPGR images for absolute volume region of interest measurements and, to correct for head size and calculate relative volumes, we used 3mm spin echo double axial images for whole brain measurements. All SPGR scans were realigned and resampled yielding isotropic voxels. The VMS was defined as striatal tissue inferior to an oblique line formed by the connection between defined points at the inferior-lateral border of the putamen and the medial border of the caudate. Using Mann-Whitney tests, we found mean left and right absolute (1.66 vs. 1.55 ml, $p<0.75$; 1.56 vs. 1.18 ml, $p=0.11$) and relative (0.114 vs. 0.102 %, $p<0.41$; 0.107 vs. 0.078 %, $p=0.064$) VMS volumes were larger in schizophrenics than in NCLs. Our results are consistent with prior reports of striatal enlargement associated with neuroleptic treatment and suggest this effect of neuroleptics occurs for both ventral and dorsal striatal structures although whether the degree of this effect is similar, or not, requires further research. Future work will further refine volumetric MRI measurement issues regarding this important but challenging structure to assess. It will also account for neuroleptic status and correlate VMS volume with treatment outcome and psychopathological symptoms in schizophrenia.

WHITE MATTER AND COGNITION IN PATIENTS WITH SCHIZOPHRENIA: A DTI VOXEL-WISE CORRELATION ANALYSIS

K. Lim,* J. Wozniak, M. Hoptman, S. Sponheim, A. Silverman, N. Davenport, A. LaFave
Psychiatry, University of Minnesota, Minneapolis, MN, USA

Correlations between behavior/performance and fractional anisotropy (FA) thus far have been examined only in discrete ROIs, which limit the generalizability of findings. Using a unique voxel-wise approach, correlations between white matter (WM) DTI measures and neurocognitive functioning were measured in patients with schizophrenia. The data reveal associations between WM integrity and performance on neurocognitive tasks. Eighteen patients with diagnoses of SZ (n = 16) or schizoaffective disorder (n = 2), and 18 matched controls participated in this collaborative study between the University of Minnesota Department of Psychiatry and the Minnesota VA Hospital. The mean age of both patients and controls was 43. A majority of subjects were male. Subjects were administered a neurocognitive battery designed to tap domains of functioning demonstrated to be impaired in patients with SZ: executive function, memory, attention, and motor skills. Specific measures and their corresponding domains included: California Verbal Learning Test (CVLT/CVLT-II) (memory); Trail Making Part B, WAIS-III Letter-Number Sequencing (executive function); WAIS-III Digit Span and Trail Making Part A (attention); and Grooved Pegboard and WAIS-III Digit Symbol (motor). DTI was performed on a 1.5T GE Signa LX Scanner. Voxel-wise correlational analyses (VCA) were conducted using custom software written in IDL. A voxel-wise computation between each FA map and the corresponding cognitive variable was performed. Because of the large number of statistical tests conducted, this method is inherently non-conservative. To address

this issue, a very conservative significance threshold was set for each voxel in the brain. (Baudewig, Dechent, Merboldt, & Frahm, 2003). Next, clusters were identified wherein the correlation at each cluster voxel met a conventional significance level. The following criteria were set: seed threshold of $p \leq .005$, a cluster threshold of $p \leq .05$, and a cluster size of 100 contiguous voxels. A significant positive correlation was found between measures of Digit Symbol performance and FA in the inferior frontal WM, globus pallidus, putamen, bilateral temporal lobe, and right cuneus; and between CVLT and FA in left parahippocampal WM, left superior temporal gurus, left middle frontal gyrus, and corpus callosum. Voxel-wise analyses of DTI data may allow for a more detailed analysis of WM networks within the brain. Supported by MH-060662 and the MIND Institute.

AUTOMATED ROI-BASED BRAIN PARCELLATION ANALYSIS OF REGIONAL BRAIN VOLUMES IN SCHIZOPHRENIA

P. Lopez-Garcia,* H. J. Aizenstein, K. A. Clark, B. E. Snitz, R. P. Walter, C. S. Carter
Psychiatry, University of California, Davis, Sacramento, CA, USA

Structural MRI studies of schizophrenia have yielded a diversity of findings most likely reflecting differences in the populations studied as well as limitations in the methodology used. To help characterize regional gray matter changes in schizophrenia we used an automated Region of Interest (ROI)-based approach that targeted frontal and temporal regions in a large group of schizophrenia patients (first episode and chronic). 63 patients (21 chronic schizophrenia patients, 22 first break schizophrenia patients and 20 first episode non-schizophrenia psychosis patients) and 47 comparison participants were studied. Automated regional volume measurement was performed in 20 ROIs, including frontal and temporal cortical subregions and hippocampus. Correlations between volume measures and duration of the illness and clinical scores were evaluated. The automated method was validated in a sample of 10 subjects through manual tracings. Chronic schizophrenia patients show gray matter volume differences in left DLPFC and right SMA. First episode psychosis patients present smaller right ACC and left DLPFC than comparison subjects. Disorganization scores and duration of illness correlated negatively with gray matter volume of DLPFC and SMA respectively in chronic schizophrenia patients. Using an automated ROI-based method we found volume reductions in lateral and medial frontal regions in both first episode and chronic schizophrenia. This automated ROI-based method can be used as a valid and efficient tool for accurate quantification of regional gray matter volume in schizophrenia in multiple regions of interest across the brains of large numbers of subjects.

CCTCC ABNORMALITIES IN SCHIZOPHRENIA AS MEASURED BY DIFFUSION TENSOR IMAGING

V. A. Magnotta,* R. Pierson, P. Cheng, A. Caprihan, N. C. Andreasen
Radiology, The University of Iowa, Iowa City, IA, USA

This study investigated connectivity abnormalities in CCTCC circuit in schizophrenia by using diffusion tensor imaging. Data was collected at the University of New Mexico and the University of Iowa. Twelve subjects with a DSM-IV diagnosis of schizophrenia spectrum disorders and ten control subjects with no psychiatric or neurological disorders were recruited into this study. Informed consent was obtained from all subjects in accordance with the Institutional review boards at both institutions. A high resolution volumetric scanning protocol was acquired and diffusion tensor data was acquired subjects twice within a 24 hour period to assess the reliability of the DTI measures obtained. Fractional anisotropy and mean diffusivity images were generated for each of the two scanning sessions. The images were co-registered with the structural MR T1 weighted scans that had been placed into a standard orientation. ROIs were defined to measure the average fractional anisotropy within several regions of the CCTCC: anterior cingulate, orbital frontal cortex, insula, corona radiata, superior temporal lobe, anterior and posterior limbs of internal capsule, the middle cerebellum peduncle, superior cerebellar peduncle, corpus medullare, and white matter just inferior to thalamus. Mean diffusivity and fractional anisotropy were measured in these regions. The average FA measures were significantly lower in the left ($p=0.0005$) and right ($p=0.04$) OFC in patients with schizophrenia as compared to the normal controls after controlling for age. The mean diffusivity was significantly higher in patients bilaterally for the straight gyrus (left: $p=0.01$; right: $p<0.0001$), anterior cingulate (left:$p=0.0002$, right: $p=0.0002$), middle cerebellar peduncle (left: $p<0.0001$; right: $p<0.0001$) and the corpus medullare (left:$p=0.03$, right: $p=0.02$). The correlations for scan/re-scan measurements were very high for FA, with all structures being above .80 with most being .85 or higher. The diffusivity findings suggest that differences may exist in the cerebellar white matter that is not apparent on the FA images. We are currently pursuing fiber tracking algorithms to obtain a better understanding of these differences.

REDUCED ANTERIOR HIPPOCAMPAL FORMATION VOLUME IN PATIENTS WITH SCHIZOPHRENIA AND WATER IMBALANCE

M. Marlow-O'Connor,* I. Torres, B. Beenken, S. Keedy, R. Gibbons, M. Goldman
Psychology, Rosalind Franklin University of Medicine and Science, N. Chicago, IL, USA

Hippocampal volume, particularly its anterior portion, is reduced in schizophrenia, but the functional significance of this is unclear. Initial studies indicate this finding is especially prominent in those with life-threatening water imbalance, whose vasopressin and HPA axis defects have been linked to anterior hippocampal pathology. Hippocampal volumes were obtained from images acquired in a 3T scanner in matched schizophrenia groups and 9 healthy controls (HC). Schizophrenia groups were: 7 hyponatremic polydipsic (HP, known to have defects in vasopressin regulation), 7 normonatremic polydipsics (NP, who, along with HP, have defects in HPA axis regulation), and 10 normonatremic non-polydipsics (NN). Hippocampi were manually traced using rules from Pantel et al. (2000) with reference to segmented, T1- and T2- weighted images using BRAINS2 software (Univ of. Iowa) (rater reliability: ICC= .72). The anterior/posterior division was made at the posterior extent of the uncus (ICC = .84). Volumes at each position (i.e. L Anter., L Post., R Anter., R Post.) were analyzed with mixed-model linear regression. Group differences were assessed with Helmert contrasts (H1:HC vs mean NN, NP, HP; H2: NN vs mean NP, HP; H3: NP vs HP). Subjects were random factors, while Helmert contrasts, L vs R side, anterior vs. posterior position, and their interactions were fixed effects. Neither total hippocampal volume nor that of its anterior segment differed

between HC and schizophrenia groups (H1 main: P = .23, H1: A/P position: P= .27). Total volume was also similar across schizophrenia groups, but the anterior segment was selectively smaller in the two polydipsic groups (H2: A/P position P = 0.02). This difference remained significant when factors known to modulate brain volume (i.e. age, gender, height, IQ, education) were sequentially added to the model (H2 A/P position for complete model P = .01). These findings confirm that anterior hippocampal volume is reduced bilaterally in individuals with schizophrenia with water imbalance relative to others with schizophrenia and to healthy controls. Converging evidence demonstrates that the water imbalance arises from the inability of the anterior hippocampus to constrain behavior and hormonal responses to psychological stimuli. Therefore these results contribute to the concept that a specific brain pathology underlies both the mental illness and associated findings in this well-characterized subset of patients.

EFFECTS OF ATYPICAL AND TYPICAL NEUROLEPTICS ON ANTERIOR CINGULATE VOLUME IN SCHIZOPHRENIA

L. McCormick,* L. Decker, P. Nopoulos, N. C. Andreasen
Psychiatry, University of Iowa Hospitals and Clinics, Iowa City, IA, USA

Objective: Abnormalities in anterior cingulate function and structure are well known in schizophrenia. We have previously found typical neuroleptic exposure to be correlated with an increase in basal ganglia and anterior cingulate volume, while atypical neuroleptics are correlated with a decrease in basal ganglia volume. However, the effect of atypicals on anterior cingulate volume and the clinical significance of anterior cingulate volume changes with neuroleptic exposure are not known. To determine if atypical neuroleptics differ from typical neuroleptics in their effect on anterior cingulate volume change and to assess the clinical significance of such changes, the authors assessed anterior cingulate volume changes in subjects with schizophrenia and compared them with normal controls. Methods: This study was designed to evaluate the morphology and clinical correlates of the anterior cingulate volume in a group of 31 neuroleptic-naive subjects with schizophrenia, compared to 18 normal controls. Anterior cingulate volume was delineated with manual traces on magnetic resonance images of the brain at admission and approximately 3 years later. Neuroleptic exposure for each subject was calculated over time using a dose-year formula. Results: After approximately 3 years, the change in anterior cingulate volume was significantly correlated to neuroleptic exposure, indicating that the greater the exposure to typical neuroleptics the larger the anterior cingulate volume ($r=0.92$, $p<0.001$), while the greater the exposure to atypical neuroleptics the smaller the anterior cingulate volume ($r=-0.57$, $p<0.006$). There was a significant relationship between increased anterior cingulate volume and psychotic symptom improvement ($r=0.78$, $p<0.010$). Conclusions: Anterior cingulate volume changes over time are directly correlated to neuroleptic medication exposure (the greater the typical neuroleptic exposure, the larger the anterior cingulate volume, while the greater the atypical neuroleptic exposure, the smaller the anterior cingulate volume). The increased volume of the anterior cingulate volume is directly correlated to improved psychotic symptoms.

ASSOCIATION BETWEEN BRAIN STRUCTURAL ENDOPHENOTYPES OF PSYCHOTIC DISORDERS AND GENOTYPIC VARIATION

C. McDonald,* E. T. Bullmore, E. Dempster, X. A. Chitnis, P. C. Sham, D. A. Collier, R. M. Murray
Division of Psychological Medicine, Institute of Psychiatry, London, United Kingdom

There is increasing interest in the utilisation of phenotypes other than the clinical syndrome in the search for genes which confer susceptibility to psychotic illness. We previously identified potential brain structural endophenotypes for schizophrenia and psychotic bipolar disorder using computational morphometry of MRI brain scans and a measure of genetic liability in families multiply affected with these disorders. In the present study we examined the association between these MRI endophenotypes and genotypic variation in selected polymorphisms linked to psychotic illness or to brain structural variation. MRI brain scans and DNA were obtained from 140 subjects, comprising 24 patients with schizophrenia, 30 of their unaffected first-degree relatives, 36 patients with bipolar disorder and 50 of their unaffected first-degree relatives. Distinctive grey matter endophenotypes were identified for schizophrenia (a network of deficit involving fronto-temporal and subcortical regions) and for bipolar disorder (deficit in right anterior cingulate and striatum). A generic white matter endophenotype was also identified for both forms of psychosis comprising left temporo-parietal deficit. DNA was genotyped for polymorphisms in selected genes, including neuregulin, Nogo, COMT, BDNF and prion protein. Multiple regression analyses controlling for confounds and employing multilevel modelling were used to examine associations between allelic variation in these polymorphisms and morphometric variation in the endophenotypic regions. Volume deficit of the generic left temporo-parietal white matter endophenotype was associated with homozygosity for a CAA insert in the 3′-untranslated region of Nogo (B=-0.24, p=0.018, 95%CI=-0.43, -0.04) and with carrying the Val allele at codon 129 of prion protein gene (B=-0.15, p=0.02. 95%CI=-0.27, -0.02). There were no significant relationships between genotypic variation and grey matter morphometry. These data demonstrate that variation of brain structural endophenotypes identified for schizophrenia and bipolar disorder is associated with allelic variation in selected candidate genes; and implicate Nogo (a neuronal growth regulator highly expressed by oligodendrocytes in myelinated tissues) and prion protein (which has role in neurodevelopment and in protection against oxidative stress) as susceptibility genes for volume deficit in a region of white matter which is endophenotypic for both schizophrenia and psychotic bipolar disorder.

VISUAL BACKWARD MASKING IN PEOPLE WITH SCHIZOPHRENIA AND HEALTHY CONTROLS: RELATIONSHIPS BETWEEN TASK PERFORMANCE AND GRAY MATTER DENSITY STUDIED WITH VOXEL-BASED MORPHOMETRY

P. Milev,* B. C. Ho, R. Pierson, N. C. Andreasen
Psychiatry, University of Minnesota, Minneapolis, MN, USA

Deficits in visual backward masking (BM) are considered to be a trait marker and a candidate endophenotype of schizophrenia and are thought to be related to malfunction in the transient visual channels.

It is not clear what brain regions are involved in BM and whether there are differences in these regions between healthy individuals and people with schizophrenia. The purpose of this study was to examine relationships between performance on BM and brain structure using voxel-based morphometry with the hypothesis that performance on BM will be related to brain regions involved in visual processing and visual-spatial attention. 52 people with first-episode or recent-onset schizophrenia and 46 healthy individuals were tested on a computerized BM test in which a visual target was presented followed by a mask. Performance on BM was measured as the percent correct target identifications and patients performed worse than healthy individuals. Optimized voxel-based morphometry was used to examine correlations between performance on BM and gray matter density (GMD) in patients and controls. In the healthy group there were several brain areas with a positive correlation: three areas consistent with the left frontal eye fields, involved in eye movements and visual-spatial attention; R anterior fusifiorm gyrus, part of the ventral visual system with a role in visual awareness; R middle frontal gyrus, with a role in visual-spatial attention; two brain regions in the L and R parietal lobe involved in the dorsal visual system and visual attention; L cerebellum, part of functional networks for eye movements and visual attention. In the patient group the only brain region with a significant positive correlation between performance on BM and GMD was R posterior fusiform gyrus, part of the dorsal visual system. In conclusion, we found that in the healthy group there were correlations between better performance in BM and higher gray matter density in brain areas that are consistent with the functional networks involved in higher order visual processing, eye movements, visual-spatial attention and visual awareness. In people with schizophrenia the only significant correlation was with an area from the dorsal visual system. Deficits in this dorsal transient system are postulated to be the reason for the BM impairment in schizophrenia. People with schizophrenia did not exhibit correlation with areas that are part of a network for visual-spatial attention.

INCREASE IN GRAY MATTER VOLUME AND DECREASE IN WHITE MATTER VOLUME IN THE CEREBRAL CORTEX DURING TREATMENT WITH ATYPICAL NEUROLEPTICS IN SCHIZOPHRENIA

V. Molina,* S. Reig, M. Desco, J. Pascau, J. Sanchez, T. Palomo, J. Sanz, C. Benito
Psychiatry, Hospital Clinico Universitario, Salamanca, Salamanca, Spain

Object: To study longitudinal changes of cerebral cortex and white matter volumes in schizophrenia patients after prolonged treatment with atypical neuroleptics Method: Eleven healthy controls and 29 patients were studied with MRI at baseline and after two years of followup. Two groups of patients were analyzed, treatment-naive patients (n=17) receiving risperidone during the followup period, and chronic treatment-refractory patients (n=12) receiving clozapine. A Talairach Atlas-based segmentation technique was used to quantify gray matter (GM) and white matter (WM) volumes Outcomes: Contrary to the controls, both groups of patients presented parietal and occpital (and also frontal in the chronic group) GM increases and WM decreases. The patients showed at baseline a deficit of GM when compared to controls There was a significant inverse relationship between the amount of baseline GM deficit and the longitudinal change during treatment. These GM and WM changes were not related to changes in weight. Conclusion: Treatment with atypical drugs appears to have a significant effect on increasing GM volume.

Regional volumes in the 3 groups

Regional volumes in the 3 groups. The baseline volume at enrollment is expressed in cc. The change in each structure is expressed as a percentage of the initial volume of the structure, adjusted for the change in intracranial volume (considered a source of measurement error between the two studies; see text). The following table shows the comparative statistics for the changes in the 3 groups, expressed as the mean (SD).

STRUCTURAL NEUROIMAGING IN FIRST EPISODES OF EARLY ONSET PSYCHOSIS

D. Moreno,* M. Desco, M. Parellada, S. Reig, M. Burdalo, A. Ruiz, A. Zabala, O. Robles, E. Baca, C. Arango
Psychiatry, Hospital General Universitario Gregorio Maranon, Madrid, Spain

The aim of the study is to compare cerebral volumes in a group of early onset first-episode psychosis (EOFEP) with matched controls. K-SADS interview, PANNS and other clinical variables were administered at baseline to 38 patients and 47 controls. T1 and T2-weighted MRI scans were acquired in a 1.5 T Philips Gyroscan. Images were segmented following SPM algorithms, and regional volumes were measured using a semiautomatic method based on the Talairach Atlas. Total CNS intracranial volumes and total white matter did not differ between patients and controls. Grey matter (830.43±59.75 and 862.17±64.20, p=0.006) and CSF volumes (251.24±40.60 and 230.25±28.43, p=0.002) were different in male patients compared with controls, but not in females. Left and right frontal, parietal and temporal grey matter volumes were significantly reduced in male patients compared with controls. No significant differences were found between patients and controls in occipital lobes, nor in any particular lobe for females. Sulcal CSF was increased compared to controls in left and right frontal, parietal and temporal lobes. Results support that at least a subgroup of patients with EOFEP experience brain changes with grey matter reduction and CSF increase before the onset of psychotic symptoms.

STRUCTURAL BRAIN ABNORMALITIES AT THE FIRST ONSET OF PSYCHOSIS: ARE SOME POPULATIONS MORE AT RISK?

K. D. Morgan,* P. Dazzan, G. Hutchinson, K. Orr, C. Morgan, X. Chitnis, J. Suckling, P. Fearon, P. Jones, R. Mallett, J. Leff, R. M. Murray
Division of Psychological Medicine, Institute of Psychiatry, London, United Kingdom

The reasons underlying the increased rate of psychosis in the African Caribbean and Black African populations in the UK are poorly understood. In socially disadvantaged groups such as ethnic minorities, factors such as stress arising from societal discrimination, may play an important role in the onset of psychosis. Higher levels of social risk factors in patients from such groups may result in lower levels of biological risk factors (e.g. structural brain changes). We investigated whether structural brain abnormalities were more extensive in white British patients when compared to patients from ethnic minorities. This investigation was part of the AESOP first-onset psychosis study. We conducted two separate analyses of an epidemiologically recruited sample of first-onset psychosis patients resident in South London, UK. 1) White British patients (n=34, male=20, mean age=28, ICD10 schizophrenia=16, other psychosis=20) were compared to white British controls (n=41). 2) African Caribbean/Black African patients (n=41, male=27, mean age=27, ICD10 schizophrenia=24, other psychosis=17) were compared to African Caribbean/Black African controls (n=35). We used dual-echo MRI data, acquired at 1.5T. Differences in grey and white matter volume between patients and controls were estimated at each intracerebral voxel after registration of the images in standard space. Compared to their ethnically matched controls: 1) white British patients had increased third ventricle volume and increased left superior temporal lobe grey matter. 2) African Caribbean/Black African patients had reduced global grey and white matter volume; increased third ventricle volume and increased lenticular nucleus and lingual gyrus grey matter (bilateral). Contrary to our predictions, fewer structural brain changes were found in white British patients. More extensive structural brain changes in the African Caribbean/Black African patients may arise from a stress related neuro-toxic effect or from variations in medication regimens.

FRONTO-TEMPORAL DISCONNECTIVITY IN SCHIZOTYPAL PERSONALITY DISORDER: A DIFFUSION TENSOR IMAGING STUDY

M. Nakamura,* R. W. McCarley, M. Kubicki, C. C. Dickey, M. A. Niznikiewicz, M. M. Voglmaier, L. J. Seidman, S. E. Maier, C. F. Westin, R. Kikinis, M. E. Shenton
Psychiatry, Brockton VAMC and Harvard Medical School, Brockton and Boston, MA, USA

Fronto-temporal connectivity abnormalities in schizophrenia have long been speculated, though their role in schizotypal personality disorder (SPD) is not known. Using Diffusion tensor imaging (DTI), we previously reported abnormalities in two critical white matter tracks in schizophrenia, the uncinate fasciculus (UF), which interconnects with the anterior temporal and inferior frontal cortices, and the cingulum bundle (CB), which connects the cingulate gyri with prefrontal, temporal and parietal areas. Here, we investigate these two bundles in unmedicated SPD subjects. 15 male SPD and 15 male controls were scanned using line-scan DTI. Fractional anisotropy (FA) and mean diffusivity (Dm) were used to quantify water diffusion, and cross-sectional area was defined using a directional threshold method. We found bilaterally reduced FA ($F=7.50$, $df=1, 28$, $p=0.01$) in the UF of SPD subjects. For CB, there was no significant group difference for FA or Dm measures and there were only small effect sizes. Additionally, in SPD, reduced FA in the right UF was correlated with clinical symptoms, including ideas of reference, suspiciousness, restricted affect and social anxiety. In contrast, left UF area was correlated with measures of cognitive function, including general intelligence, language, verbal and visual memory, and executive performance. These findings suggest altered fronto-temporal connectivity via the UF in SPD, similar to findings in schizophrenia, and also intact neocortical-limbic connection via the CB in SPD, the latter in marked contrast to findings in schizophrenia. Further, clinical and cognitive correlates of UF DTI measures suggest that altered UF may play an important role in the phenomenology of SPD, with right-sided correlations associated with clinical symptoms and left-sided correlations associated with more cognitive abnormalities.

CORTICAL THINNING IN CINGULATE AND OCCIPITAL CORTICES IN FIRST EPISODE SCHIZOPHRENIA

K. L. Narr,* A. W. Toga, P. Szeszko, P. M. Thompson, R. P. Woods, D. Robinson, S. Sevy, Y. Wang, K. Schrock, R. M. Bilder
Neurology, UCLA School of Medicine, Los Angeles, CA, USA

Cytoarchitectural abnormalities have been observed in the cingulate cortex in schizophrenia. The regional specificity of changes in neural/glial structure and density, however, remain uncertain given the labor intensiveness of postmortem measurement techniques. Advances in computational image analysis methods now allow cortical thickness to be examined at high spatial resolution in vivo that may better characterize neuropathological processes in schizophrenia than volumetric measures. These methods have not been applied to examine cortical thickness changes in cingulate and other cortical regions bordering the medial walls of the cerebral hemispheres in first episode schizophrenia. We used high-resolution T1-weighted MR images and cortical pattern matching methods to compare cortical thickness between 72 (51m/21f) first episode patients and 78 (33m/44f) healthy subjects, similar in age. Cortical thickness, the 3D distance between the cortical white-gray matter boundary and the hemispheric surface, was measured at sub-voxel resolution at thousands of spatially equivalent cortical locations. Effects of Diagnosis were compared at all locations after covarying for sex. Results, mapped onto the average cortex to identify highly localized changes in thickness, were confirmed by permutation testing. Statistical maps showed significant cortical thinning within cingulate cortex bilaterally, with pronounced effects in caudal-anterior and posterior cingulate gyrus (Brodmann Areas 24, & 33) in schizophrenia. Patients further showed cortical thinning in occipital and frontopolar regions, and no significant thickness increases in any cortical location compared to controls. Disease-related patterns of cortical thinning showed some differences within males and females: thinning was pronounced in the left paracentral lobule in male patients and in the right posterior cingulate in female patients compared to same sex controls. First episode patients show reductions in cortical thickness in cingulate and occipital regions within medial cortices. Localized reductions may correspond to previously described cytoarchitectural and neurochemical abnormalities observed in the same or proximal anatomic locations. Cortical thinning may also relate to specific functional impairments observed in schizophrenia and point to

systems-wise disturbances that include heteromodal association cortices where cortical thinning has been shown previously in the same schizophrenia study group.

LONGITUDINAL ASSESSMENT OF THE EFFECTS OF NEUROLEPTIC MEDICATIONS ON GLOBAL CEREBRAL MEASURES IN SUBJECTS WITH SCHIZOPHRENIA

P. Nopoulos,* B. C. Ho, M. Pressler, L. McCormick, N. C. Adnreasen
Psychiatry, University of Iowa, Iowa City, IA, USA

Background: Previous studies from our lab have shown that neuroleptic medications directly affect the volume of small cortical regions (anterior cingulate, insula, and superior temporal plane) with the typical antipsychotic medications causing an increase in volume and the atypical antipsychotic medications cause a decrease in volume over time. The current study was designed to evaluate the longitudinal effects of neuroleptics on a more global basis, evaluating change in measures of the entire cerebrum and its component tissues. Methods: A sample of 62 patients with schizophrenia had an MRI scan before treatment and again two to five years later. They were compared to healthy controls (N=35) evaluated in the same manner. The patient group was divided into those exposed to mostly atypical medications (n=41) and those exposed to mostly typical medications (n=21), with the amount of medication exposure calculated for each class. Measurements of the cerebrum, cerebral white matter, and cerebral gray matter were obtained in an automated fashion. Difference scores were calculated by subtracting time2 volumes from time1 volumes. ANCOVA was used to compare the change in volumes across the three groups (controls, aypticals, typicals). Results: There was a significant effect of group status ($F=3.67$, $p = 0.029$) on the change in cerebral volume over time with minor increases in volume in the controls (mean =5.2 cc) and the atypical group (mean=1.6 cc) while the typical group had more substantial increase in volume (16.9 cc). This pattern held true for measures of gray matter in which the controls and atypical group showed little change over time while volumes of gray matter increased in the typical group. In contrast, cerebral white matter showed no change in volume in the controls, while both patient groups had significant decreases over time. Conclusions: Effects on global measures of cerebral gray matter are a similar pattern our previous studies with more regional cortical effects showing typical neuroleptic exposure associated with increasing volume over time and atypical neuroleptic exposure correlating with deceasing volume over time, a pattern also seen by our lab and others in the basal ganglia. The fact that both patient groups saw a decrease in volume in white matter over time suggests this morphologic change may be mediated by disease process rather than medication effect yet should be investigated further.

WHITE MATTER BRAIN ASYMMETRY IN SCHIZOPHRENIA AS STUDIED WITH DIFFUSION TENSOR IMAGING

H. Peuskens,* S. Sunaert, M. De Hert, P. Van Hecke, J. Peuskens
UC St.-Jozef Kortenberg, Kortenberg, Belgium

Diffusion tensor imaging is a magnetic resonance scanning modality that allows for non-invasive quantitative assessment of white matter organization of the brain. Recently, DTI has been shown to be highly suited to map white matter brain asymmetry linked to language organization in the human brain using both region of interest analysis (Cao et al, 2003) or voxel based whole brain analysis (Buchel et al, 2004). In schizophrenia, a number of findings have indicated a decrease in normal lateralization of the cerebral cortex and considering these findings, it was hypothesized that in schizophrenia white matter tracts show reduced difference between left and right hemisphere. In order to test this hypothesis, we acquired diffusion tensor images in a group of 20 schizophrenic patients and in a group of 20 healthy controls, matched for age, gender and dexterity. In conjunction with this study, we obtained magnetization transfer images allowing for assessment of gray matter integrity and since we were especially interested in mapping white matter tracts connecting language related brain areas, we performed this study in conjunction with a functional brain imaging experiment mapping expressive and receptive brain regions. We will report on our analysis of diffusion tensor images and we will aim to integrate our findings with results of other scanning modalities. References: Buchel C, Raedler T, Sommer M, Sach M, Weiller C, Koch MA. (2004) White matter asymmetry in the human brain: a diffusion tensor MRI study. *Cereb Cortex*. 14(9):945-51. Cao Y, Whalen S, Huang J, Berger KL, DeLano MC. (2003) Asymmetry of subinsular anisotropy by in vivo diffusion tensor imaging. *Hum Brain Mapp*. 20(2):82-90.

MAPPING BRAIN CONNECTIVITY DEFECTS IN SCHIZOPHRENIA BY DIFFUSION TENSOR MRI

A. Preda,* L. Arlinghaus, K. Fernandez, R. Loch, A. Anderson, R. Hoffman
Psychiatry, Dallas VA Medical Center, Dallas, TX, USA

Previous work in schizophrenia documents functional and anatomical disturbances in a number of brain regions yet fails to demonstrate a discernible pattern to these pathological findings. Our hypothesis is that schizophrenia is characterized by brain connectivity abnormalities, shown as structural defects in the neuronal fiber tracks connecting different regions of the brain. Specifically, we tested this hypothesis by using diffusion weighted MRI to analyse fractional anisotropy (FA) and visualize white matter axon fascicles in subjects diagnosed with schizophrenia versus normal controls and patients diagnosed with a severe mental disorder other than schizophrenia (bipolar disorder with psychotic features). All subjects were scanned using high resolution T1-weighted and diffusion tensor imaging sequences. Data sets with significant artifacts or low signal-to-noise ratio were discarded, leaving 12 schizophrenic, 9 bipolar and 11 control studies. The mean and standard deviation of fractional anisotropy (FA) of diffusion were calculated for each group at each voxel position in the standard space. These were used to calculate the t-statistic of FA differences between groups (i.e., schizophrenia versus control, schizophrenia versus bipolar, bipolar versus control). The acceptable FA maps were analyzed using two methods. First, regions of interest were defined by hand on color-coded FA maps. The regions included the left and right cingulum, left and right uncinate, and the genu and splenium of the corpus callosum. Using this method the only significant difference between group ROI measurements was increased FA in the left uncinate in schizophrenics compared to the bipolar and normal control groups. This result should be interpreted with caution however, given the small sample size and the difficulty in identifying the uncinate in the relatively low resolution DTI images. In the second analysis method, the FA maps were registered in a standard image space. This was accomplished by calculating a rigid transformation to align the DTI and high resolution image sets

of each subject, followed by a non-linear transformation from the high resolution image set to a "standard" image space. Group comparisons were then made on a voxel-by-voxel basis in the standard space. The schizophrenic group again showed higher FA in focal regions in the left superior temporal and occipital lobes compared to the bipolar and normal control groups.

BRAIN STRUCTURAL DIFFERENCES BETWEEN FIRST-EPISODE PSYCHOSIS AND CHRONIC SCHIZOPHRENIA

P. Premkumar,* V. Kumari, P. Corr, T. Sharma
College Research Unit, Royal College of Psychiatrists, London, London, United Kingdom

Some studies suggest that schizophrenia is characterised by progressive brain abnormality. Longitudinal studies may not be long enough to detect brain volume change. Cross-sectional comparisons enable comparing patients from different illness stages, though their findings may function in informing longitudinal studies, given the various assumptions made in drawing such comparisons. The present study compared patients with first-episode psychosis (duration of illness <1 year, n = 34, mean age (S.D.) = 23.71 (4.96)) or chronic schizophrenia (duration of illness >3 years, n = 54, mean age (S.D.) = 40.12 (10.24)) and healthy controls for each patient group matched for age, gender, ethnicity and parental socio-economic status (n = 18 and 21 respectively). MRI brain volumes for sixteen total and grey-matter regions covering the cerebrum and sub-cortex were measured using voxel-based morphometry. The brain volumes were analysed by specifying an interaction term for illness stage and diagnosis. A logarithmic regression was performed between duration of illness and brain volume. Chronic schizophrenia patients had smaller total prefrontal cortex (F, 5.25; $p < 0.05$), prefrontal cortex grey matter (F, 11.49; $p < 0.05$) and grey matter of parieto-occipital cortex (F, 4.25; $p < 0.05$) compared to the first-episode patients. They had larger premotor cortex (F, 8.18; $p < 0.05$) and lateral ventricles (F, 6.35; $p < 0.05$) compared to first-episode patients. These differences were reflected in the logarithmic regression relation between duration of illness and brain volume. In addition, there was a logarithmic regression relation between duration of illness and thalamus ($R2 = 0.1$, $F = 9.33$, $df = 81$, $P = 0.003$) and cortical grey matter ($R2 = 0.08$, $F = 7.27$, $df = 81$, $P = 0.009$). There is a difference in brain volume between patients at two different stages of psychosis over and above that in healthy controls. This difference is not unitary across the cerebrum, but is pronounced in the frontal and occipito-parietal and ventricular regions. Factors other than chronicity might explain the differences between the patient groups, such as the duration of active psychosis and patients experiencing their first psychotic episode not being typical of the schizophrenia population since the early stages of psychosis are characterised by clinical instability.

CHANGE OF THE INSULAR CORTEX OVER TIME IN SCHIZOPHRENIA: RELATIONSHIP TO NEUROLEPTIC EXPOSURE

M. E. Pressler,* P. Nopoulos, B. C. Ho, N. Andreasen
Psychiatry, UIHC, Iowa City, IA, USA

The insular cortex is a limbic integration region engaged in emotional and cognitive functions. Previously, we found neuroleptic naïve subjects had abnormally small insular volumes compared to controls, with volume directly related to severity of psychotic symptoms. In a cross-sectional sample, we found that higher levels of exposure to typical neuroleptics were associated with larger volumes of the insula, a pattern seen by our lab and others in the basal ganglia as well as other regions of the cortex. To further investigate insular cortex abnormalities and their functional correlates, we measured insular gray matter volume and cortical surface size using magnetic resonance images among 35 neuroleptically naïve patients with schizophrenia and a matched control group, and again after two years. Neuroleptic medication exposure (dose-years) was calculated for the atypical class and the typical class, accounting for both dose and exposure over time. Change in volume of the insula over time did not differ between patients and controls. Among patients, however, atypical neuroleptic exposure correlated negatively with right insular surface area. This trend correlated strongest among those patients who had been exposed to atypicals only. Among those patients exposed to both types of neuroleptics, typical dose-years correlated positively with right insular surface area. Increase in insular mean cortical depth correlated with improvement in positive symptoms and with improvement in delusions. Exposure to atypical neuroleptics correlates with a reduction in insular surface area, while exposure to typical neuroleptics are associated with surface area increase. The clinical manifestation of these different effects is unclear, as both types of neuroleptic are known to be effective treatments. However, the structural changes seen with exposure to typical neuroleptics was directly associated with clinical improvement. Further research is needed to investigate the potential relationship between changes in the insula from neuroleptic exposure and clinical outcome.

PROGRESSIVE LOSS OF FRONTAL GREY MATTER IN FIRST EPISODE SCHIZOPHRENIA; A VOXEL-BASED MORPHOMETRY STUDY

G. Price,* M. Cercignani, M. S. Bagary, T. R. Barnes, E. M. Joyce, M. A. Ron
Neuroinflammation, Institute of Neurology, London, United Kingdom

There is converging evidence from cognitive and functional imaging studies that frontal lobe abnormalities occur in schizophrenia. Neuropathological studies have also described neuronal and glial abnormalities, but the relationship between frontal structural and functional abnormalities and their natural history is still unresolved and structural MRI studies have given conflicting results. Here we report the findings of a longitudinal, voxel-based morphometry study in first-episode schizophrenia. Sixteen first-episode schizophrenic patients (12 males, with a mean age of 26.3 years, range 16-45) were recruited after first presentation to psychiatric services and followed up after a mean interval of 1329 days. High-resolution T1-weighted volumetric images were acquired using a 1.5T MR scanner at baseline and follow-up, and processed using voxel-based morphometry (SPM2), allowing whole brain analysis. Analysis was performed using custom-made templates composed of baseline and follow-up images for each subject. We assessed symptom severity (SAPS, SANS), cognition (CANTAB) and social functioning (The Social Function Scale) at baseline and follow-up. Statistically significant bilateral loss of grey matter volume was present in prefrontal areas (precentral gyrus, inferior, middle and superior frontal gyrus and Brodmann areas 8,9,10 and 46) in the first-episode schizophrenia group. Symptom severity, cognition and social functioning showed no deterioration over time, but a trend was observed for greater loss of prefrontal grey matter in those patients with poorer symptom severity, cognition and social functioning. This study suggests a progressive loss of prefrontal grey

matter in the early stages of schizophrenia. Longer follow ups of larger cohorts are required to determine whether this grey matter loss continues throughout the course of the illness and whether there is any long-term association with cognitive and social function. This study was supported by programme grant funding from the Wellcome Trust.

CINGULATE CORTICAL THICKNESS VARIABILITY ON THE GRAY/WHITE SURFACE

A. Qiu,* D. Bitouk, L. Wang, J. Ratnanather, J. Csernansky, M. Miller
Dept. of Electrical and Computer Engineering, Johns Hopkins University, Baltimore, MD, USA

Ante-mortem neuroimaging studies as well as post-mortem studies suggest that neuroanatomical abnormalities of the cerebral cortex are common in schizophrenia. So that cortical abnormalities can be characterized precisely in subjects with schizophrenia, methods to more fully investigate the neuroanatomical features of the cerebral cortex in living human beings are needed. In particular, the capacity to measure cortical thickness, which may reflect neuronal organization better than cortical volume in some cortical regions, may be critical for studies of schizophrenia. Cortical thickness varies locally across the brain from 1.3mm to 4.5mm. For example, cortical thickness in the anterior segment of the cingulate is generally thicker than in the posterior segment of the cingulate gyrus. The present study was performed to develop specific tools to visualize and quantify the variability of cortical thickness in a specific region of the brain (i.e., cingulate gyrus). The boundary between gray and white matter (i.e., the gray/white matter surface) was used as a reference plane. By using automated Bayesian segmentation of the cortex and the generation of a gray/white matter surface composed of a fine triangulated mesh of points, each voxel was labeled as gray, white, or CSF as a function of distance from the gray/white matter surface. We previously named this method labeled cortical mantle distance maping (LCMDM)[1]. In the present study, we used LCMDM to augment the information available for each voxel by determining the distance between the voxel and the closest vertex on the gray/white surface. Thus, for each vertex on the gray/white surface, all gray matter voxels that belonged to it and its neighbors were found. The histogram of the distances from the surface to the voxels allowed for the direct calculation of the statistics of cortical thickness and variation as a function of position on the surface. Cortical thickness was then defined using the 90th percentile of these distances and the thickness measure was superimposed onto a map of the cingulate gyrus gray/white surface in a population of five healthy control subjects. Reference: [1] Miller M. I. et. al., 2003, PNAS, 100:15172-15177. Supported by grants: MH-71616.

TEMPORAL CORTICAL DYSMATURATION IN OFFSPRING OF SCHIZOPHRENIA PATIENTS

R. Rajarethinam,* S. Sahni, D. Rosenberg, J. Stanley, M. Keshavan
Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, MI, USA

Superior Temporal Gyrus (STG) consisting of primary auditory and auditory association areas is believed to play a significant role in the pathology of schizophrenia. STG has been found to be smaller in schizophrenia, including in drug naive patients. Recently we reported STG volume reduction in young offspring of schizophrenia patients who are at increased risk of future schizophrenia. Maturation of brain follows a non linear path with temporal lobe volume peaking around age 16 but maturational changes of the STG among genetically at risk are not known. We examined our hypothesis that the offspring will not follow the normal pattern of peak and decline during teen years using a cross sectional analysis of STG volumes. MRI (124 T1-weighted 1.5-mm coronal) from 29 healthy offspring (15 males, 14 females, mean age=14.9 years, SD=3.4) of one parent with schizophrenia or schizoaffective disorder and 27 healthy comparison subjects (14 males and 13 females, mean age=16.9 years, SD=5.7) with no family psychiatric history were used to measure intracranial volume and STG (gray and white). No difference was found in age, IQ, and intracranial volume between the groups. STG was found to be smaller bilaterally in high risk (reported earlier). To examine the age related change (maturation) in the STG, partial correlation analysis was performed with age in each group controlling for total brain volume. Among the normal control subjects, the total STG (R=-0.402, D.F=25 P=0.03), left STG (R=-0.398, D.F=25, P=0.04) and left anterior (R=-0.473, D.F=25, P=0.01) and right anterior STG (R=-0.40, D.F=25, P=0.039) showed significant negative correlations with age but none of them showed any significant correlation in the offspring. The distribution of the volumes in comparison subjects followed the expected nonlinear path with a peak at the age of 15 but no such distribution was observed in the offspring. There is growing support for the involvement of language related brain areas in schizophrenia prior to the onset of psychosis. These data suggest a possibility of differential maturation/development of STG in genetically at risk young offspring of schizophrenia patients. This maturational difference may reflect a failure in the early development and/or mistimed or inadequate pruning of STG that may reflect increased vulnerability. Further studies with large samples and longitudinal follow up will help elucidate the neurodevelopmental underpinning of this crucial area.

VENTRICULAR ENLARGEMENT AS A PREDICTOR OF THERAPEUTIC RESPONSE IN SCHIZOPHRENIA: A STRUCTURAL MRI STUDY

P. C. Sallet,* H. Elkis, T. M. Alves, J. N. Henna, J. R. Oliveira, C. Campi de Castro, G. F. Busatto, W. F. Gattaz
Psychiatry, University of Sao Paulo, Sao Paulo, Brazil

Background: The identification of predictive factors concerning therapeutic response in schizophrenic patients is important to the choice of effective antipsychotics and prevention of unnecessary side effects. On a neuropathological point of view, after several morphometric studies the issue of ventricular enlargement or cortical atrophy as predictors of poor outcome remains controversial. The aim of present study is to investigate brain structure as putative predictor of therapeutic response in schizophrenic patients. Methods: Forty schizophrenic patients (DSM-IV, 24 males and 16 females, age of 34 (8) years, duration of illness of 15.8 (8.4) years) under conventional antipsychotics were studied with brain MRI at baseline. Structures investigated were brain volume (right plus left hemispheres), hippocampus, planum temporale and ventricular-brain ratio (VBR). Psychopathology was assessed by the Positive and Negative Syndrome Scale (PANSS) at baseline and after a 6-week follow-up (in which 28 patients were switched to atypical antipsychotics). Changes in symptom scores were measured as a percent of change relative to the baseline score (PANSSbaseline - PANSS6th week / PANSSbaseline). Results: Bivariate correlation analyses showed

significant negative correlations between change in symptom scores and VBR (Pearson r= -0.34; p= 0.03). Such correlation remained significant after controlling for gender, age, duration of illness, and type of antipsychotic (r= -0.35; p= 0.03). There were no other significant correlations between change in symptom scores and morphometric parameters. Conclusion: This study supports the notion that schizophrenic patients with ventricular enlargement are less responsive to antipsychotic therapy, no matter if conventional or atypical ones.

CAN STRUCTURAL MRI MEASURES PREDICT OUTCOME IN FIRST-EPISODE SCHIZOPHRENIA?

J. Schroeder,* C. Bottmer, M. Essig, S. Bachmann
Psychiatry, University of Heidelberg, Heidelberg, Germany

Objective: Brain pathomorphology is often found in schizophrenia with ventricular enlargement and gray matter (GM) decrease being the most unequivocal abnormalities. These structural abnormalities seem to be related to function and outcome. We studied the question whether pathomorphology detected in the first episode of schizophrenia already points to specific outcome characteristics. Method: Twenty-five patients in remission of their first psychotic episode were included in the study and examined with established instruments to assess diagnoses, psychopathological symptoms, and predictors of outcome. They were reexamined 14 months later using the same instruments. MRI scans had been obtained as part of the diagnostic work-up with a 1.5-T whole body scanner (Magnetom Vision, Siemens Med. Systems, Germany). Scans were analyzed according to Tailarach spaces using BRAINS software. Results: During the follow-up period, 22 individuals adhered to psychiatric treatment regularly. Psychopathological symptoms and predictors of outcome had remained almost unchanged, and 17 patients were in recovery at follow-up. Regression analyses revealed that frontal GM bilaterally played an important role in the prediction of first episode schizophrenia patients′ one-year symptomatic outcome, and that adherence to medication was of importance for both symptomatic and functional outcome. Conclusions: Compliance with medication and frontal GM may predict outcome in first-episode schizophrenia. The underlying pathophysiologic processes have not been fully identified but may consist of persistent psychosis exerting an unfavorable influence on structure.

INCREASED WATER DIFFUSIVITY IN THE FRONTO-TEMPORAL LOBE OF SCHIZOPHRENIA

Y. Shin,* D. Kim, T. Ha, H. Park, J. Lee, W. Moon, E. Chung, J. Kwon
Department of Psychiatry, Seoul National University College of Medicine, Seoul, South Korea

The notion that schizophrenia, as conceived by Kraepelin, is a neurodegenerative disorder has been challenged by the lack of brain pathology manifesting the distinct process of neuronal degeneration. Recent developments in magnetic resonance imaging including the diffusion tensor imaging (DTI) enable the subtle changes in brain cytoarchitecture to be probed. To investigate the cytoarchitectural integrity of schizophrenia, twenty patients with DSM-IV schizophrenia and twenty matched control subjects underwent DTI and structural MRI. Apparent diffusion coefficient (ADC) as an index of the degree of tissue damage was determined from DTI and analysed using voxel-based morphometry. As a result, there was increased ADC in the extensive bilateral fronto-temporal regions in patients with schizophrenia compared with controls. The findings of increased water diffusivity in the bilateral fronto-temporal regions in schizophrenia suggest that there may be wide spread non-focal brain tissue disintegrity in schizophrenia.

LONGITUDINAL CHANGES IN BRAIN VOLUME IN PATIENTS WITH FIRST-EPISODE SCHIZOPHRENIA: AN EXPLORATORY ANALYSIS OF 91 PATIENTS

R. Steen,* G. Gerig, H. Gu, D. Perkins, R. Hamer, J. A. Lieberman
University of North Carolina, Chapel Hill, NC, USA

Introduction: There are robust deficits in brain volume in chronic schizophrenia (SZ), yet it is not clear when such deficits emerge. We undertook a study using magnetic resonance imaging (MRI) to determine if volume deficits are present in patients at diagnosis, and whether these changes are progressive. Methods: We prospectively compared 91 first episode patients to 37 age-similar controls at baseline, and a subset of 48 patients and 26 controls in a longitudinal study at 6 month follow-up (FU). Patients were recruited from local clinical psychiatric services, and healthy controls were recruited by print and radio advertisements. Patients were included if they met DSM-IV criteria for SZ or schizophreniform disorder, were age 16-40, had a lifetime exposure to anti-psychotic medication of < 16 weeks, and were free of other medical disorders. Controls were recruited if they had no personal or family history of an Axis I disorder. All MRI was performed on a 1.5T GE Signa, using T1-weighted (T1W) and T2-weighted (T2W) sequences. A 3D inversion recovery (IR)-prepped spoiled-GRASS T1W was followed by a fast spin-echo T2W multi-planar acquisition. Brain volumes were measured with programs developed in our laboratory and available on the web (http://www.cs.unc.edu/~gerig/soft.html) with documentation. Baseline data were registered to an atlas (and FU data were registered to baseline); 3-channel segmentation used an automated, atlas-based program; images were parcellated into 16 Talairach coordinate boxes that coarsely represent left and right brain lobes; and ventricular volume was measured. Results: There were no significant differences between 91 patients and 37 controls at baseline. However, in both patients and controls, there was a significant ($p < 0.02$) decrease in frontal gray matter (GM) volume over 6 months, which may be age-related. There were also significant volumetric changes over 6 months that were unique to patients, including: a 5% increase in ventricular volume ($p = 0.0009$); a 1% increase in whole brain white matter (WM) volume ($p = 0.02$); a 2% increase in parietal WM volume ($p = 0.006$); and a 5% increase in occipital WM volume ($p = 0.01$). Conclusions: Brain volume changes in patients occur in the context of ongoing developmental changes that affect the healthy brain. Patient volumetric changes prior to diagnosis are subtle, if present at all, but volumetric changes characteristic of SZ may begin to emerge at diagnosis.

DECREASED FRONTAL CORTICAL THICKNESS IN PATIENTS WITH FIRST-EPISODE SCHIZOPHRENIA WHO ARE NONRESPONSIVE TO AYTPICAL ANTIPSYCHOTICS

P. R. Szeszko,* D. R. Robinson, K. L. Narr, J. M. Kane, P. M. Thompson, R. P. Woods, Y. P. Wang, A. W. Toga, R. M. Bilder
Department of Psychiatry Research, The Zucker Hillside Hospital, Glen Oaks, NY, USA

Introduction: The identification of predictors of response to antipsychotic medications in patients with schizophrenia is an important goal for imaging research. Conventional magnetic resonance (MR) imaging morphometry has been used to predict outcome with some success, but this approach may be less sensitive compared to more advanced cortical pattern matching algorithms that can control for inter-individual differences in anatomy and allow highly localized changes in gray matter thickness to be compared between groups. Methods: Magnetic resonance (MR) imaging exams consisted of 124 coronal images (slice thickness = 1.5 mm) acquired using a 3D Fast SPGR with IR Prep (TR = 12.7 or 14.7, TE=4.5 or 5.5ms, FOV=22cm, matrix=256x256) at 1.5T. Forty-five (35M/10F) patients experiencing a first-episode of schizophrenia who were enrolled in a treatment trial comparing the efficacy of risperidone (dosage range = 1 to 6mg) versus olanzapine (dosage range = 2.5 to 20mg) received MR imaging exams either prior to or close to the onset of treatment (median days on medication before MR exam was 0; longest period was 36 days). Treatment response was operationally defined as meeting the following criteria on 1 or more ratings during the first 16 weeks of trial participation: a rating of 3 or less on the following SADS-C items: severity of delusions, severity of hallucinations, impaired understandability, derailment, illogical thinking, bizarre behavior and a rating of 1 or 2 on the Clinical Global Improvement scale. Thirty-two of the 45 subjects met response criteria. Results: Statistical maps, obtained by comparing cortical thickness at thousands of homologous locations across the cortical mantle, showed significant regional grey matter thinning in the frontal lobes extending to the frontal pole and orbital frontal region bilaterally in the nonresponders compared to the responders. Regional increases in thickness in nonresponders compared to responders were largely absent with the exception of some subtle increases observed in mesial temporal cortices. Conclusion: These preliminary findings suggest that cortical pattern matching algorithms may be useful in identifying a subgroup of patients with first-episode schizophrenia who are nonresponsive to atypical antipsychotics at standard dosages.

EARLY DEVELOPMENTAL MILESTONES AND BRAIN STRUCTURE IN PATIENTS WITH SCHIZOPHRENIA AND CONTROL SUBJECTS

J. M. Veijola,* P. Tanskanen, J. Miettunen, E. T. Bullmore, P. B. Jones, K. Ridler, G. Murray, M. K. Isohanni
Psychiatry, University of Oulu, Oulu, Finland

Background: Schizophrenia has been regarded as a neurodevelopmental disorder. We collected information on infant developmental milestones and adult brain structure in individuals with psychosis and members of the general population. Methods: The ages at which individuals of the Northern Finland 1966 Birth Cohort members learned to stand, speak, and became potty-trained, were recorded at a 1-year examination. All Cohort members been admitted in hospital due to psychosis in adolescence or adulthood were invited for a field survey in 1999-2001 including structural MRI scan of the brain. Control subjects (N=94) with no history of psychosis were randomly selected from the same birth cohort. Volumes of CSF and gray and white matter were measured in 51 schizophrenia patients and in 20 subjects with other psychotic disorders. Results: The volume of CSF in male control subjects was associated statistically highly significantly with age of learning to stand without support. Male control subjects who had learned to stand without support earlier had smaller volumes of CSF than those who had learned the skill later, but in schizophrenia, no relation between development and adult brain CSF was seen. Conclusions: We found that there was a positive association between age of learning to stand and volume of cerebrospinal fluid in control subjects. In subjects with schizophrenia no such association was found. To our knowledge, this is the first study to provide direct evidence that the links between infant development and adult brain structure are different in schizophrenia and the general population.

FIRST-EPISODE THALAMIC VOLUME ASSESMENT WITH MAGNETIC RESONANCE

F. Vila,* B. Khorram, D. Lang, H. Emmerton, G. MacEwan, W. Honer
Docencia, Sant Joan de Deu SSM, Sant Boi de Llobregat, Barcelona, Spain

Background: The thalamus is hypothesized to be a central node of pathophysiology in schizophrenia. Structural abnormalities are reported mainly in chronic patient samples, particularly smaller thalamic volumes in patients with schizophrenia. We conducted a structural magnetic resonance (MR) assessment of the thalamus in first-episode schizophrenia patients. Subjects: 21 DSM-IV schizophrenia patients (mean age 20.7 years; 15 male) at the first presentation of illness (patients had less than 8 weeks of lifetime exposure to antipsychotic treatment) and 26 age and gender-matched volunteers (mean age 20.8; 13 male) were recruited. Method: 1.5mm thick axial SPGR images were obtained on a GES 1.5 T MRI scanner. Manual tracing on axial slices of thalamus by a trained rater (FV) was performed using Multi Tracer software, which allowed visualization in 3 planes simultaneously. Results: Reliability studies showed intra-rater ICC of 0.98 as well as inter-rater ICC of 0.99, for thalamic measurements. Mean total thalamic volumes were 11257.6 mm3 (SD=1398) in schizophrenia subjects and 11005.3 mm3 (SD=1157) in control subjects. There were no significant effects of diagnosis ($F=.72$, $df=1,41$, $p=.39$) gender ($F=.21$, $df=1,41$, $p=.64$) or age ($F=1.17$, $df=1,41$, $p=.28$) whereas intracranial volume had a significant effect ($F=37.55$, $df=1,41$, $p<.01$). There was no diagnosis-by-gender interaction ($F=2.92$, $df=1,41$, $p=.09$). In a separate analysis there was no significant effect of hemisphere ($F=.751$, $df=2,90$, $p=.47$) nor was there a group-by-hemisphere interaction ($F=.877$, $df=1,90$, $p=.35$). Conclusions: No abnormalities in whole thalamic volume in first-episode schizophrenia patients were found. Further analyses are required to test for localized thalamic differences.

ASSOCIATION BETWEEN WHITE MATTER MICROSTRUCTURE AND CSF VOLUME IN SCHIZOPHRENIC SUBJECTS

J. P. Vuchetich,* N. D. Davenport, S. R. Sponheim, K. O. Lim
University of Minnesota, Minneapolis, MN, USA

Brain ventriculomegaly has long been implicated as a pathological finding in schizophrenia. Recently, a reduced level of white matter directional coherence, reflected in fractional anisotropy, has also been found in schizophrenic subjects. We here examine the relationship between these two disparate indices of brain pathology in 14 schizophrenic subjects. The percentage of total brain volume consisting of cerebrospinal fluid (percentage CSF) was obtained from structural magnetic resonance images of whole brain. This comprised our measure of relative ventricular size. Measures of frontal white matter fractional anisotropy (frontal FA) were obtained using diffusion tensor imaging. Percentage CSF is strongly negatively correlated with frontal FA in these patients. A similar correlation was noted in a small group of normal control subjects. Subject age but not gender was found to correlate with percentage CSF and frontal FA. Significant correlations remained between these two pathologic indices after controlling for relevant demographic variables. This work was supported by MH060662, the MIND Institute, and the Department of Veterans Affairs.

VOLUME, SURFACE AREA, AND THICKNESS OF THE CINGULATE GYRUS IN SCHIZOPHRENIA SUBJECTS

L. Wang,* J. C. Trein, M. H. Gado, M. Hosakere, J. T. Ratnanather, M. I. Miller, J. G. Csernansky
Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA

Post-mortem studies of schizophrenia subjects have suggested that abnormalities of the architecture of the cingulate gyrus, especially its anterior segment, may be a characteristic of the disease. In this study, high-resolution magnetic resonance (MR) scans and labeled cortical mantle distance mapping were used to make independent assessments of volume, surface area and thickness of the anterior and posterior segments of the cingulate gyrus. T1-weighted MR scans were collected in 54 schizophrenia subjects and 68 healthy controls matched for age, gender and parental socioeconomic status. The cingulate surface at the gray matter/white matter interface was then defined using a triangulated graph, and each gray matter voxel was labeled by its distance to the nearest triangle vertex on this graph. These distances were then used to produce a histogram to characterize cingulate cortical gray matter in each subject. Volumes were calculated by summing the histogram. Normalizing the histogram gave rise to a cumulative distribution function (CDF), and then per subject average GM thickness was defined as a percentile of the CDF (e.g., median distance in mm at the 50th percentile). Surface areas were calculated as the sum of areas of each triangle in the surface. All values were covaried for total cerebral volume. In the anterior segment of the cingulate gyrus, the schizophrenia subjects demonstrated a smaller volume ($p=.0009$), 50th-percentile mantle thickness ($p=.015$) and surface area ($p=.046$) as compared to the healthy controls (one-tailed). In the 50th-percentile mantle thickness measure, there was also a significant L>R asymmetry ($p < .0001$), but no group by hemisphere interaction. In the posterior segment of the cingulate gyrus, schizophrenia subjects demonstrated a smaller volume ($p<.0001$) and 50th-percentile mantle thickness ($p=.026$) (one-tailed), and a trend toward a smaller surface area ($p=.085$). In this region, there was also highly significant asymmetry in the surface area (hemisphere effect $p=.0085$) and 50th-percentile mantle thickness measure (hemisphere effect $p = .029$), but no group by hemisphere interactions. These results suggest that the cingulate gyrus is smaller overall in schizophrenia subjects as compared to healthy controls. Support Contributed By: MH56584,MH71616,P41-RR15241.

CLINICAL CORRELATES OF WHITE MATTER INTEGRITY IN PATIENTS WITH CHRONIC SCHIZOPHRENIA

J. R. Wozniak,* A. B. Silverman, S. R. Sponheim, N. D. Davenport, A. E. LaFave, K. O. Lim
Psychiatry, Univ. of Minnesota, Minneapolis, MN, USA

Eighteen patients with schizophrenia (SZ) and matched controls (CTL) underwent neuropsychological evaluation and Diffusion Tensor Imaging (DTI). Mean age was 43 and the majority were male. Patients had diagnoses of SZ (n=16) or schizoaffective disorder (n=2) based on DSM-IV criteria from the Diagnostic Interview for Genetic Studies (DIGS) or Structured Clinical Interview for DSM-IV (SCID). Subjects were given a battery tapping domains consistently impaired in SZ: executive function, memory, attention, and motor skill. Premorbid intellectual functioning was assessed. The SZ group displayed lower scores on all domains and pre-morbid IQ. MRI scanning was performed on a 1.5T GE Signa LX Scanner. For DTI, six non-collinear directions were collected with four averages (pulsed gradient single shot EPI, TR/TE=6000/95 ms, FOV 240 mm, b=800 s/mm2, 18 slices, 5 mm thick, 0 mm gap, oblique axial, AC-PC aligned, NEX=4). Eddy current corrections were applied prior to computation of fractional anisotropy (FA). ROIs were placed bilaterally by hand, blind to subject group, in superior & inferior frontal and occipital white matter. Repeated measures ANOVA revealed group differences (SZ vs. CTL). Follow-up ANOVAs revealed that SZ patients had 10% lower FA than CTL in superior frontal regions and 9% lower FA than CTL in inferior frontal regions. No group difference was found in occipital regions. The data replicate our prior findings of white matter abnormality in SZ. Using ROIs, the relationship between frontal FA and symptom pattern was examined. A significant inverse correlation was found between BPRS negative symptoms and right inferior frontal FA ($r=-.56$, $p=.03$). The correlation with left inferior frontal FA was nearly significant ($r=-.49$, $p=.06$). This finding replicates our earlier findings using the SANS. We also explored the potential disruptive effects of SZ on brain maturation over the lifespan. In healthy CTL, we observed a significant correlation between age and FA values in superior frontal WM bilaterally ($r=-.66$, $p=.003$). In contrast, there was no correlation in patients with SZ ($r=.07$). The data suggest a disruption in normal brain maturation in SZ. This relationship between age and FA is not evident in more posterior white matter for either healthy CTL ($r=-.06$) or patients with SZ ($r=.19$). Overall, our findings suggest that DTI measures of white matter integrity are associated with important

clinical phenomena. Supported by MH-060662 & the MIND Institute.

CLINICAL CORRELATES OF MRI BRAIN VOLUMES IN FIRST EPISODE PSYCHOSIS

R. B. Zipursky,* H. Gu, C. Charles, T. Sharma, A. I. Green, R. E. Gur, R. S. Kahn, D. Perkins, R. Keefe, R. M. Hamer, G. D. Tollefson, M. Tohen, J. A. Lieberman
Psychiatry, University of Toronto, Toronto, ON, Canada

Reports of clinical correlates of MRI-derived brain volumes in schizophrenia have been inconsistent likely as a result of small sample sizes, differences in patient sampling and processing of MRI data. We sought to investigate clinical correlates of MRI-derived brain tissue and fluid volumes using a large sample of MRI scans acquired for an industry study of first episode schizophrenia. All subjects enrolled in a randomized clinical trial comparing olanzapine and haloperidol for the treatment of a first episode of non-affective psychosis underwent an MRI scan within the first 2 weeks of the protocol. Scans were acquired at baseline from 239 patients at 14 sites in North America and Europe and compared with scans acquired from 57 healthy age, sex and race matched healthy comparison subjects scanned at 4 of the sites. Scans were processed using software developed to classify brain voxels as representing gray matter, white matter or cerebrospinal fluid. In order to evaluate MRI changes associated with disease, we controlled for the effects of age, gender, ethnicity and body size by fitting a model for each structure using these variables. The estimated models were used to generate residual values which reflected the difference between observed and predicted values for each patient. These residual values were then used to investigate clinical correlates using a backward model selection procedure for each brain measure. After adjustment for age, gender, race and height, significant deficits in volumes were found for intracranial volume (2.5%, p=.01), total gray matter volume (2.6%, p=.03) and total white matter volume (3.1%, p=.01). Using the backward model selection, gray matter and white matter measures were not found to be associated with baseline measures of symptom severity or duration of untreated illness. Smaller total intracranial volume, tissue volume and gray matter volumes were significantly associated with a history of previous antipsychotic treatment. In summary, small deficits in total volume as well as gray and white matter volumes were identified in this large group of subjects presenting with a first episode of psychosis. These differences may in part be related to previous treatment with antipsychotic medications. This work was supported by Eli Lilly and Co., Indianopolis, IN.

WHOLE-BRAIN DEFORMATION BASED MORPHOMETRY MRI STUDY OF SCHIZOPHRENIA

R. C. Gur,* C. Davatzikos, D. Shen, X. Wu, Y. Fan, P. Hughett, B. I. Turetsky, R. E. Gur
Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

Neuroanatomic abnormalities in schizophrenia may underlie behavioral manifestations and their characterization is required for interpreting functional data. Frontotemporal abnormalities have been documented with predetermined regions of interest approaches, but deformation based morphometry permits examination of the entire brain. We applied an automated MRI segmentation (1) and parcellation method (2) and feature classifier (3) using high-dimensional shape transformations in 69 patients with schizophrenia (46 men and 23 women) and 79 healthy participants (41 men and 38 women) and examined its sensitivity to diagnosis, sex differences and medication effects. Reduced GM and increased ventricular CSF in patients were found for the whole brain and in specific foci: the hippocampus and adjacent white matter, the cingulate and orbitofrontal cortex, frontal and parietal-temporal areas, and in occipital areas near the lingual gyrus. The classifier had excellent diagnostic sensitivity and acceptable specificity in men, while in women specificity was superior to sensitivity. Patients treated with neuroleptics (N=37) showed increased basal ganglia volume and reduced temporal volume relative to neuroleptic naive patients (N=32). Our study confirms previous findings on frontotemporal reduced volume and suggests new hypotheses, especially involving occipital association and speech production areas. The results also suggest finer localization of volume reduction in the hippocampus and other limbic structures, and in the frontal lobe. Used in conjunction with a nonlinear pattern classification technique, these morphological measurements were sensitive and specific for the diagnosis of schizophrenia, suggesting the utility of MRI as a diagnostic tool. Supported by NIH grants R01AG14971, MH60722, MH64045. 1. Gur RE, et al. (1999). Reduced gray matter volume in schizophrenia. *Arch Gen Psychiatry*, 56:905-911. 2. Davatzikos C, et al. (2001). Voxel-based morphometry using the RAVENS maps: Methods and validation using simulated longitudinal atrophy. *Neuroimage*, 14:1361-1369. 3. Shen DG, Davatzikos C. (2003). Very high resolution morphometry using mass-preserving deformations and HAMMER elastic registration. *Neuroimage*, 18:28-41.

PROGRESSIVE BRAIN CHANGES IN PATIENTS WITH SCHIZOPHRENIA: A 5-YEAR LONGITUDINAL MRI STUDY ACROSS THE COURSE OF ILLNESS

N. E. van Haren,* H. E. Hulshoff Pol, W. Cahn, H. G. Schnack, R. Brans, D. L. Collins, A. C. Evans, R. S. Kahn
Department of Psychiatry, Rudolf Magnus Institute of Neuroscience, Utrecht, Netherlands

Patients with schizophrenia show decreases in whole brain volume, particularly gray matter, and increases in ventricular and peripheral cerebrospinal fluid (CSF) volume as compared to healthy subjects. However, it is unresolved whether these changes are static or progress over time. Two high resolution Magnetic Resonance Imaging brain scans were obtained with a mean interval of 4.89 (sd=0.44) years from 96 patients with schizophrenia and 113 healthy comparison subjects between 16 and 57 years of age. Volume changes of whole brain, cerebral gray and white matter, cerebellum, third and lateral ventricles and peripheral cerebrospinal fluid were compared between patients and healthy subjects. To investigate progressive changes in focal brain areas a voxel-based analysis on the gray and white matter "density" maps was carried out. Patients with schizophrenia showed a larger decrease in whole brain volume (-1.2%) as compared to the comparison subjects (-0.5%) during the scan-interval, irrespective of age. This decrease in whole brain volume could be explained mainly by a larger decrease in cerebral gray matter volume. Also, a larger increase in third and lateral ventricular volumes was found in patients. The voxel-based morphometry analysis revealed excessive decreases in gray matter density in patients with schizophrenia in the left superior frontal (medial and anterior: Brodmann

areas 9 and 10), left superior temporal gyrus, right caudate nucleus, and right thalamus as compared to healthy individuals. The excessive gray matter density decrease in the superior frontal gray matter was related to an increased number of hospitalizations while a higher cumulative dose of clozapine or olanzapine during the scan interval was related to a smaller decrease in this area. A decrease in density of the caudate nucleus was related to lower use of typical antipsychotic medication. Schizophrenia is characterized by progressive loss of brain tissue across the entire course of the illness. Excessive focal gray matter density loss occurs predominantly in left-sided frontal and temporal cortices. Moreover, the progression in left frontal density loss appears to be related to an increased number of psychotic episodes, with atypical antipsychotic medication attenuating these changes. Thus, the pathological process in schizophrenia may be particularly related to progressive tissue loss in left-sided frontal and temporal gray matter areas.

14. Neuroimaging, Functional

PROPOSAL OF A PARADIGM TO INVESTIGATE THE HUMAN REWARD SYSTEM IN SCHIZOPHRENIC PATIENTS WITH FUNCTIONAL MAGNETIC RESONANCE IMAGING

B. Abler,* S. Erk, H. Walter
Department of Psychiatry, University of Ulm, Ulm, Germany

The capacity to seek rewards as goals is essential to get along in everyday life. Rewards are defined as all stimuli that positively reinforce animal as well as human behaviour. Animal studies have helped to find out that reward processing in the brain is highly associated with activation of orbitofrontal areas, the ventral tegmental area and the basal ganglia, especially the ventral striatum/nucleus accumbens. Dopamine is considered to be the essential neurotransmitter in this mesolimbic circuit. Dysfunction in the mesolimbic dopamine system is considered to contribute to symptoms of schizophrenic patients. Receptors in this circuit are targeted by neuroleptics (Kapur, 2003). In our study we developed a paradigm for investigating the human reward system in schizophrenic patients with functional magnetic resonance imaging (fMRI). In previous fMRI studies money has been found to reliably activate the human reward system (Knutson et al., 2001). Therefore, we chose a simple gambling task. 12 healthy subjects (6 male, 6 female; aged 21-33) with no history of psychiatric disease took part in the study. We used a 1.5 Tesla Siemens Sympony Scanner (TR=1.5 sec, TE=40 msec, 17 slices) to acquire EPI images. Subjects were instructed to react with a button press to two different stimuli to have a 60% chance to win a previously announced amount of money (1 Euro or 20 Cent). In 40% of the trials subjects were not rewarded with the announced amount of money despite pressing the correct button. In the control trials no money was announced, subjects only had to press an arbitrary button and could not win any money. Data were analysed event related using the BrainVoyager Software (BrainInnovation, Maastricht). As intended, analyses of group as well as single subject data showed reliable activation of the reward circuit, especially of the nucleus accumbens/ventral striatum. All subjects did not have difficulties in understanding the task and hardly made any mistakes in performing it. The task was considered as exciting but easy to perform. This makes our task suited for investigating the reward system in schizophrenic patients. Kapur, S. (2003). Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry* 160, 13-23. Knutson, B., Adams, C. M., Fong, G. W., and Hommer, D. (2001). Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci* 21, RC159.

AUDITORY FMRI DIFFERENCES BETWEEN SCHIZOPHRENIC PATIENTS WITH AUDITORY HALLUCINATIONS AND CONTROL SUBJECTS ARE MAINLY RELATED TO THE EMOTIONAL CONTENT OF THE STIMULI

E. J. Aguilar,* J. J. Lull, L. Marti-Bonmati, J. Sanjuan, D. Moratal, M. Robles, J. C. Gonzalez
Psychiatry, Hospital de Sagunto, Sagunto, Valencia, Spain

Our aim was to investigate, using functional magnetic resonance imaging (fMRI), the differences in the response to emotional versus non-emotional words in control subjects and schizophrenic patients with auditory hallucinations. Auditory hallucinations seem to implicate areas involved in the physiological perception of speech, including association areas of the right hemisphere implied in the processing of prosodic aspects of language. An emotional response paradigm was designed to replicate those related to hallucinatory experiences. Both emotional and non-emotional auditory stimuli were given to 10 healthy control subjects and 12 DSM-IV schizophrenic patients. All patients were chronic hallucinators and experienced hallucinations during data acquisition. Whole brain fMRI was performed with a GRE-EPI sequence (2000/50/65°). Two fMRI experiments (hearing words with and without emotional content) were acquired, each with 80 dynamic series, each one lasting 2 seconds, with a block design alternating 20 seconds of rest and 20 seconds of verbal stimuli. Statistical analysis was performed by means of SPM2. Pixel activation amount under emotional stimuli was significantly larger in the schizophrenic group. Both patients and subject had a larger population of pixels under emotional than non-emotional stimuli. In schizophrenic patients with emotional stimuli, the activation was largely bilateral and involved the temporal, frontal and parietal lobes (Table). In control subjects with emotional stimuli, activation was mainly right, but also bilateral, with only the superior temporal gyrus being involved. With no-emotional stimuli, in both patients and controls activated pixels were located only at the right superior temporal gyrus. Our data supports the existence of a similar auditory pathway for schizophrenic patients and controls when non-emotion auditory stimuli are involved. However, under emotional stimuli the brain functions as a whole. These striking differences involving association areas of the right hemisphere give also support to the hypothesis of a broad cerebral network involved in the auditory hallucinatory experience.

numbers=pixel activation

THE NEURAL CORRELATES OF EXTERNAL SPEECH MISATTRIBUTIONS IN PATIENTS WITH HALLUCINATIONS

P. Allen,* E. Amaro, L. C. Johns, C. Fu, S. Williams, P. K. McGuire
Psychological Medicine, Institute of Psychiatry, London, London, United Kingdom

Cognitive models of auditory verbal hallucinations (AVHs) propose that they arise from a breakdown in the monitoring of the intention to generate inner-speech. Psychological and neuroimaging studies of tasks designed to engage verbal-self monitoring (VSM) have provided data consistent with this model. However these findings could be also reflect a problem with the appraisal of degraded sensory stimuli. We modified the VSM task such that participants did not speak aloud but instead passively listen to recording of their own and another's speech, effectively eliminating the self-monitoring component. In a function MRI study it was predicted that a) patients who were prone to AVHs would be more likely than patients who were not prone to AVHs and controls to misidentify distorted recordings of their own auditory speech as alien; and b) that this misattribution in

these patients would be associated with increased activation of temporal cortex. Participants were scanned using fMRI whilst listening to pre-recorded words, in an event-related design. The source (self/non-self) and acoustic quality (undistorted/distorted) were varied across trials. Subjects indicated whether the words were spoken in their own or another person's voice via a button press. Ten patients with schizophrenia who were currently experiencing hallucinations and delusions, ten patients with no history of hallucinations and eleven healthy controls were compared. The data were analysed using X-BAM v3. Analysis of the behavioural data revealed that Hallucinators made significantly more misattribution errors than both Nonhallucinators and controls. Analysis of the fMRI data showed that in controls and nonhallucinators, but not hallucinators, the correct identification of self-speech when it was distorted was associated with activation of the anterior cingulate gyrus. Conversely, the hallucinators but not the other groups showed greater activation in the right superior temporal gyrus when making misattributions. The misattribution of speech seen in patients with AVHs was evident during a task that did not appear to involve self-monitoring. In patients with AVHs the function of the anterior cingulate and right superior temporal corticies appears to be altered relative to both healthy volunteers and patients who are not prone to AVHs when making judgements about the source of perceived speech. Misattributions in this group may reflect abnormal communication between these cortical areas.

FUNCTIONAL DEFICITS IN INDIVIDUAL THALAMIC NUCLEI IN SCHIZOPHRENIA AND THE RELATIONSHIP TO STRUCTURE AND COGNITION

J. Andrews,* J. G. Csernansky, L. Wang, D. M. Barch
Psychology, Washington University in St. Louis, St. Louis, MO, USA

Functional MRI during working memory, encoding, and recognition tasks was used to investigate the role of thalamic function in individuals with schizophrenia and healthy controls. Specifically, we were interested in the degree to which cognitive-task related alterations in thalamic activity occurred in the same thalamic nuclei that have been found to show altered volume and shape measures in schizophrenia, namely the anterior nucleus (AN), the mediodorsal nucleus (MDN), and the pulvinar (PUL). Thirty-six patients and 28 healthy controls matched on age, gender, race and parental socioeconomic status participated in the study. All subjects underwent structural and functional scanning while performing a series of memory tasks, including a 2-back version of the N-back task (working memory), intentional memorization of a series of pictures or words (episodic encoding), and a yes-no recognition task. Whereas previously published studies report global activation differences between the two groups (Barch et al, 2002), the current study focused on activation patterns within 7 individual thalamic regions of interests defined by anatomical and functional criteria. Decreased functional activation within the AN and the MDN was found in patients. These nuclei overlap with sub-regions of the thalamic surface that we previously reported to exhibit morphological abnormalities in schizophrenia (Csernansky et al, 2004). However, there were no significant correlations between specific measures (i.e. eigenvectors) used to capture information about variation in the surface and the corresponding activation patterns within thalamic nuclei. Better behavioral performance during the working memory task among patients was associated with increased functional activation in the AN, the MDN, and the PUL. These results suggest important correspondences between morphological and functional alterations in the thalamus in schizophrenia, and highlight the importance of investigating relationships between brain structure and function. Barch DM, Csernansky JG, Conturo T, and Snyder AZ (2002). Working and long-term memory deficits in schizophrenia: is there a common prefrontal mechanism? *J Abnorm Psycho*l 111(3): 478-94. Csernansky JG, Schindler MK, Splinter NR, Wang L, Gado M, Selemon LD, Rastogi-Cruz D, Posener JA, Thompson PA, and Miller MI (2004). Abnormalities of thalamic volume and shape in schizophrenia. *Am J Psychiatry* 161(5): 896-902.

SCHIZOPHRENIA PATIENTS FAIL TO ACTIVATE THE RIGHT INFERIOR FRONTAL CORTEX DURING A CUE PREDICTING INHIBITION: EVIDENCE FOR LACK OF CONTROLLED PROCESSING

E. Arce,* M. P. Paulus
Department of Psychiatry, UCSD, San Diego, CA, USA

Behavioral inhibition is an important function for daily life and, generally, is defined as the act of withholding or terminating a behavioral response. This investigation tested the hypothesis that individuals with schizophrenia (SZ) do not activate neural substrates to cues that are important for inhibitory control, i.e. fail to activate inhibitory neural substrates when presented with a cue that predicts the withholding of a behavioral response. We compared 16 individuals with chronic SZ (medicated, 16.45 average years of illness) and 16 healthy control subjects matched for age and education. Participants from both groups completed a visual (large square, large circle, small square, small circle) Go/No-go task while undergoing functional magnetic resonance imaging. A particular go cue, a large square, during the Go/No-go paradigm predicted a subsequent no-go trial (small square). The behavioral results demonstrate that participants with SZ and controls do not differ significantly in task performance. There was an overall trend towards greater number of false alarms (i.e., responding to a no-go stimulus) in the SZ group. Finally, when presented with the large square, schizophrenia patients relative to the comparison subjects showed an attenuated response in the right inferior frontal cortex (IFC), an area that has been shown previously to activate during inhibitory tasks. These results support the hypothesis that individuals with SZ lack activation of neural substrates important for inhibition when presented with cues that predict the need to inhibit an action. Thus, lack of inhibitory functioning in SZ may be related to inadequate control mechanisms that are in place to detect behaviorally relevant cues in the environment, a process critically regulated by the right IFC.

FUNCTIONAL MRI EVIDENCE FOR SEMANTIC FAR-SPREADING ACTIVATION IN SCHIZOPHRENIA PATIENTS WITH FORMAL THOUGHT DISORDER

M. Assaf,* C. H. Kuzu, M. A. Kraut, K. M. Groth, V. D. Calhoun, T. Benios, P. R. Rivkin, J. Hart, G. D. Pearlson
Olin Neuropsychiatry Research Center, Institute of Living, Hartford, CT, USA

In the current study we explored the neural correlates of semantic memory retrieval with Formal Thought Disorder (FTD) in schizophrenia using an imaging task that assessed semantic feature-binding. Sixteen healthy controls and 16 schizophrenic patients, whose

FTD symptoms were measured with the Thought Disorder Index, completed a verbal binding task during functional MRI. Participants were presented with two words that described object features which either evoked a semantic concept (i.e., semantic retrieval, also referred to as 'bind' word pairs) or did not bind together to reliably elicit an idea ('non-bind' word pairs). For example, the features 'honey' and 'stings' evoke the recall process for the object 'bee'. Analysis of the behavioral data showed that schizophrenia patients tended to over-bind non-binding feature pairs and to perform more slowly. This over-binding tended to correlate positively with positive symptoms and FTD severity. Functionally, during feature-binding patients overactivated bilateral caudal and rostral anterior cingulate cortex (ACC), temporo-occipital junction, temporal pole and parahippocampus, right inferior frontal gyrus and dorsolateral prefrontal cortex; while underactivating bilateral inferior parietal lobules. Rostral ACC activation positively correlated with FTD severity during correctly bound pair trials. These results support the theory of far-spreading semantic activation underlying the pathophysiology of FTD. Schizophrenia patients showed semantic memory network overactivation, possibly retrieving more distantly-related semantic responses, and abnormal activation of areas involved in verbal working memory and in monitoring and suppression of conflicting responses. These abnormalities potentially led the patients to manifest overbinding in our task and FTD symptoms in general. This work was partially supported by NIMH grants: RO1 MH-60504, R01 MH43775-14 and RO1 MH-52886 (PI: G.D. Pearlson).

FMRI STUDY OF VISUOSPATIAL WORKING MEMORY IN CHILDREN AND ADOLESCENTS WITH VELO-CARDIO-FACIAL SYNDROME

R. Azuma,* L. Campbell, E. Daly, D. Murphy, K. Murphy
Psychological Medicine, Institute of Psychiatry, London, United Kingdom

Background: Velo-cardio-facial syndrome (VCFS) is a genetic disorder that is associated with a microdeletion in the Chromosome 22q11. High prevolence of psychiatric disorder in this population has been known, and especially, about a third of them have been reported to develop schizophrenia in their adolescence and early adulthood. Children with VCFS typically have mild learning disabilities and show deficiencies in specific cognitive areas such as visuospatial, working memory, mathematics abilities and executive functions. Recent imaging studies showed that the VCFS patients have structural abnormalities in various brain regions, including parietal and frontal lobes that are known to be involved in visuospatial and mathematical processing. In this study, we investigated visuospatial working memory processing in VCFS, using functional Magnetic Resonance Imaging (fMRI), to investigate how cognitive deficits are related to the structural brain abnormalities. Method: Fourteen children and adolescents with VCFS and fourteen control children (aged 8-17 for both groups) were scanned while performing a visuospatial working memory task. Results: Both groups showed task related activation in dorsolateral prefrontal cortex (DLPFC) and bilateral parietal association cortices that are associated with working memory. However, the normal group showed gigantically higher levels of activation in these areas. In addition, the normal group showed activation in insula, putamen, premotor cortex and SMA that are related to decision making processes. Conclusions: Previous studies suggested structural abnormalities in these areas in the VCFS population. The results from the current study suggest that genetically determined functional abnormalities in DLPFC and parietal regions may underlie cognitive disorder in VCFS.

CHALLENGING THE SOCIAL BRAIN IN SCHIZOPHRENIA: A SOCIAL JUDGMENT PARADIGM

D. Baas,* A. Aleman, R. S. Kahn
Universiteit Utrecht, Utrecht, Netherlands

Dysfunctional emotional and social information processing appear to be central features of schizophrenia. Earlier research has demonstrated amygdala involvement during processing of social and emotional information in healthy subjects. In order to examine possible abnormalities of amygdala function during social information processing in schizophrenia the need has arisen for a paradigm that can be used to reliably measure amygdala activation. Here, we present a method for measuring abnormalities in social information processing in schizophrenia. The paradigm is taken from earlier research in neurological patients with bilateral amygdala damage. 120 frontal images of faces with a neutral emotional expression were presented to subjects during an fMRI experiment. Subjects (N=8) were required to make trustworthiness judgments about these faces, judging whether the faces are trustworthy or untrustworthy. After scanning subjects are asked to judge these same faces with regard to trustworthiness, this time giving ratings on a scale ranging from one to seven. During subsequent fMRI analyses, these trustworthiness ratings are used as a parametric regressor to locate brain areas that are active during social information processing. We observed an increased response in both the left and the right amygdala during the evaluation of untrustworthy faces (right amygdala; $Z = 3.54$; $p < 0.001$; left amygdala; $Z = 4.63$; $p < 0.001$). In a second experiment, analyses of behavioral data from 18 patients with schizophrenia and 20 healthy control subjects revealed that patients judge faces to be more trustworthy than healthy comparison subjects do; an effect that is most pronounced for faces that healthy control subjects find untrustworthy. The method we present here is a powerful paradigm that yields useful fMRI data (robust bilateral activation of amygdala in healthy people) and behavioral data capable of shedding light on the brain processes that are involved in social information processing in schizophrenia.

PREFRONTAL CORTEX, CONTEXT PROCESSING, AND VULNERABILITY TO SCHIZOPHRENIA

D. M. Barch,* K. Haut, J. G. Csernansky
Psychology, Washington University, Saint Louis, MO, USA

Individuals with schizophrenia reliably demonstrate impairments in dorsolateral prefrontal cortex (DLPFC) activity in a range of cognitive tasks. We have suggested that such impairments reflect deficits in the ability to represent and maintain context information, due to impaired dopaminergic function in DLPFC (Barch et al., 2001; MacDonald et al., in press). Previous research has shown that individuals at risk for schizophrenia (Barch et al., in press; MacDonald et al., 2003) also demonstrate behavioral deficits in context processing. The goal of the current study was to examine whether the unaffected siblings of individuals with schizophrenia also show altered DLPFC activity during context processing. Participants were 19 unaffected siblings of individuals with schizophrenia, 37 healthy controls, and 36 siblings of the controls. Participants completed an AX-CPT task measuring context processing while fMRI was used to measure brain activity. In this task, par-

ticipants see a series of cue-probe pairs and are told to respond target to an X, but only when it follows an A. One run had a short delay (1 sec) between cue and probe and the other run had a long delay (7.5 sec; higher demand for context maintenance). The schizophrenia siblings demonstrated behavioral evidence of deficits in context processing that included both impaired BX trial performance and relatively improved AY trial performance (trials on which intact context normally causes errors and slowed reaction times). The siblings of individuals with schizophrenia showed greater bilateral dorsolateral and inferior prefrontal cortex activity in response to general task demands as compared to controls (e.g., across both short and long delay conditions as compared to fixation). The controls showed increased bilateral DLFPC activity in the long compared to short delay condition. The schizophrenia siblings only demonstrated such increased activity in left DLPFC and not the right DLPFC. These results suggests that individuals at risk for the development of schizophrenia may experience reduced DLPFC in response to specific task demands in the context of a more generalized hyper-DLPFC activity (e.g., inefficient) in response to global tasks demands. These results provide further evidence that deficits in context processing, as well as disturbances in DLPFC function are present in individuals at risk for the development of schizophrenia, but who do not yet have the manifest illness.

THE FUNCTIONAL IMAGING OF NON-CLINICAL AUDITORY HALLUCINATIONS IN NON-CLINICAL HIGH SCHIZOTYPES

E. Barkus,* J. Stirling, R. S. Hopkins, S. Lewis
Neuroscience and Psychiatry, Manchester University, Manchester, United Kingdom

Introduction: The neural basis of auditory hallucinations has been investigated in imaging studies of patients using various activation methods. However, interpretation is complicated by effects of medication and psychotic state. Experimental studies using non-clinical samples avoid these problems but tasks often require training suggesting they do not engage innate processes. Method: We developed an auditory signal detection paradigm which elicits false perceptions in non-clinical samples. The task required participants to detect a voice in 3-second segments of white noise. There was a voice present in 60% of the segments of white noise. In two third of the segments the voice was presented at auditory threshold and at suprathreshold in the remainder. No voice was present in the remaining 40% segments. Eight high-schizotypes were tested inside a 1.5T MR scanner. Brain activations associated with false-perceptions were revealed using event-related analysis. Results: Three subtractions revealed responses to hearing a voice which was present, hearing one which was not, and the difference between false and true perception of a voice. True perceptions were associated with auditory activations although these were predominantly on the right rather than the left. False perceptions of a voice evoked areas of activation in regions previously associated with auditory hallucinations, including the superior temporal lobes, medial temporal lobes, parahippocampus, cingulate and anterior cingulate. Conclusion: Non-clinical auditory hallucinations appear to activate regions previously associated with auditory hallucinations in patients with schizophrenia. High schizotypal subjects show evidence of reversed laterality of auditory processes but further studies are required to substantiate this.

THE EFFECT OF GRM3 GENOTYPE AND OLANZAPINE TREATMENT ON PREFRONTAL CORTICAL FUNCTION IN PATIENTS WITH SCHIZOPHRENIA

A. Bertolino,* G. Caforio, V. Petruzzella, V. Latorre, V. Rubino, S. Di Malta, M. P. De Candia, A. Torraco, B. Kolachana, S. Papa, M. Nardini, D. R. Weinberger, T. Scarabino
Department of Neurology and Psychiatry, University of Bari, Bari, Italy

Earlier studies have suggested that variation within GRM3 (the gene for a type II metabotropic glutamate receptor) alters prefrontal physiology and cognition, increasing risk for schizophrenia. Moreover, chronic exposure to olanzapine up-regulates the expression of type II metabotropic glutamate receptors in prefrontal cortex. Therefore, we evaluated the effect of GRM3 genotype on prefrontal activation during working memory (WM) in patients with schizophrenia treated with olanzapine for eight weeks. 24 Caucasian untreated patients (DSM-IV criteria, 22 males, mean age 26.4±6.9) participated and were treated with olanzapine for eight weeks (fixed dose between four and eight weeks, mean+SD: 20.4±7.6 mg/day). Symptomatology was assessed with the Positive and Negative Symptoms Scale (PANSS) at days 0, 7, 14, four and eight weeks. fMRI was performed with a 3T GE magnet using a gradient-echo pulse sequence (TR 2000 ms, TE 30 ms, voxel 3.75x3.75x5mm) during performance of the N-Back WM task at four and eight weeks of treatment. All fMRI data were processed within SPM99. Patients were genotyped for GRM3 SNPs (previously shown to be associated with schizophrenia - P2627, P2239, and P2633) and COMT val^{158}met. The three GRM3 SNPs were analyzed separately to evaluate the effect of risk alleles. The distribution of COMT val^{158}met genotype was controlled for in all group analyses. ANOVA of PANSS total score did not show any differential effect of any GRM3 SNP on symptoms (all $p>0.1$). ANOVA of performance data (accuracy and reaction time) did not indicate any significant difference at any time point between the groups (all $p>0.1$). Second level (random effects) ANOVA on WM fMRI data indicated no effect of the high risk alleles at four weeks. However, at eight weeks the risk alleles of all three GRM3 SNPs were associated with inefficient activation of prefrontal cortex ($p=0.01$, FWE corrected, $k=3$). These data suggest that, in terms of prefrontal physiology, patients with the risk GRM3 alleles benefit less from treatment with olanzapine. They further suggest that genetic associations with brain phenotypes are much stronger than with clinical phenotypes.

THE INFLUENCE OF ENCODING STRATEGY ON EPISODIC MEMORY AND CORTICAL ACTIVITY IN SCHIZOPHRENIA

A. Bonner-Jackson,* K. M. Haut, J. G. Csernansky, D. M. Barch
Psychology, Washington University in St. Louis, St. Louis, MO, USA

Research suggests that impairments in the ability to spontaneously apply effective encoding and/or retrieval strategies contribute to episodic memory deficits in schizophrenia. The goal of this study was to examine the effect of providing encoding strategies on brain activation during encoding and on subsequent recognition performance in individuals with schizophrenia. Participants with schizophrenia and control subjects underwent fMRI scans while performing encoding and recognition tasks of words and non-famous faces.

During encoding, subjects made either semantic (deep encoding) or orthographic (shallow encoding) judgments for words and gender (deep encoding) judgments for faces. During recognition, subjects indicated whether given words or faces had been seen previously. Individuals with schizophrenia demonstrated better memory for words encoded deeply than shallowly and activated semantic processing regions (left BA 45/47) for deep as compared to shallow encoding tasks. Interestingly, the patients also demonstrated more deep encoding-related activity than controls in anterior left inferior prefrontal regions, as well as activation of homologous right BA 47, perhaps reflecting compensatory memory processes. When oriented towards appropriate strategies, individuals with schizophrenia showed left lateralized prefrontal activity for words and right lateralized prefrontal activity for faces. However, during recognition memory individuals with schizophrenia no longer showed left lateralized prefrontal activity for words, though controls did. When given advantageous strategies, individuals with schizophrenia show enhanced subsequent memory performance and engage task appropriate neural systems. However, when strategy is unconstrained, individuals with schizophrenia show abnormal patterns of brain activity and impaired task performance.

BRAIN ACTIVITY IN RELATION TO EMOTIONAL STIMULI: AN EXPLORATORY FMRI STUDY IN SCHIZOPHRENIA PATIENTS WITH AND WITHOUT PROMINENT AUDITORY HALLUCINATIONS

L. J. Boulay,* E. Stip, A. Mancini-Marie, C. Fahim, A. Mendrek, L. Ait Bentaleb
Psychiatry, University of Ottawa Institute of Mental Health Research, Ottawa, ON, Canada

Background: Functional Magnetic Resonance Imaging (fMRI) has been used to delineate how the normal brain processes different emotions. Some of the regions thought to be involved are the limbic regions, the frontal and temporal cortices, the cerebellum as well as subcortical structures. Persons with schizophrenia often have difficulty interpreting as well as expressing emotion. fMRI studies have demonstrated that these patients do not consistently activate brain regions which appear to be crucial in emotional processing. However, it is difficult to interpret these results since most fMRI studies do not examine patients based on their clinical profile. Objective: To examine if patients who suffer from prominent auditory hallucinations differ in their ability to perceive and experience emotions relative to those who do not have prominent auditory hallucinations. Methods: 19 patients diagnosed with schizophrenia according to DSM-IV criteria were recruited. Of these, 11 presented with prominent auditory hallucinations (Hall) and the remaining 8 did not (No-Hall); based on scores of 4 or more on the hallucination item of the Positive and Negative Syndrome Scale. Using a block design paradigm, all subjects underwent fMRI scanning on one occasion while they viewed two short films: one with sad content and the other with emotionally neutral content. Results: SPM2 was used for data analysis. Since this study was exploratory, alpha was adjusted to .0005 and the extent voxel threshold was set at 5. The neutral condition was subtracted from the sad using random effects modelling. Single sample t-tests revealed that the Hall group showed significant activation in the right parietal region only (BA2) whereas the No-Hall group significantly activated the left inferior temporal gyrus, the left medial temporal lobe, the left medial frontal gyrus, the right middle frontal gyrus, and the left and right cerebellum. Conclusion: This exploratory study suggests that Hall patients process emotional stimuli differently than No-Hall patients. More specifically, the latter group has more diffuse brain activity when processing this type of information. An alternative explanation may be that patients with prominent auditory hallucinations consistently activate brain regions associated with emotional processing regardless of emotional content. This may explain why there was an overall lack of activity in the Hall group resulting from the subtraction method used in this study.

WORKING MEMORY DEFICITS IN INDIVIDUALS WITH SCHIZOPHRENIA AND THEIR HIGH RISK SIBLINGS

S. B. Brahmbhatt,* K. M. Haut, J. G. Csernansky, D. M. Barch
Psychology, Washington University, St. Louis, MO, USA

Individuals with schizophrenia demonstrate impaired working memory and deficits in functional brain activation within dorsal lateral prefrontal cortex (DLPFC). A question of interest is whether these deficits are a component of vulnerability to schizophrenia, or occur only in individuals with the manifest illness. To address this question, this study evaluated working memory and brain activation in unaffected siblings of patients with schizophrenia who are at higher risk for developing schizophrenia. We administered a 2back version of the nback task, a well-validated measure of working memory and executive control, while fMRI was used to measure brain activity. Participants were 36 controls, 36 siblings of controls, 18 patients with schizophrenia and 19 siblings of patients. Participants saw a sequence of stimuli and were told to push one button (target) any time they saw a stimulus that was the same as the stimulus they saw two trials back and another button if the stimulus was not the same as the one presented two trials back (non-target). An additional manipulation included repeated trials (items whose prior presentation was not in the correct nback position), which allowed us to investigate whether patients and their siblings differ in their ability to code the temporal order of items. The results demonstrated that patients and their unaffected siblings performed significantly worse than controls on repeated lure trials, while their performance on repeated target trials was facilitated, suggesting an impairment in the ability to encode the temporal order of items within working memory. In addition, both patients and their siblings demonstrated abnormal brain activation in DLPFC, such that patients had hyperactivation in response to verbal stimuli (i.e., words) and hypoactivation in response to nonverbal stimuli (i.e., faces). These results provide further evidence that disturbances in working memory and DLPFC activation may be endophenotypic markers of vulnerability to schizophrenia. Supported by a Conte Feasibility Center for Neuroscience Research (MH071616-01).

ARE TWO TASKS BETTER THAN ONE?: MULTI-TASK COUPLING OF FMRI INDEPENDENT SOURCES IN SCHIZOPHRENIA

V. Calhoun,* K. A. Kiehl, G. D. Pearlson
Olin Neuropsychiatry Research Center, Institute of Living and Yale University, Hartford, CT, USA

It is becoming common to collect data from multiple fMRI paradigms on a single individual. The data from these experiments are typically analyzed separately and sometimes directly subtracted

on a voxel-by-voxel basis. These approaches, though useful, do not directly take advantage of the joint-information between tasks. To remedy this, we propose a method to extract maximally spatially independent maps for each task, which are "coupled" together by a shared loading parameter. We first compute a first-level activation map for each task followed by the estimation of a joint statistical model at the group level. We demonstrate our approach on a data set derived from healthy controls and schizophrenia patients, each of whom performed an auditory oddball task and a Sternberg working memory task. Results reveal one component that demonstrated significantly decreased connectivity in patients including temporal, frontal, thalamic, basal ganglia and cerebellar regions which have been implicated in several previous models of schizophrenia. Two dimensional task-by-task histograms of the identified voxels were consistent with increased task-specialization in controls (the between-task correlation was greater in patients). It was concluded that analyzing both tasks in a unified statistical framework provided a more complete picture of the fMRI activation maps than subtractive analyses, revealed a common network that was significantly attenuated in patients, and enabled new questions to be posed about fMRI data from multiple paradigms. Our approach can also be applied to data using more that two tasks. It thus provides a way to integrate and probe brain networks using a variety of tasks, and may increase our understanding of coordinated brain networks and the impact of pathology upon them.

NEURAL CIRCUITRY ACTIVITY ASSOCIATED WITH OCULAR MOTOR DELAYED RESPONSE TASK PERFORMANCE IN NORMAL AND SCHIZOPHRENIA SUBJECTS

J. Camchong,* K. A. Dyckman, P. F. Buckley, J. E. McDowell
Psychology, University of Georgia, Athens, GA, USA

Deficits in inhibition and working memory, two characteristics potentially associated with schizophrenia, are presumably mediated by prefrontal cortex dysfunction. To further explore this hypothesis, the present fMRI study compared neural activity of 12 schizophrenia patients and 12 healthy controls while they performed an ocular motor delayed response (ODR) task and fixation. Correct performance of an ODR task may require both inhibition and working memory. During ODR, subjects fixate on a centrally presented target and remember the spatial location of a peripherally presented stimulus flash without moving their eyes toward the stimulus (inhibition). After a 1.7 or 3.4 sec delay period, subjects move their eyes to the remembered location (working memory). The schizophrenia group generated more error saccades during the delay period. Schizophrenia patients showed less ODR-related BOLD signal than normal subjects in the neural circuitry that supports saccade performance: frontal and supplementary eye fields and posterior parietal cortex. Furthermore, while healthy subjects showed increased ODR-related bilateral prefrontal cortex (PFC) activation, the pattern was not evident in schizophrenia subjects. The present results suggest that inhibition and working memory dysfunction in schizophrenia subjects during an ODR task may be associated with neural pathway abnormalities in the PFC and other saccade related regions. This study was supported by a grant from the National Institute of Mental Health.

FUNCTIONAL REORGANIZATION OF CORTICAL ACTIVITIES DURING MOTION PROCESSING IN SCHIZOPHRENIA

Y. Chen,* E. Grossman, L. Bidwell, D. Yurgelun-Todd, S. Gruber, D. Levy, K. Nakayama, P. Holzman
Psychiatry, Harvard Medical School/McLean Hospital, Belmont, MA, USA

Research has significantly increased knowledge about the neural and cognitive mechanisms underlying schizophrenia but many critical questions remain unanswered. In addition to cognitive dysfunctions, schizophrenia patients show deficits in performing sensory and motor tasks that cannot be attributed to a generalized deficit. We previously showed that schizophrenia patients performed poorly in motion discrimination, a sensory task that is normally mediated in the posterior extrastriate cortex. It remained unknown what are the neural correlates of the behavioral deficit in schizophrenia. In this study, we examined functional activation during performance of motion and non-motion visual discrimination tasks to determine whether the posterior cortical system is responsible for the motion discrimination deficit, and what other cortical systems are involved. We used two motion tasks, direction discrimination and velocity discrimination, and a non-motion visual task, contrast discrimination. We employed fMRI methods to examine the pattern of cortical activation while schizophrenia patients (n=10) and normal controls (n=8) performed the three tasks. Psychophysical methods were used to assess behavioral performance before and during the scans. In the middle temporal area (MT) of the posterior cortex, neural activation of schizophrenia patients, measured with BOLD signal changes, was significantly reduced during the direction and the velocity discrimination tasks ($p < 0.02$), but not during the contrast discrimination task. In contrast, neural activation of the patients was significantly increased in the inferior convexity of the prefrontal cortex (ICPFC) during the two motion discrimination tasks ($p < 0.01$), but not during contrast discrimination. These specific patterns of cortical activations indicate that neural processing of visual motion signals, normally mediated in the posterior cortex, is shifted towards the anterior cortex in schizophrenia, implicating altered neural processing at both sensory and cognitive levels in the degraded behavioral performance. The recruitment of cognitive cortical areas to compensate for deficient sensory processing represents one manifestation of neural reorganization in schizophrenia.

A COMPARATIVE FMRI INVESTIGATION OF THE EFFECTS OF CHRONIC CANNABIS USE AND FIRST EPISODE SCHIZOPHRENIA ON CEREBRAL ACTIVATION REQUISITE FOR EXECUTIVE FUNCTION

M. Cohen,* P. Johnston, U. Schall, P. Ward, V. Carr
Centre for Mental Health Studies, Hunter Mental Health, Newcastle, NSW, Australia

Objective The long term heavy use of cannabis has been reported to impair frontal lobe associated functions, including the capacities for attention, concentration and working memory. These deficits have been proposed to be a useful model for understanding the development of neurocognitive dysfunction associated with the negative symptoms of schizophrenia. This study investigates the potential affected common neural substrate that may underpin the frontal lobe impairments associated with first episode schizophrenia and chronic cannabis use. Methods Blood Oxygenation Level Dependent

(BOLD) functional Magnetic Resonance Imaging data were collected for twelve non-psychiatric chronic cannabis users, twelve patients with first episode schizophrenia (no illicit drug use), and twelve matched control subjects, whilst subjects performed the Tower of London (TOL) task. Results In agreement with previous functional Tower of London functional imaging studies, the group random-effects t-statistic across all subjects demonstrated prefrontal, cerebellar and parietal cortex activation [n=26] (P<0.001 uncorrected). The between group random-effects analyses demonstrated that schizophrenia patients showed reduced BOLD activation of the right inferior frontal gyrus when compared to healthy controls (P<0.001 uncorrected). Cannabis users showed reduced BOLD activation of the right inferior frontal gyrus, claustrum and precentral gyrus when compared to healthy controls (P<0.001 uncorrected). There were no significant differences in reduction of BOLD activation between cannabis users and schizophrenia subjects. Conclusion Deficit activation of the right inferior frontal gyrus in the first episode schizophrenia and cannabis using groups suggests a common neural basis for task set switching and response inhibition deficits commonly reported in both groups. Control subjects activation in the right precentral gyrus was significantly greater than cannabis using subjects that may reflect a possible effect of swallowing or other motor linked cortical activation, whilst right claustrum activation differences suggest potential deficits of multimodal sensory integration. These findings are discussed in the context of schizophrenia and cannabinoid physiology.

SCHIZOPHRENIA PATIENTS SHOW DECREASED ACTIVATION OF THE RIGHT PREFRONTAL CORTEX DURING A SPATIAL WORKING MEMORY TASK

M. J. Coleman,* S. Matthysse, D. L. Levy, D. Yurgelun-Todd, J. Rogowska, S. Gruber, P. S. Holzman
Psychology Research Laboratory, McLean Hospital, Belmont, MA, USA

Several independent studies have reported that spatial working memory is impaired in schizophrenia patients. Neuroanatomical and neurophysiological studies of nonhuman primates suggest that the prefrontal cortex, particularly the dorsolateral prefrontal cortex, plays a crucial role in spatial working memory. Human functional imaging studies have demonstrated right-sided specialization of the prefrontal cortex for spatial working memory tasks. We conducted a functional neuroimaging experiment using a spatial delayed-response task in a 1.5 Tesla GE scanner. We tested 10 normal control subjects (4M, 6F) and 13 schizophrenia patients (8M, 5F) at 20-sec and 250-msec delay intervals. Subjects were all right handed and matched for age, estimated verbal IQ, and years of education. Compared with controls, schizophrenia patients showed less activation of the right prefrontal cortex during the 20-sec delay but not during the 250-msec control task. Identifying Brodmann areas 9, 10, and 46 as our regions of interest and using a multiple comparison permutation method, we found that during the 20-sec delay schizophrenia patients activated significantly less ($p < .05$) in area 9 on the right side compared with the controls. There was also a trend for schizophrenia patients to activate more in area 10 on the left compared with controls, suggesting that a generalized failure to activate does not explain our results. Area 46 showed very little activation in both groups. As a group, schizophrenia patients were significantly less accurate than controls ($p < .004$) on the 20-sec delay task but a subgroup of patients performed comparably to the controls. Functional activation was not related to performance in these subgroups of schizophrenia patients. These results support previous findings suggesting a relationship between the right dorsolateral prefrontal cortex and impaired spatial working memory in schizophrenia.

EARLY AUDITORY SENSORY PROCESSING IN SCHIZOTYPAL PERSONALITY DISORDER: A FMRI STUDY

C. C. Dickey,* M. Kubicki, I. Morocz, M. E. Shenton, M. Dreusicke, E. Connor, L. J. Seidman, M. Voglmaier, M. Niznikiewicz, V. Paynter, R. W. McCarley
Psychiatry, Harvard Medical School, Brockton, MA, USA

Males with schizotypal personality disorder (SPD) have been shown using structural MRI to have reduced volumes in the left superior temporal gyrus (STG) gray matter and, more specifically, in Heschl's gyrus. Heschl's gyrus, similar to Brodmann area 41, primary auditory cortex, is critical for the processing of tones. How these regions function in processing auditory information in SPD subjects, however, is less well-known. The aim of this study was to examine simple, early, auditory processing in SPD using a passive, auditory fMRI task. Neuroleptic-naive male subjects were recruited from the community and diagnosed with SPD. 13 SPD and 14 comparison subjects completed the experiment. Subjects heard 30 seconds blocks of tones followed by rest. The blocks consisted of tones of intermixed frequencies (500 Hz, 75% probability, and 2000 Hz, 25% probability), high, or low pitched tones (100ms/tone). Images were acquired obliquely (6mm,1mm gap). Data has been processed (SPM2) for 6 SPD and 6 comparison subjects. WFU Pick Atlas was used to identify the activation in the STG and Brodmann areas 41 and 42. The extent of activation and peak activation was compared between the 2 groups with t tests. Six SPD subjects demonstrated fewer activated voxels in Brodmann area 41 on the left compared with six controls while listening to blocks of tones of differing frequencies and, at the trend level, while listening to blocks of tones of a single frequency. On the right side, SPD subjects demonstrated fewer activated voxels in area 41 at the trend level compared with controls while hearing tones of differing frequencies. In area 42 on the left, SPD subjects demonstrated fewer activated voxels at the trend level while hearing single tones compared with controls. Preliminary data suggests that SPD subjects compared with controls, have abnormalities in processing simple, auditory inputs. This is demonstrated by SPD subjects activating fewer voxels in the primary auditory cortex while hearing tones of differing frequencies and possibly while hearing a single frequency. This is particularly the case in area 41 on the left. Although firm conclusions await complete analysis of the remaining subjects, this suggests that some of the deficits in SPD language processing may occur at very early stages. Support: VA Advanced Career Development Award (CCD), VA REAP Award (RWM), Brigham & Women's Hospital Translational Neuroscience Award (CCD, MK), and NIMH RO1 awards (RWM, MES).

LANGUAGE PROCESSING INVOLVING THEORY OF MIND IN SCHIZOPHRENIC PATIENTS: A FMRI STUDY

S. Dollfus,* A. Razafimandimby, P. Lebain, A. M. Melot, E. Mellet, P. Delamillieure, P. Brazo, G. Perchey, N. Tzourio-Mazoyer
Centre Cyceron, UMR 6194 CNRS/CEA/University Caen/University Paris V, Caen, France

Comprehension of stories involving persons requires not only a lexico-syntactico-semantic analysis but also the ability to infer the men-

tal states of the characters. Deficits of comprehension in schizophrenic patients could be due as well to language disorders related to atypical (right) hemispheric specialization (HS) (Dollfus, 2004) or to deficit in their ability to elaborate a model of other mental states (Theory Of Mind processing (TOM)). In order to clarify this point, we selected patients with typical left HS for language to investigate the existence of functional cerebral impairments during the listening of a story for which its comprehension necessitates the representation of the mental content of individuals (Mazoyer, 1993). Among 31 schizophrenic (DSM IV) patients matched on 31 controls on sex, age and level of education, we selected 21 pairs of subjects who presented a left HS for language evaluated with fMRI (Dollfus, 2004). The task consisted in listening to the story in French and Tamil alternatively. A comprehension score was calculated after fMRI. With the French-Tamil contrast maps, we conducted a group analysis (SPM t-test) and individual analyses on individual signal variations in the functional region of interest. Patients compared to matched controls presented significant lower comprehension scores. They also exhibited lower signal variations in the left superior medial prefrontal region (Zscore = 7.89, $p < 0.05$ corrected; x, y, z = - 6, 54, 16) which has been shown to be a key area in TOM processing (Gallagher, 2003). Individual analyses in the medial prefrontal showed that all controls except 3 (86%) presented activation of this area while 76% of the patients had negative signal variations. No correlation was observed between comprehension scores and signal variations in any groups. The absence of recruitment of the left superior medial prefrontal cortex could be taken as the neural correlate of a defect of TOM processing in schizophrenic patients with normal hemispheric specialization, leading to impaired story comprehension.

ABNORMAL RETROSPLENIAL CORTEX ACTIVATION DURING THE ENCODING AND RECALL OF EMOTIONAL WORDS IN SCHIZOPHRENIA

L. Flashman,* A. J. Saykin, R. M. Roth, R. M. Vidaver, H. A. Wishart, B. C. McDonald, M. J. Friedman, K. T. Mueser
Psychiatry, Dartmouth Medical School, Lebanon, NH, USA

A growing body of literature has suggested that the retrosplenial cortex is involved in evaluating the emotional salience of information from external sources in healthy controls. Because schizophrenia (SCZ) has been associated with disturbed processing of emotional information, we examined brain activation patterns of patients with SCZ relative to healthy controls when encoding and recalling trauma-related words using functional MRI (fMRI). Nine patients who met DSM-IV criteria for SCZ were compared with nine healthy demographically matched controls. All patients were assessed on medication. In the event-related tasks, participants heard 40 words, 20 neutral and 20 trauma-related, equated in terms of parts of speech, syllable length, frequency, imageability, and concreteness. For the encoding tasks, participants were instructed to "think about the meaning of each word" and to "try to form a mental picture or visual image closely related to the word." In the memory task, participants heard 20 words previously presented in the encoding task (10 neutral, 10 trauma), and 20 new words, and were asked to indicate whether each word had been heard before. fMRI analyses were performed on a voxel by voxel basis using a GLM approach with random effects as implemented in SPM2 to contrast trauma vs. neutral stimuli. A critical threshold of .01 at the voxel level was employed. Examination of word type (trauma > neutral) for the encoding task indicated activation of the retrosplenial cortex and other regions in healthy controls, as has been reported in the literature. In contrast, retrosplenial activation was noted in patients with SCZ for the neutral > trauma words contrast. For the memory task, there was a similar differential response when remembering trauma > neutral words, with healthy controls demonstrating the expected activation of the retrosplenial cortex among other regions, which was absent in patients with SCZ. These results suggest a differential response to emotional words, whereby patients with SCZ do not activate the same circuitry as healthy controls when processing emotional information. The findings suggest that during processing of neutral words, patients with SCZ activate circuitry normally associated with processing of emotional stimuli.

THE EFFECTS OF NICOTINE UPON BRAIN ACTIVITY AND NEUROCOGNITION IN SCHIZOPHRENIC SMOKERS

K. Fleming,* S. G. Potkin, J. Fallon
University of California, Irvine, Irvine, CA, USA

Approximately 90% of schizophrenics (SC) smoke compared with rates of less than 25% in the general population in the United States. The rate of smoking in SC is much higher than in other severe mental illnesses, and neither substance abuse, institutionalism nor antipsychotic use can account for this high rate. We hypothesize that nicotine compensates for a defect in frontal lobe function and hypometabolism in SC. In this study we examined the neuronal circuitry involved in the effects of nicotine and of nicotine withdrawal via Flurodeoxyglucose (FDG) Positron Emission Tomography (PET). Comprehensive neurocognitive evaluations and mood ratings were also obtained. Subjects were scanned twice following overnight abstinence from nicotine: once while wearing a 21 mg nicotine patch, and once while wearing a placebo patch. The CPT was used as the activation task. Thus far 10 SC smokers and 19 normal controls (NC) smokers have been assessed. In the withdrawal condition the SCs demonstrated broad bilateral reductions as compared to the NCs, consistent with the well-established pattern of hypoactivity in SC. Following nicotine administration, there were no significant changes in brain activity for the NCs. Conversely, SCs reacted dramatically to the nicotine with overall bilateral activations. Most significant were increases in the dorsal stream and the left nucleus accumbens and thalamus ($p<0.001$). Further, nicotine significantly enhanced memory in the SCs. By elucidating the specific brain mechanisms involved in nicotine and schizophrenia, it is hoped that new treatments may be developed to aid smoking cessation in SC. Supported by the Tobacco Related Disease Research Program.

A NEW LOOK AT THE NEUROBIOLOGICAL SUBSTRATES OF CREATIVE THINKING IN THE SCHIZOPHRENIA SPECTRUM: NEAR INFRARED IMAGING OF THE PREFRONTAL CORTEX AND DIFFUSION TENSOR IMAGING OF WHITE MATTER COHERENCE AND INTEGRITY

B. Folley,* C. Gibson, A. Anderson, J. Lee, S. Park
Department of Psychology, Vanderbilt University, Nashville, TN, USA

First degree relatives of psychotic patients and schizotypes have shown enhanced creative ability; however the mechanisms underlying this creative facilitation are unknown. Two suggestions have been

raised concerning creativity and the brain: 1) that the neurobiological mechanisms inherent in psychoses may also facilitate creative thinking, thereby providing a compensatory mechanism for schizophrenia, and 2) neural connectivity provided by synaptic proliferation and axonal branching may provide enhanced neural pathways that support creative thinking. We evaluated creative ability using a divergent thinking (DT) paradigm that allowed subjects to juxtapose alternate uses for objects. Creativity is a multifaceted construct, and DT is an essential component of the creative thinking process, predicting some forms of creative achievement. We assessed DT in schizophrenics, psychometric schizotypes and normal controls using an alternate uses task that was designed as a modified block design task that allowed acquisition of quantitative functional brain imaging in prefrontal cortex as well as qualitative creative response data for single runs. Functional brain activation was assessed using near infrared optical tomography (NIROT), and indices of white matter connectivity were gathered using diffusion tensor imaging (DTI). The integrity and coherence of prefrontal and hippocampal white matter pathways were assessed using fractional anisotropy (FA), mean diffusivity, and principal diffusivity (λ_1) indices calculated from ROI analyses of diffusion tensor images. Therefore, we were able to assess creative fluency as well as underlying oxyhemoglobin and axonal distribution data from individual subjects. Our results indicate that enhanced creative thinking is more likely to occur in schizotypes, especially those with odd speech and eccentric behavior traits, but that it is relatively preserved in schizophrenics. NIROT data indicate that schizotypes and schizophrenics, unlike control subjects, recruit bilateral prefrontal cortices during DT. Overall, DTI indices indicate that DT is inversely associated with FA, diffusivity, and λ_1 indices in prefrontal-hippocampal circuits (cingulum) and in the corpus callosum. Therefore, enhanced creative thinking may be facilitated by bilateral prefrontal cortex activation and decreased axonal organization between hemispheres, and this may be a common pathway linking creativity with psychosis.

SCHNEIDERIAN FIRST RANK SYMPTOMS ARE ASSOCIATED WITH RIGHT PARIETAL CORTICAL HYPERACTIVITY: A REPLICATION UTILISING FMRI

V. Ganesan,* S. A. Spence
Academic Psychiatry, University of Sheffield, Sheffield, United Kingdom

Schneiderian First Rank Symptoms (FRS) of schizophrenia have been related to a deficit in monitoring of one's own intentions and actions, and to impairments of networks involved in attributing actions to self or others. Parietal cortex is an important node in such networks. A PET study[1] of voluntary movement in schizophrenia patients experiencing delusions of alien control demonstrated hyperactivity of right inferior parietal cortex (Brodmann Area, BA, 40). Subsequently, a resting state PET study[2] found Schneiderian FRS to be associated with right parietal hyperactivity. We are unaware of any previous fMRI study examining the FRS in schizophrenia using a voluntary movement paradigm. Using an event-related fMRI, we examined the functional neuroanatomical basis of Schneiderian FRS in the context of spontaneous movement. Functional imaging data were acquired on a 1.5T system in 13 right-handed, male schizophrenia patients, each studied twice. Patients with FRS (n=7) did not differ from those without FRS (n=6) in age, premorbid-IQ, illness duration, medication dose and extrapyramidal symptoms. Patients performed spontaneous movements (at moments of their own choosing) in an event-related fMRI paradigm[3]. Image analysis was performed using random effects analysis in Statistical Parametric Mapping 2 (SPM2). The validity of parametric analysis results was examined using nonparametric permutation test. SPM2 analysis showed that patients with FRS had significant hyperactivation of right inferior parietal lobule (BA 40; $p<0.0001$; FWE corrected $p=0.015$ [SVC]) relative to those without FRS. Nonparametric test using 5000 permutations confirmed the validity of this finding ($p=0.0002$). This study replicates the findings of two previous PET studies[1,2] insofar as it implicates right parietal dysfunction in the pathophysiology of FRS. Importantly, the present data are derived through applying an ecologically valid spontaneous movement paradigm; the aim being to approximate 'truly' spontaneous behaviour, as might occur outside the scanner. Right parietal cortex is hyperactive in those who experience themselves as being under external (alien) control. The cognitive basis of such aberrant experience awaits elucidation but may comprise a deficit in 'forward modelling'[4]. References 1)Spence et al *Brain* 1997;120:1997-2011 2)Franck et al *J Neuropsychiatry Clin Neurosci.* 2002;14:277-82 3)Hunter et al *NeuroImage* 2003;20:1264-69 4)Spence *Cognitive Neuropsychiatry* 2002;7:211-20.

INTEGRITY OF MYELIN: IMPAIRMENT DURING PSYCHOSIS, PARTIAL REPAIR DURING RESMISSION AS SHOWN BY DTI AND DIFFUSIVITY

D. L. Garver,* J. Christensen
Psychiatry & Behavioral Science, U of Louisville, Louisville, KY, USA

Background: Evidence of altered connectivity (correlation between neuronal activity at remote sites) has been reported in some patients with schizophrenia. Such altered connectivity suggests a failure of functional wiring between information processing centers in brain. Further support of altered connectivity has come from diffusion tensor imaging (DTI) and anisotropy, which indicated impaired directionality of myelinated fiber tracts in some schizophrenics. Previous studies have also indicated evidence of immune activation within the CNS of some schizophrenics during psychosis exacerbation. Methods: We investigated such central immune activation together with white matter diffusivity (Dm) using DTI in schizophrenics subsequently found to be good respoders (GR) and poor responders (PR) during 28 days of antipsychotic drug treatment. Results: GR patients evidenced elevation of the pro-inflammatory cytokine interleukin-6 (IL-6) in the CSF ($p < 0.05$) at neuroleptic-free baseline and demonstrated increased Dm of central white matter ($p = 0.008$) during psychosis exacerbation. Increased Dm is consistent with extracellular edema. The pathological Dm at baseline was reduced ($p < 0.03$) following reduction of psychotic symptoms by 84% during treatment with antipsychotic drugs. PR patients had neither elevation of IL-6 or Dm at baseline, nor was there significant change during the course of antipsychotic treatment. Conclusions: GR patients with schizophrenia manifest an episodic functional-disconnect-syndrome (FDS) during psychotic episodes which is associated with inflammatory cytokine elevation, disruption of white matter integrity, and of information processing. Remission of psychosis is associated with partial recovery of white matter integrity.

MONITORING OF CEREBRAL DYSFUNCTION DURING WORKING MEMORY PERFORMANCE IN FIRST-EPISODE SCHIZOPHRENIC PATIENTS

F. L. Giesel,* N. Hohmann, U. Seidl, T. Wuestenberg, H. von Tengg-Kobligk, P. Schonknecht, M. Essig, J. Schroder
Radiology, German Cancer Research Center, Heidelberg, Germany

Introduction: Previous studies using functional magnetic resonance imaging (fMRI) with the n-back paradigm as a visuo-spatial working memory task have demonstrated that performance and cerebral activation may depend on many factors, such as training effects, age and clinical status. To further investigate the temporal stability of activation changes, we compared the fMRI-BOLD-response and performance in patients with first-episode schizophrenia and controls at baseline and at a two-week follow-up. Material and Methods: Up to now, five patients with first-episode schizophrenia (DSM-IV) and seven healthy subjects matched for age, gender and education were scanned on two occasions (interval of 14 days) performing the n-back task. The patients received neuroleptic treatment and were in partial remission. The working memory block-paradigm (n-back) was performed with 4 repetitions at a 1.5 T clinical scanner using the standard head coil and a GE-EPI sequence (Matrix=128x128x15, FOV=(240x240)mm, TR=4500ms, TE=54 ms). Image analysis was performed using SPM99. Activated voxels were identified by the "General Linear Model" approach. Results: Performance in the n-back task was significantly lower in patients than controls; in addition, performance remained similar on both occasions. However, patients showed a slight improvement of psychopathological symptoms. On both occasions, the controls showed a rather stable activation pattern involving bilaterally the frontal inferior/medial gyrus (IFG/MFG), intra-parietal sulcus (IPS) and anterior cingulate gyrus (GCa) in the 2-vs.- 0-back contrast. At baseline, patients presented with a markedly decreased activation compared to the controls with a left hemispheric dominance in IFG/MFG and IPS. After two weeks, the activation increased and the patients showed a similar activation pattern as the healthy controls in the 2-vs.-0-back contrast, despite of a slight difference in the frontal areas. Conclusion: According to these results, fMRI activation patterns under a n-back task remain stable and reproducible in healthy controls. While patients initially showed a marked reduction of activation in the IFG/MFG with a lateralization towards the left hemisphere, this "hypofrontal" activation pattern resolved during follow-up. Obviously, these findings refer to potential effects of practise and clinical stabilisation and demonstrate that these factors should be carefully considered in fMRI studies.

REGIONAL ANALYSIS OF HIPPOCAMPAL FUNCTION IN SCHIZOPHRENIA

T. A. Girard,* B. K. Christensen, A. P. Crawley, D. J. Mikulis
Centre for Addiction and Mental Health, Toronto, ON, Canada

In addition to psychosis, schizophrenia (SCZ) is characterized by significant memory impairment. Moreover, verbal memory is a prime predictor of functional outcome in patients with SCZ. However, the neural mechanisms underlying specific processes (e.g., encoding, retrieval) require further study to inform efforts aimed at early recognition and treatment of the disease. The hippocampus is intimately involved in memory processes and it figures prominently in recent theories of SCZ. Importantly however, the hippocampus is not a unitary structure and may be segregated along its longitudinal axis. In this regard, neuroimaging studies implicate the anterior portion in encoding, novelty detection, and/or forming associations, whereas retrieval of learned information preferentially engages the posterior region. Growing evidence suggests that the anterior region is particularly disturbed in SCZ, raising the possibility that disproportionate regional pathology might lead to selective functional morbidity or symptom production. The current study assesses regional hippocampal function in relation to memory tasks. Persons with SCZ and community controls (CON) underwent event-related fMRI (functional magnetic resonance imaging) while performing two computerized memory tasks. First, in the anterior task participants studied nouns and made relational judgments about their category membership (e.g., fruit?). Words were presented in lists of semantically related exemplars (e.g., apple, pear); however, the second part of each list introduced contextually novel oddballs (e.g., sofa). Following a 10-min high-resolution anatomical scan, the posterior task tested recognition memory for the studied items. Results indicate comparable behavioural performance across groups. Consistent with hypotheses, analyses of CON fMRI data within the medial temporal lobes revealed right-anterior and left-posterior hippocampal activation during encoding and retrieval, respectively. In contrast, SCZ images only revealed smaller clusters of activity in surrounding parahippocampal cortices. These findings suggest distributed hippocampal dysfunction in SCZ. Future efforts will employ more detailed analyses focusing on individually and anatomically based regions of interest to better define hippocampal function in SCZ as it relates to key mnemonic processes.

CB1 RECEPTOR GENOTYPE MEDIATES WORKING MEMORY PERFORMANCE AND ACTIVATION IN SCHIZOPHRENIA

N. Giuliani,* K. M. Groth, M. R. Johnson, J. Gelernter, J. Covault, G. D. Pearlson
Institute of Living, Olin Neuropsychiatry Research Center, Hartford, CT, USA

Many family studies have shown a strong genetic component to schizophrenia (SZ). Several genes have been identified as unfavorable to cognitive efficiency and information processing, which may contribute to schizophrenia vulnerability. SZ patients and their non-SZ first degree relatives regularly show deficits in working memory (WM), which recruits the dorsolateral prefrontal cortex (DLPFC) and inferior parietal lobule (IPL). Therefore, specific functional polymorphisms may influence WM behavior and/or related fMRI activation. One gene implicated in SZ vulnerability is the CB1 cannabinoid receptor type 1, which modulates GABAergic interneurons in response to binding of endogenous cannabinoids. Cannabis smoking in teens has been shown to double their risk of SZ, and infusions of THC in healthy controls (HC) disrupt WM and can provoke psychotic symptoms. The Sternberg working memory task is well documented as a measure of WM function. We hypothesized that SZ patients and relatives would perform worse on the Sternberg task than matched controls, and that variants in the CB1 receptor gene would influence both behavior and activation. We scanned 12 HC, 14 SZ patients and 9 of their first degree relatives in 3.0T MR scanner during performance of the Sternberg. SZ patients performed worse than relatives, who in turn performed worse than healthies (SZ 86% correct, relatives 90%, HC 94%; HC vs. SZ p=0.06). For genetic analyses, we combined the SZ patients and their relatives to increase statistical power and compared behavior and activation by CB1 gene subtype: gg vs. ga+aa. The gg group performed significantly better

than the ga+aa group (gg: N=14, mean 90% correct; ga+aa: N=9, 81% correct; p=0.028). fMRI activation also followed this pattern. SZ patients and first degree relatives with the gg genotype activated more in WM circuit areas (left DLPFC and IPL) than those with ga and aa genotypes at p<0.05. In controls, the patterns of gg performing significantly better (gg: N=6, 96% correct; ga+aa: N=6, 91%; p=0.04) and activating more (gg>ga+aa: right DLPFC and IPL, p<0.05) persists. These data suggest that, for working memory, gg is the more favorable form of the CB1 cannabinoid receptor gene.

CONTRASTING MNEMONIC PROCESSES IN SCHIZOPHRENIA: NEUROPSYCHOLOGICAL AND FUNCTIONAL NEUROIMAGING EVIDENCE FOR DISRUPTED MEMORY CONTROL

D. C. Glahn,* J. Barrett, C. Franklyn, P. T. Fox, D. I. Velligan
Division of Schizophrenia and Related Disorders, Department of Psychiatry, University of Texas Health Science Center San Antonio, San Antonio, TX, USA

Memory impairment is closely linked to schizophrenia (SCZ), yet which memory related processes is disrupted in SCZ remains unclear. Here, we contrast the ability to generate novel memory representations (linked to medial temporal cortex) with the ability to control existent representations (associated with prefrontal executive circuits). This distinction is closely related to the putative specialization of the medial temporal and lateral prefrontal lobes. We propose that the ability to control items in memory is relatively more impaired in SCZ than the ability to create new internal representations. This differential effect will be evidenced by poorer performance and reduced prefrontal activity on a task requiring controlling memoranda compared to a task requiring creation of new representations. 40 SCZ patients and 40 matched healthy controls participated in a behavioral assessment and 25 SCZ patients and 25 matched controls were examined with fMRI. To contrast creating memory representations with controlling them, we developed a delayed match to non-sample task where the total number of stimuli used in blocks of 30 trials was manipulated while keeping the number of memoranda fixed for each trial. In the memory control condition, the same stimuli were repeated, in random position, on each trial making performance dependant on remembering when a stimulus appeared in a particular trial, rather than the identity of the stimuli. In contrast, each stimulus appeared only once in the novelty condition, making creating new memory representations critical. In an intermediate condition, each stimulus appears 10 times, making both generation and control of internal representations critical. Both groups performed worse on the intermediate condition compared with the other conditions and patients showed less advantage for the memory control condition than comparison subjects. Both groups showed similar level of improvement for the novelty condition. While both groups activated hippocampal and dorsolateral prefrontal regions in response to each condition, patients were significantly hypofrontal on the memory control condition. We find that SCZ patients are relatively more impaired when asked to organize internal representations than when asked to create new memory stores and that this impairment is linked to aberrant prefrontal function. Together, these findings suggest that the control of memories and/or hypofrontal activity may be appropriate targets for treatment.

PRELIMINARY EVIDENCE FOR DIFFERENT BOLD RESPONSE BETWEEN PATIENTS WITH PSYCHOTIC DISORDERS AND HEALTHY CONTROLS DURING OLFACTORY PROCESSING

K. P. Good,* H. M. Schellinck, L. Gates, R. A. Leslie, H. I. Milliken, R. E. Brown, E. M. Haacke, L. C. Kopala
Psychiatry, Dalhousie University, Halifax, NS, Canada

The neural substrates involved in olfactory processing are well established. Olfactory deficits are common in patients with psychotic disorders, but the underlying pathophysiology of these deficits remains unclear. We used BOLD fMRI to examine the functional topography of the olfactory system in patients with first episode psychosis and healthy control subjects. Twelve normosmic (scored within the normal range on the University of Pennsylvania Smell Identification Test) subjects participated: 7 healthy controls (mean age 28.6) and 5 patients (mean age 25.8) with DSM-IV confirmed diagnosis of schizophrenia. A manually-controlled olfactometer delivered the stimulus (amyl acetate) to the subjects during the fMRI scan. Twenty-six second on-off epochs (5 odour, 4 no-odour) were presented. During odour presentation, healthy controls demonstrated activity in previously defined olfactory regions (left superior, middle and inferior frontal gyri, right orbitofrontal cortex, and right insula), along with left basal ganglia and left superior temporal gyrus (p<.001). In patients, odour administration was only associated with increased activity in the left superior frontal gyrus and posterior cingulate (p<.001). In this study, patients failed to recruit secondary olfactory cortices in response to an odour. These data provide further clarification of some of the regional functional brain abnormalities associated with olfactory identification deficits in patients with psychotic disorders.

ABNORMAL FACE PROCESSING IN PATIENTS WITH SCHIZOPHRENIA: AN FMRI STUDY WITH FACE DISCRIMINATION TASK

T. Ha,* J. Park, K. Kang, W. Moon, E. Chung, J. Kwon
Psychiatry, Seoul National University College of Medicine, Seoul, South Korea

It has been known that patients with schizophrenia exhibit deficits in face processing which may disturb their social functioning. Perception of faces other than objects is unique in that it greatly depends on holistic processing that produces the inversion effect. Recognition of inverted faces is more impaired with faces differing in configuration than with faces differing in features. Some brain regions including lateral fusiform gyrus have been proposed to be specialized for face processing. We used functional magnetic resonance imaging (fMRI) to study face processing in 11 schizophrenic patients diagnosed according to DSM-IV criteria with SCID IV and age-, sex-matched normal controls. To maximize the characteristics unique to face processing, faces differing in configuration were used as stimuli. During subjects performing discrimination tasks in which upright pairs of faces, Mooney faces and chairs, and inverted pairs of faces and Mooney faces were presented, blood oxygen level dependent signal changes were measured at a 1.5T Philips scanner. A stimulus was presented for 2000 ms after 500 ms ISI and 500 ms '+' as a prompt, and subjects had to decide whether two photos in the stimulus were same or different. A run consisted of 14 blocks each of which included 7 stimuli, thus lasted for 21 seconds, interleaved with 4 fixation blocks of 12 seconds. Acquired images were preprocessed

and analyzed using SPM99. Patients discriminated upright and inverted faces more inaccurately than controls but not Mooney faces and chairs. Regardless of orientation, faces activated the bilateral superior temporal gyri and ventral temporal regions including the fusiform gyri. It was revealed in a random effect analysis that patients had significantly less activation of the bilateral fusiform gyri and cuneus than controls during face discrimination. These results suggest a dysfunction of a specialized neural system for face processing in schizophrenia. It should be elucidated in the future how the deficit is related to the impairment of social functioning in schizophrenia.

DIFFERENTIAL CEREBRAL CORRELATES OF THE INTERACTION OF NEGATIVE OLFACTORY STIMULATION AND WORKING MEMORY IN SCHIZOPHRENIA PATIENTS AND HEALTHY CONTROLS

U. Habel,* M. Klein, T. Kellermann, K. Koch, V. Backes, N. Seiferth, T. Kircher, K. Amunts, N. J. Shah, F. Schneider
Department of Psychiatry, University of Aachen, Aachen, Germany

In schizophrenia, impairments in both emotion and cognition are prominent and characterize its psychopathology. However, interactions between emotion and cognition have not been investigated in greater detail in patients. Similarly, in healthy persons there are only a few and rather contradictory studies exploring the effects of emotion on cognitive function. Hence, the present study used functional magnetic resonance imaging (fMRI) to examine the neural correlates of the interplay between cognitive and emotional processing in further detail in 20 schizophrenia patients and 20 matched comparison subjects. Working memory was assessed by a 0-back/2-back continuous performance test. Simultaneously, negative emotion was induced by olfactory stimulation. A preceding behavioral study confirmed the validity of the paradigm providing the basis for fMRI applications. According to subjective ratings mood induction was successful in both groups. Negative mood was associated with a significant decrease in the mean number of correct reactions during working memory performance (2-back) in healthy controls while only a similar trend could be observed in patients. Whereas for the main effect of working memory (2-back - 0-back) we found a significant activation mainly in the fronto-parietal network, this activation was reduced in patients compared to healthy controls. Examining the differential effects of negative affect on these neural correlates in patients and controls, a specific hypoactivation in the anterior cingulate and prefrontal cortex characterized the activation pattern of patients for the interaction effect of emotion and cognition, indicating dysfunctions in regions critically involved in emotional evaluation and control as well as in cognitive control and attention, hence important sites of emotional-cognitive integration and regions known to be involved in the pathophysiology of schizophrenia.

INCREASED HIPPOCAMPAL RECRUITMENT DURING EPISODIC MEMORY IN SCHIZOPHRENIA

S. Heckers,* M. Zalesak, O. Freudenreich, I. DeWitt, T. Ditman, D. Goff, A. Weiss
McLean Hospital, Harvard University, Belmont, MA, USA

Previous studies have shown that the neural basis of impaired memory in schizophrenia involves abnormal patterns of hippocampal recruitment. Here we explored the neural basis of episodic memory, a hippocampal-based form of memory retrieval, in 18 male schizophrenia and 15 control subjects. After studying a wordlist, subjects were presented with a randomized list of original and novel words during scanning in a 1.5 T MRI scanner. We employed a slow event-related fMRI design to compare brain activation during the correct remembering of details of the encoding episode (Remember-response) with brain activation during the sense of familiarity (Know-response). We used a mixed-effect model in SPM99 to compare brain activation between the two groups. Schizophrenia subjects were less accurate in recalling the previously learned words (overall hit rate), but this difference was not significant. We did not find evidence for a selective impairment of episodic memory in our sample of schizophrenia patients: both groups had similar Remember-response rates (.46 in controls and .42 in schizophrenia subjects). Mean hippocampal volume was significantly larger in the control subjects (main effect of group: $F=17.64$, $p<0.01$). Both groups showed significant left hippocampal activation during episodic memory retrieval, but only schizophrenia subjects showed significant right anterior hippocampal recruitment during episodic memory retrieval (between-group difference with peak difference at coordinates 28, -10, -16, $z=4.42$). In contrast, control subjects revealed more significant activation of a neural circuit involving Brodmann area 30, thalamus, and caudate nucleus. The result of this study, i.e., increased hippocampal recruitment in the context of normal memory retrieval, complements previous studies of decreased hippocampal recruitment in the context of impaired task performance in schizophrenia.

NEURAL CORRELATES OF PREPULSE INHIBITION OF ACOUSTIC STARTLE

L. Heidinger,* K. Kulkarni, A. Solodkin, D. C. Zhu, D. G. McLaren, S. L. Small, R. Gibbons, M. B. Goldman
Psychiatry, University of Chicago, Chicago, IL, USA

Blunted prepulse inhibition (PPI) is a robust finding in schizophrenia that has been linked to thought disorder. 14 controls (25.5yrs, 7m) with > 40% PPI in a simulated MRI scanner, underwent functional MRI. In an event-related design, subjects heard 107dB acoustic pulses in two types of events: one in which the pulse was preceded 120 ms earlier by an 88dB prepulse (PP+P) and the other in which pulse occurred alone (P). 100 trials of each type were dispersed over four 10-min runs with an ISI of 8-16sec. Data were analyzed using the general linear model, assuming a hemodynamic response (HDR) of 14sec. Functional and structural data were transformed into stereotactic space, and the mean signal intensity during the peak of the HDR (4-8secs) entered into a mixed effects two-way ANOVA. To localize major regions of activity, we limited ourselves to clusters > 3 contiguous voxels with a single voxel p<10-9 (see first 7 structures and their volumes(mls) in Table (column: Stim)). To localize regions of difference across trial types, we identified regions of difference with > 3 voxels at p< 5.0X10-3 and then filtered this result by areas showing significant pulse activity (i.e. corrected p<.05=20 contiguous voxels all p<10-4). This assured that differences were in areas with significant HDR (see structures #3-10 and volumes (column:Diff)). In contrast to P trials, which showed classic HDR in all regions, PP+P trials showed similar (=) or blunted (—-) HDR (Classic), with (+++) or without (0) marked initial downturns suggestive of transient inhibitory activity (Negative). This negative response was most apparent in the region of the pedunculopontine nucleus (known source of PPI), the left hippocampus, and the cerebellum. This pattern could be a signature of the protective neural processes

that are disrupted in schizophrenia, suggesting this method offers a means of characterizing defects in information processing.

FMRI-GUIDED RTMS FOR PATIENTS WITH PERSISTENT AUDITORY HALLUCINATIONS

R. E. Hoffman,* R. J. Buchanen, K. Wu, M. Varanko, D. D. Spencer, J. H. Krystal, M. Hampson
Psychiatry, Yale University School of Medicine, New Haven, CT, USA

Background: The pathophysiological basis of verbal auditory hallucinations, which occur in ~70% of patients with schizophrenia, remains unknown. We report a study combining functional magnetic resonance imaging and suppressive 1-hertz repetitive transcranial magnetic stimulation designed to better understand the neurobiological basis of these experiences. Methods: 17 right-handed patients with schizophrenia or schizoaffective disorder and severe auditory hallucinations were studied. For patients with frequent intermittent hallucinations (N=8), BOLD signal maps of brain activation comparing hallucination and non-hallucination periods were generated. For patients with continuous, uninterrupted auditory hallucinations (N=9), maps of BOLD signal correlations calculated relative to Wernicke's region were generated. The latter were hypothesized to delineate brain regions "hypercoupled" to Wernicke's region. 3-6 regions per subject were targeted for 1-Hz rTMS based on these two types of fMRI maps. Targeted regions varied from patient to patient but tended to include Wernicke's region, primary auditory cortex, Broca's region and right-sided homologous regions. Each patient also received sham stimulation. Patients and clinical raters were masked regarding stimulation condition. Results: Stimulation sites producing greatest improvement in hallucinations following rTMS varied widely across patients and included Broca's region and different posterior temporal cortical regions. The only stimulation site producing statistically significant improvement relative to sham stimulation across subjects was left Wernicke's region (see Table). Among the group of intermittent hallucinators, more neuroanatomically widespread brain activation during hallucination periods robustly predicted reduced clinical response to 1-Hz rTMS (R= -.94). Conclusions: Auditory hallucinations arise from a broadly distributed network of language processing areas with locations that vary across patients. A final common pathway leading to expression of auditory hallucinations is activation of Wernicke's region.

***Data averaged over all rTMS sessions delivered to a particular cortical region. Data expressed as mean ±SD. Numbers in parantheses refer to number of patients stimulated in this region. Wern < Sham (two tailed p = .04).**

SPATIAL WORKING MEMORY ACCURACY CORRELATES SIGNIFICANTLY WITH BOLD RESPONSE IN THE PARIETAL LOBE OF SCHIZOPHRENIC VOLUNTEERS

H. H. Holcomb,* L. Beason-Held, C. A. Tamminga, M. A. Tagamets
MPRC, University of Maryland, Baltimore, MD, USA

Introduction. Spatial working memory requires the participation of cingulate, frontal, and parietal brain systems in healthy volunteers. In patients with schizophrenia it is not clear to what extent various brain systems are used for memory functions. They appear to use the parietal system for spatial memory, but not the dorsal anterior cingulate region. These observations show that the schizophrenic group displays strong correlations between spatial working memory accuracy and parietal BOLD response. This is surprising in light of the extensive literature demonstrating poor visuospatial performance in this group. Methods. All subjects gave informed consent. Nine healthy subjects (mean age=28.1,5.8 S.D.) and ten clinically stable, medicated schizophrenic outpatients (mean age = 35.4, 7.4 S.D.) participated. Event related fMRI, 1.5 T, using standard echoplanar protocols provided two runs of a high error spatial task from each subject. Each acquisition consisted of twelve memory trials and eight control trials. The memory task consisted of two stimuli, each a solid black rectangle enclosed in a line-drawn frame. Subjects judged whether the two stimuli were the same. The black rectangles were either the same height or slightly different, 1-7% disparity. Stimuli were presented for 0.5 seconds and were separated by 5.5 seconds. A 1.5 sec. response time was allowed following the second stimulus. The intertrial interval was jittered, 8 seconds. Control trials required the subject to match the button press hand with the side to which the rectangle was displaced. Control trials displayed exactly the same configurations in the first and second stimuli. Results. Healthy participants averaged 72.5% accuracy and schizophrenic volunteers averaged 67.1% accuracy. The range of the former was 54-96%, and of the latter group, 42-88%. Memory-minus-Control-Trial contrasts generated robust difference clusters in dorsal anterior cingulate, insula and parietal lobe for normal volunteers. In the schizophrenic group no significant clusters were generated. This group did, however, exhibit significant parietal activity during both the memory and the control trials. They also displayed significant BOLD response correlations with accuracy, in the parietal system. Comment. These findings suggest that the schizophrenic group is able to engage the parietal lobe in the service of spatial memory but may not be able to modulate it in association with alternating memory demands.

INCREASED MEDIAL TEMPORAL LOBE RESPONSES TO EMOTIONAL AND NEUTRAL FACIAL EXPRESSIONS IN SCHIZOPHRENIA

D. J. Holt,* L. Kunkel, A. P. Weiss, D. C. Goff, C. I. Wright, L. M. Shin, S. L. Rauch, J. Hootnick, S. Heckers
Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA

Deficits in face recognition and in discrimination of emotional facial expressions have been demonstrated in schizophrenia. Functional

imaging studies have revealed medial temporal lobe (MTL) deficits in schizophrenia patients while they performed cognitive tasks during the presentation of human faces. We sought to identify changes in MTL function in schizophrenia during the passive viewing of faces displaying neutral, fearful, and happy emotional expressions. To test the hypothesis that schizophrenia patients exhibit elevated MTL responses during the initial evaluation of potentially threatening stimuli, we measured MTL activation during the first presentation of each facial expression. 15 patients with schizophrenia and 16 healthy comparison subjects were studied using functional magnetic resonance imaging (fMRI). Both subject groups demonstrated bilateral MTL activation in response to all three facial expressions. In a direct comparison between the two groups (two-sample t-test, random effects analysis), schizophrenia patients showed significantly more activation of the left hippocampus while viewing all three facial expressions (fearful vs. baseline (fixation): (x, y, z) -22, -24,-14, z=3.42; happy vs. baseline: -22, -24, -14, z=2.95; neutral vs. baseline: -22, -22, -12, z=2.91). When the initial response of the MTL to each facial expression was measured, schizophrenia patients displayed increased right amygdala activation during the first presentation of fearful faces in comparison to healthy subjects (28, 0, -24; z=3.30). These findings suggest that abnormalities in MTL-based memory and emotional perception systems may underlie deficits in face processing and social cognition in schizophrenia.

THE EXTINCTION OF AVERSIVE ASSOCIATIONS: AN FMRI STUDY

J. Jensen,* I. Vitcu, S. Kapur
PET Centre, CAMH, Toronto, ON, Canada

Memory and learning are greatly affected and contribute significantly to the disability experienced by patients with schizophrenia. The mesolimbic dopaminergic system is critically involved in reward learning and is also implicated in schizophrenia and its treatment. The purpose of this study was to use fMRI to examine whether this system, with special focus on the ventral striatum and orbitofrontal cortex, play a role in the extinction of aversive associations. Thirty-three healthy subjects undertook two scanning sessions. In the first session, all subjects went through aversive conditioning and were imaged using fMRI. As unconditioned stimulus (US) we used aversive electrical stimulations to the index finger where the intensity was titrated to when it was "unpleasant but tolerable". A neutral colored circle (CS+) was paired with the US while another circle (CS-) was never paired. In the break between the two sessions one group (I: Intervention+extinction) were informed that there would be no further US exposure. Another group (E; Extinction) was not informed about that fact that there would be no further US, but, were expected to learn by experience that no CS predicted US while a third group (Control; C) was exposed the same CS-US paradigm in both sessions. Data were realigned, normalized, spatially smoothed and temporally filtered. The main comparison of interest was CS+ to CS- in the second session with the first session as baseline using a random effects analysis in SPM. The analysis showed stronger activations in the prefrontal/orbitofrontal cortex for both I and E as compared to C. However, the activation in this region was also stronger for E than for I suggesting that this region is mediating natural extinction learning. It has been suggested that orbitofrontal cortex stores long-term extinction memory and this is thought to inhibit amygdala activation in subsequent fear exposure and thereby leading to the behavioral expression of extinction. Since dysfunction in this region as well as reward learning/memory problems are reported in schizophrenia- this paradigm provides a valuable tool to understand how patients learn and extinguish aversive associations.

BOLD FMRI ACTIVATION IN PATIENTS WITH SCHIZOPHRENIA PERFORMING AN IMPLICIT MEMORY TASK

P. Johnston,* U. Schall, E. Halgren
Centre for Mental Health Studies, University of Newcastle, Callaghan, NSW, Australia

People suffering from schizophrenia display problems in short and medium term memory which are putatively associated with dysfunction of the medial temporal lobe, particularly the hippocampal formation and associated structures including the dentate gyrus, enthorinal cortex, parahippocampal gyrus, amygdala and subiculum. In this study brain activation in 10 schizophrenia patients and 10 matched controls was assessed whilst performing a verbal implicit memory task. In a block design fMRI study subjects were asked to perform a size judgement task, making a decision as to whether the objects or animals designated by the (visually) presented words exceeded more than 30cm in any of their dimensions. Subjects were pre-exposed to a subset of the stimuli in a training session prior to the onset of the experiment. This subset of stimuli was repeatedly presented in blocks throughout the experiment, whereas all other stimuli were presented only once, blocks of novel and repeated stimuli were interspersed with blocks wherein a fixation stimuli was presented. Each subject performed 4 runs of the experimental paradigm in which 80 EPI brain volumes were collected in a 1.5T MRI scanner. During each of these runs subjects were exposed to 4 blocks of novel stimulus words and 4 blocks of repeated stimulus words. Data preprocessing and analysis was performed using the MEDx 4.1 software, and involved spatial filtering, intensity normalisation, high pass filtering, coregistration to a structural volume and spatial normalisation to the MNI template. Statistical contrasts were performed comparing brain activation to words versus fixation and repeated versus novel words across groups. Preliminary analysis revealed a consistent set of brain regions activated across groups to words versus fixation. Major regions of activation included the (predominantly left) fusiform gyrus, inferior frontal gyrus, anterior cingulate and precuneus. Healthy controls displayed differences in regional brain activation to novel versus repeated words, novel words being associated with greater activation of the hippocampal formation and associated structures, fusiform gyrus and left inferior frontal gyrus, whilst repeated words were associated with greater activation of the posterior cingulate gyrus. These differences were less pronounced in patients, possibly implying that patients may have been performing the task anew to repeated words rather than relying upon previously stored representations.

ABERRANT CEREBRAL MAGNETIC FIELDS IN SCHIZOPHRENIA DURING CONTROLLED PROCESSING IN SPATIAL WORKING MEMORY

S. Kang,* S. R. Sponheim, J. J. Stanwyck, M. V. Chafee
Psychology, University of Minnesota, Minneapolis, MN, USA

Working memory dysfunction has been considered a candidate endophenotype in schizophrenia. Some imaging studies have reported that working memory deficits in schizophrenia are associated with abnormal activation of prefrontal cortex (PFC). In addition, primate cell recordings provide evidence that PFC mediates spatial working

memory by modulating visual input to posterior parietal cortex through reciprocal projections. To reveal the nature of abnormal neural processes associated with spatial working memory deficits in schizophrenia we developed a visual object construction (VOC) task to characterize dynamics of the distributed PFC-parietal cortical system subserving spatial working memory. To elicit processes more indicative of the complex spatial working memory operations awry in schizophrenia, the VOC requires a subject to perform analysis of spatial dimensions of visual input in comparison to material in spatial working memory. We collected magnetoencephalography MEG data from normal control and schizophrenia subjects during the VOC task. Preliminary analyses revealed schizophrenia patients to exhibit impaired performance on the VOC task, especially when object complexity was high. Source localization with normal control data indicated that after controlled processing of spatial working memory material there was dipolar activity in dorsolateral PFC at 160 ms and posterior parietal cortex at 195 ms. We hypothesize that schizophrenia patients will show abnormal neural activity in posterior parietal cortex as well as in PFC during spatial working memory. The specific timing of abnormal magnetic fields during spatial working memory will provide information regarding the neural basis of this candidate endophenotype in schizophrenia.

FUNCTIONAL MRI OF DYNAMIC EMOTION PROCESSING IN SCHIZOPHRENIA: PRELIMINARY FINDINGS

K. S. Kee,* T. Wong, J. Osowsky, A. Bellack, J. Quintana
Psychiatry and Biobehavioral Sciences, University of California Los Angeles (UCLA), Los Angeles, CA, USA

Little is known about the neurobiological underpinnings of emotion processing deficits in schizophrenia. Neuroimaging studies have usually focused on perception of static facial expressions (i.e., still photographs) yet, in real life, emotion perception relies on the integration of multiple contextual cues that are conveyed in a protracted, dynamic manner. We are using fMRI techniques to identify and characterize the neural substrates of emotion perception deficits in schizophrenia using interpersonal vignettes as emotion activation stimuli in stabilized schizophrenic outpatients and healthy subjects. Data are acquired while subjects perform four block-design runs. A run consists of five blocks: three resting blocks, during which subjects are only required to look at a fixation point on the screen and two activation blocks, each of which includes a series of 7 scenes that are projected on the screen for a total duration of 90 secs. The activation blocks preceded by a 2-sec white screen instructing subjects to pay attention to the emotion or body position of the predominant character in the scene. During the last 3 secs of each scene, four cartoon drawings depicting basic facial emotions (happy, angry, afraid, or sad) or figures of body orientations (sitting, standing, lying on a bed, or sitting at a table) are displayed at the bottom of the screen. Subjects are asked to select one of them by pressing one of four contiguous buttons on a magnetic-compatible mouse device. For the analyses, data are available for 2 control subjects and 1 patient. Images were preprocessed and analyzed using FSL FEAT 5.1 ($p = 0.01$). Brain activations for the emotion identification task were significant for visual cortex (left for controls, right for patient) and bilateral dorsolateral prefrontal cortex (DLPC) in both subject groups. Also, in the control subjects, we found significant activations of the right lateral fusiform gyrus, anterior cingulate, and bilateral amygdala. For the body orientation task, activations occurred in both groups for the following areas: bilateral visual cortex, motor cortex, DLPC, and right orbito-frontal cortex (OFC). In the patient, a significant activation of the bilateral superior parietal cortex was also found. For the emotion minus body position (control) condition, an activation of the bilateral visual cortex was found in both groups. We also found additional activations of the right superior parietal and OFC in the patient.

THE NEUROCOGNITIVE CORRELATES OF BOLD ACTIVATION IN THE DORSOLATERAL PREFRONTAL CORTEX OF PATIENTS WITH SCHIZOPHRENIA: AN FMRI INVESTIGATION

A. S. Kemp,* J. A. Turner, H. J. Lee, L. C. Trondsen, K. N. Gooch, D. Mirski, S. G. Potkin, 1. FIRST BIRN
Psychiatry and Human Behavior, University of California, Irvine College of Medicine, Orange, CA, USA

Numerous studies have implicated the dorsolateral prefrontal cortex (DLPFC; BA 9&46) in the pathophysiology of the neurocognitive dysfunctions which characterize many patients with schizophrenia. The purpose of the current investigation was to identify the neurocognitive correlates of BOLD activation in the DLPFC of patients diagnosed with schizophrenia. Twenty medicated outpatients, providing informed consent, were administered a comprehensive battery of neurocognitive assessments on the Computerized Multiphasic Interactive Neurocognitive Diagnostics System (CMINDS) and received a series of fMRI scans on a Picker Eclipse 1.5T scanner while performing a Sternberg working memory task (Manoach et al., 1999). Subjects responded to whether visually presented probe numbers were included in a memory set of 2 or 5 digits. SPM2 was used to analyze the images contrasting the 5- and 2-digit conditions. Region of interest analyses were conducted using the WFU Pickatlas (Maldjian et al., 2003) to summate the average contrast t values for BA 9&46. Pearson r comparisons yielded a consistent pattern of significant positive correlations between performance on the Auditory Verbal Learning Test (AVLT-15 words) for both immediate and delayed memory, and DLPFC activation, on the left more than the right hemisphere (Table 1). Also, a ratio of the left to right hemisphere extent of activation ($p < .01$, $k=5$) correlated with perseverative responses on the Card Sorting Test, a common measure of executive dysfunction in schizophrenia research ($r=.62$; $p=.005$). These preliminary analyses illustrate a relationship between the functional activation of the DLPFC and verbal memory and executive function task performance, both of which are characteristically disrupted in schizophrenia. The relationship between hemispheric asymmetry and perseverative errors is consistent with published literature demonstrating a failure to activate the right DLPFC, relative to the left, in patients with schizophrenia (e.g., Barch et al., 2003; Perlstein, et al., 2001). Support Contributed By: NCRR (NIH), 5 MOI RR 000827, www.nbirn.net; and by Novartis Pharmaceuticals.

Table 1: Pearson r coefficients (p value)

DIFFERENT BRAIN RESPONSES TO THE AUDITORY EMOTIONAL STIMULI IN SCHIZOPHRENIC PATIENTS WITH AND WITHOUT AUDITORY HALLUCINATION

J. Kim,* J. H. Seok, J. W. Jeon, S. K. An, H. S. Cho, H. S. Lee, S. K. Lee, H. J. Park
Department of Psychiatry, Yonsei University College of Medicine, Seoul, South Korea

Introduction: Emotional deficits have been considered to be one of the major symptoms of schizophrenia. This study aims to investigate characteristics of the brain responses to the auditory emotional stimuli in patients with schizophrenia using functional magnetic resonance imaging. Methods: Twenty two patients with schizophrenia and 22 healthy control subjects were administered auditory stimuli such as a laugh, a cry and a neutral utterance of 'ah' during fMRI. A spin-echo, T2*-weighted sequence with 26 contiguous axial slices was acquired on a 1.5 T MR scanner. All subjects performed a discrimination task for a gender of voices. Event-related data were analyzed by Statistical Parametric Mapping. Results: There were widespread activations in auditory areas and emotional processing-related areas including frontotemporal circuits in all subjects. However, those frontotemporal activation patterns were different according to positive and negative emotional conditions between the patients and controls. Furthermore, differential activation patterns in the frontotemporal circuits were observed between the patient subgroups with and without auditory hallucination. Conclusion: This results suggests that hallucinatory patients have obvious differences in brain function processing emotional stimuli. Schizophrenia, a heterogeneous disorder, may be pathophysiologically different according to the existence of auditory hallucination.

CEREBRAL DYSFUNCTIONS DURING COGNITIVE AND EMOTIONAL PERFORMANCE IN FIRST-EPISODE SCHIZOPHRENIA PATIENTS: A MULTICENTER LONGITUDINAL FMRI STUDY

M. Klein,* U. Habel, T. Kellermann, M. Wagner, S. Ruhrmann, B. Mueller, R. Thienel, R. Schloesser, D. F. Braus, A. Schmitt, E. Meisenzahl, T. Kircher, F. A. Henn, H. Sauer, F. Schneider
Department of Psychiatry and Psychotherapy, RWTH Aachen, University, Aachen, Germany

In the context of this ongoing multi-center functional Magnetic Resonance Imaging (fMRI) project, 80 first-episode schizophrenia patients and 80 healthy controls (matched for gender, age and parental education) were investigated while performing a modified version of the Continuous Performance Test (CPT). Phantom measurements (Siemens standard phantom) are used for quality control of scanner performance and in vivo data. Patients were double blind medicated (either with Haloperidol or Risperidone). Reassessments are carried out after 6, 12 and 24 months, in order to focus on cerebral reorganization processes. Subjects performed sequences of 0-back and 2-back tasks, with intermediate baseline phases (fixation of letters). The 0-back task requires attention capacities, while the 2-back task creates a demand on working memory abilities. A subgroup of patients and controls underwent emotional paradigms (emotion discrimination and mood induction). The functional data indicate abnormal activations during the CPT in medio frontal, posterior cingular regions, as well as in precuneus in schizophrenia patients as compared with healthy controls. The emotional tasks revealed notably limbic and fronto-temporal activation patters. Follow up measurements showed normalization and cerebral reorganization processes in subgroups of patients which could be correlated with psychopathological improvements. To our knowledge, this is the first multi-center fMRI study to verify such dysfunctions at the onset of schizophrenia.

STRIATAL DYSFUNCTION DURING PROCEDURAL LEARNING IN FIRST EPISODE SCHIZOPHRENIA: A FUNCTIONAL MRI INVESTIGATION

V. Kumari,* A. Kumar, I. Aasen, M. Mitershifhaler, T. Sharma
Psychology, Institute of Psychiatry, London, London, United Kingdom

Procedural learning (PL) is a type of rule-based learning in which performance facilitation occurs with practice on task without the need for conscious awareness. Striato-frontal regions are known to have important role in procedural learning. Patients with schizophrenia have often been found to show impaired procedural learning. We previously demonstrated dysfunction using functional magnetic resonance imaging (fMRI) and a relatively simple non-verbal procedural learning task in patients with chronic schizophrenia on conventional antipsychotics [1]. The present study examined functional brain dysfunctions in first episode psychosis patients, compared to age and sex matched healthy subjects. All subjects underwent whole brain fMRI during a blocked, periodic procedural learning (sequence-learning) task. The results confirmed involvement of the striatum in procedural learning, and revealed evidence for striatal dysfunction in patients who were experiencing their first psychotic episode and had no or minimum exposure to antipsychotic medication. [1] Kumari V, Gray JA, Honey GD, et al. Procedural learning in schizophrenia: A functional magnetic resonance investigation. *Schizophr Res* 2002, 57 (1), 97-107.

COGNITIVE EFFECTS OF ZIPRASIDONE IN FIRST EPISODE PSYCHOSIS: AN FMRI STUDY

N. Lancaster,* V. Kumari, R. Mehrotra, A. Kumar, T. Sharma
Clinical Neuroscience Research Centre, Dartford, United Kingdom

Antipsychotic drug treatment of first episode psychosis may be complicated by side effects of widespread dopaminergic antagonism, including exacerbation of negative and cognitive symptoms due to prefrontal hypodopaminergia. Cognitive deficits in first episode psychosis have been well documented. Second generation antipsychotic drugs have had a big impact on treatment of early psychosis due to the lack of neurological side effects. To elucidate the neural mechanisms of the effects of ziprasidone on attention and working memory in first episode psychosis, this study examined behavioral performance and blood-oxygenation-level-dependent regional brain activity (BOLD), using functional magnetic resonance imaging (fMRI), during a parametric n-back working memory task in 10 subjects with first episode psychosis who were treated with ziprasidone. They were compared to patients who had received conventional antipsychotics. Functional MRI was carried out in these two groups

of patients at baseline and 6 weeks later. The ziprasidone treated group had significantly greater response at 6 weeks in dorsolateral prefrontal cortex, supplementary motor area and parietal cortex ($p< 0.005$) These data provide the first direct evidence for enhanced prefrontal cortical function in first episode psychosis patients following treatment with ziprasidone and indicate the potential value of fMRI as a tool for longitudinal assessment of psychopharmacological effects on cerebral physiology.

INCREASED BRAIN ACTIVATION DURING EYE GAZE DISCRIMINATION IN SCHIZOPHRENIA

J. W. Loughead,* K. Ruparel, T. Indersmitten, R. C. Gur, R. E. Gur, C. G. Kohler
University of Pennsylvania, Philadelphia, PA, USA

Functional brain imaging studies of healthy individuals show fusiform and superior temporal gyri activation during eye gaze discrimination. Early studies of individuals diagnosed with schizophrenia reported gaze discrimination impairment for patients, particularly misidentification of averted gaze as making eye contact. However, two later studies failed to replicate these findings. Gaze detection's localization to superior temporal sulcus, an area strongly implicated in the pathopysiology of schizophrenia, makes eye gaze paradigm an ideal cognitive challenge for temporal lobe function. 5 stable schizophrenia subjects and 7 healthy controls underwent a novel task of gaze discrimination, which included 24 face stimuli at 0, 4 and 8 degree deviation presented in random order. Subjects were asked to identify whether a face was making eye contact. fMRI was acquired with BOLD imaging using a 15 slice, single-shot gradient-echo (GE) echo-planar (EPI) sequence (TR/TE=1000/30 ms, FOV=240 mm, matrix= 64 X 64, slice thickness/gap=3/0mm). Image processing and analysis was carried out in SPM2 using standard procedures. Speed and accuracy did not differ between groups. Comparing groups in 0 degree gaze trials, patients showed increased BOLD response in the right medial dorsal thalamic nucleus and right inferior frontal gyrus (BA 45). During the 8 degree trials, patients showed increased activation including left fusiform gyrus (BA 19), bilateral lingual gyrus (BA 18), precentral gyrus (BA 6), right superior temporal gyrus (BA 22) and thalamus. All regions survived correction for spatial extent using a height threshold of $z \geqq 3.73$ and a cluster probability of $p \leqq 0.05$. No difference was observed for the 4 degree gaze contrasts. Our findings indicate that despite similar gaze discrimination performance, schizophrenia subjects exhibit increased brain activation, as indicated by blood flow, in areas of visual processing and gaze detection. This preliminary finding may relate to common symptoms in acute schizophrenia, such as paranoia and ideas of reference. Future studies, using more subtle degrees of gaze deviation and in larger and more symptomatic patient groups are needed to further explore this finding.

SOCIAL COGNITION IN SCHIZOPHRENIA PATIENTS WITH AN ADDICTION HISTORY: AN FMRI STUDY

A. Mancini-Marie,* S. Potvin, C. Fahim, B. Mensour, J. Roy, E. Stip
Psychiatry, Centre de Recherche Fernand-Seguin, Louis-H Lafontaine Hospital, University of Montreal, Montreal, QC, Canada

The lifetime prevalence of substance use disorders among schizophrenia patients is close to 50%. It has been suggested that in order to sustain the lifestyle of substance abuse, addicted schizophrenia patients should display better social abilities than abstinent patients. Supporting the model, clinical studies have shown that addicted patients with schizophrenia have less negative symptoms, better social skills, and better frontal cognition. We hypothesized that patients with a history of addiction would have increased prefrontal activations in response to social emotional stimuli, when compared to abstinent ones. Schizophrenia patients (DSM-IV) were divided into two groups: patients with (n=12) and without (n=11) an addiction history (alcohol and/or cannabis). Using functional magnetic resonance imaging (fMRI), patients were scanned during passive viewing of a film depicting a sad social interaction. Random effect (2-sample T-test) showed increased activations in the left medial prefrontal cortex (LMPFC BA10) and the right temporoparietal junction (R BA39) in the addiction group, which reported higher subjective emotional experience on a self-report scale (from 0 to 8). To our knowledge, this is the first fMRI study to assess social emotional processing among addicted schizophrenia patients. Our results suggest that social cognition would be less impaired among them, and that the functioning of the medial prefrontal cortex, thought to be impaired in patients with prominent negative symptoms, would be more preserved in the dual diagnosis patients.

THE HYPOFRONTALITY AND WORKING MEMORY

V. Mangubi
Psychiatry, Kharkov State Medical University, Kharkiv, Ukraine

Regional cerebral blood flow or rCBF is a measurement of blood circulation levels to specific areas of the brain using transcranial sonography (Doppler sonography) by BIOSS (Russia). By monitoring rCBF while the patients participated in the Wisconsin Card Sort (WCS), a task relying heavily on working memory. In the study conducted by our Research Center blood flow to the DLPFC (Dorsolateral Prefrontal Cortex) was investigated in 70 schizophrenic patients and 65 non schizophrenics. All participants were subjected to three separate conditions or tasks in which rCBF in brain blood vessels were determined. We investigated indexes of line blood speed Front brain arteries (FBA), Middle brain arteries (MBA), Posterior brain arteries (PBA) The first of the three psychometric tasks was labeled the resting condition. This condition allowed participants to become acclimated with the experimental conditions. The next two conditions were counterbalanced among the participants in random order to discount the possible effect of task order on results. These two tasks were together labeled the activation condition and consisted of participants performing either the Wisconsin Card Sort (WCS) or the number matching control task while experimenters assessed rCBF. We try to conduct a study to control for all the possible confounds of past research on working memory and the DLPFC. We used transcranial sonography again, but changed neuropsychological, the research team manipulated working memory load on all schizophrenic patients and all healthy control subjects. This task required the participants to identify the digit initially presented zero, one, two, or three frames before the one currently viewable. The accomplishment of this task requires participants to actively store and compare units of separate information at differing working memory loads. As the working memory load became larger, activation levels of the DLPFC between increasingly differed between groups. At the two digit loading level, patients began to drop off in DLPFC activation. Our study suggest that there is a significant role of the DLPFC in working memory, correlating its activation negatively with cognitive disorganization, a symptom of schizophrenia possibly responsible

for many of the negative symptoms. These results clearly suggest working memory and the right DLPFC dysfunction as playing significant roles in schizophrenic symptoms.

EMOTIONAL PROCESSING AND EPISODIC MEMORY IN SCHIZOPHRENIA: AMYGDALA AND ORBITAL-MEDIAL PREFRONTAL CORTEX ACTIVATION

J. R. Mathews,* D. M. Barch
Psychology, Washington University, St. Louis, MO, USA

A growing literature suggests that individuals with schizophrenia provide relatively intact self-reports of valence and arousal in response to affect eliciting stimuli and also show an intact influence of emotional valence and arousal on subsequent memory. However, less is known about the integrity of the neural systems that support the processing of emotional information and the influence of emotional valence on memory. This study was designed to examine whether individuals with schizophrenia demonstrate appropriate activation of regions involved in the processing of emotional information when presented with either emotional words or pictures, and whether the degree of activation in such regions predict subsequent memory for those stimuli. We used fMRI to measure brain activity while controls and individuals with schizophrenia made valence and arousal ratings on a series of words and pictures using the SAM rating system. The words and pictures varied in emotional valence (positive, negative, neutral) and arousal (high versus low). After scanning, participants were given surprise recall tests for the words and pictures, followed by recognition tests that asked participants to make remember/know/guess judgments. Participants were 20 patients with schizophrenia and 10 demographically similar healthy controls. Results suggest that individuals with schizophrenia rate emotional stimuli (for both words and pictures) as less valenced (i.e. less positive and less negative) than do controls, but that both groups show similar arousal ratings. The individuals with schizophrenia displayed overall worse recall, but displayed an intact influence of emotion on subsequent recall and remember/know judgments (higher remember judgment for negative as compared to either neutral or positive stimuli). Additional analyses will focus on patterns of activation in regions such as amygdala and orbital-medial prefrontal cortex during initial encoding within each group, as well as on the ability of amygdala and orbital-medial prefrontal activation to predict subsequent memory for specific stimuli.

MOTOR INHIBITION AND PSYCHOTICISM

K. J. McGill,* W. E. Semple, P. F. Goyer, G. Jaskiw, B. Donovan, L. Rugle, E. A. Callihan, D. Leibling, K. McCutcheon, N. Krudelbach, A. B. Slifkin
Radiology, Louis Stokes Veterans Administration, Brecksville, OH, USA

We tested the hypothesis of impaired motor inhibition of language production in psychoticism. A mixed group of 25 volunteers (6 normals, 8 substance abuse disorder, 8 PTSD, and 3 gamblers) were administered the Eysenck Personality Questionnaire and underwent positron emission tomography (PET) scans for regional cerebral blood flow (rCBF) using O15-butanol. Brain images were spatially normalized (Friston, 1995). Regions of interest were applied to the PET images to measure rCBF at Broca's area determined by the coordinate system of Talairach and Tournoux (1988). Volunteers with high psychometric psychoticism had higher rCBF at Broca's area compared to volunteers with low psychoticism ($t(23) = 2.31$, $p = .03$). This supports the idea that increased psychoticism is associated with impaired inhibitory motor processing for language.

AN FMRI STUDY OF SEX DIFFERENCES IN EMOTION PROCESSING IN SCHIZOPHRENIA

A. Mendrek,* C. Fahim, A. Mancini-Marie, M. Boualem, E. Stip
Psychiatry, Centre de Recherche Fernand-Seguin, University of Montreal, Montreal, QC, Canada

There is now ample evidence that brains of men and women differ. While some aspects of the normal sexual dimorphism appear to be preserved in schizophrenia, recent findings suggest that other features might be reversed. Specifically, a significant reduction in the anterior cingulate volume has been observed in schizophrenia women relative to healthy women, but there was no difference between men with and without the diagnosis (Goldstein et al., 2002). Moreover, while healthy women were found to have a higher orbitofrontal cortex to amygdala ratio than men (Gur et al., 2002), this sexually dimorphic characteristic was reversed in schizophrenia (Gur et al., 2004). Because the brain regions that show reversed sexual dimorphism in schizophrenia have been strongly implicated in emotion processing, we hypothesized that relative to women, men with schizophrenia will exhibit different pattern of cerebral activation during affective task. Nine women and 15 men diagnosed with schizophrenia underwent functional magnetic resonance imaging (fMRI) during passive viewing of either sad or emotionally neutral film excerpts. Despite lack of significant differences between the sexes in the subjective rating of the emotions felt during viewing of the film clips, the fMRI data analysis, performed with the statistical parametric mapping software SPM 99, revealed an overall larger extent and intensity of activation in men than in women during sad relative to neutral condition. In addition, direct comparison between the groups using a random-effects model disclosed significantly greater activity in the premotor cortex and cingulate gyrus in men relative to women. These results imply that relative to women, man with schizophrenia might be characterized by enhanced neurophysiological response to emotional stimuli and as such the findings are consistent with recent claims of potential "masculinization" of females and "feminization" of males with schizophrenia.

DIFFERENTIAL ACTIVATION OF FUSIFORM GYRUS DURING FEARFUL FACE PROCESSING IN SCHIZOPHRENIA

P. Michalopoulou,* L. Morley, G. T. Samson, O. O'Daly, V. Giampietro, R. M. Murray, S. S. Shergill
Psychological Medicine, Institute of Psychiatry, London, United Kingdom

The crucial role of the fusiform or occipitotemporal gyrus in face recognition has been supported by findings from neuropsychological, brain lesion as well as functional neuroimaging studies. These findings suggest a crucial role of this region in finely discriminating and processing invariant aspects of the human face information, including the emotional facial expressions. Recent functional neuroimaging studies suggest a direct role of the fusiform gyrus in the processing of fearful facial expressions; it has been demonstrated that this region shows statistically significant greater activation during the processing of fearful compared with neutral faces. In addition,

increasing activation of the fusiform gyrus with increasing intensity of facial fear has been demonstrated. A growing body of evidence suggests that patients with schizophrenia have a deficit in recognition of facial affect and that recognition of fearful emotions may be differentially affected in patients with schizophrenia. We hypothothesized that patients with schizophrenia would demonstrate attenuated activation of the fusiform gyrus during the processing of fearful compared with neutral faces and that this would differ from activation seen in a matched group of healthy volunteers. FMRI data was acquired on a GE signa 1.5T system in eleven stable patients with a DSM-IV diagnosis of schizophrenia and nine age and gender matched healthy comparison subjects. All subjects were required to perform a gender discrimination task while viewing fearful, sad or neutral faces, presented in an event-related design. Data were analysed using the standard software of the Institute of Psychiatry. Healthy subjects demonstrated significantly greater activation of the right fusiform gyrus during the processing of fearful compared to neutral faces. Interestingly, patients with schizophrenia did not show this difference. In the between group comparison, patients with a diagnosis of schizophrenia when compared with the healthy subjects had significantly less activation within the fusiform gyrus during the processing of fearful faces Our data indicate that the fusiform gyrus displays a differential pattern of activation during the processing of fearful faces in schizophrenic patients compared to healthy controls. This may underlie the difficulties of the patients in social interaction and play a role in the evaluation of persecutory beliefs.

DISRUPTED TASK RELATED ACTIVATION TO ACTION SELECTION AND CONFLICT RESOLUTION IN PATIENTS WITH SCHIZOPHRENIA

R. A. Morey,* S. Inan, G. Rosania, S. Hardy, A. Belger
Psychiatry, Duke University, Durham, NC, USA

Impairments in the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (dlPFC) observed on target detection tasks such as the visual oddball are well recognized in schizophrenia research. The ACC is an important neurofunctional node in attentional paradigms involving action-selection and conflict-resolution, such as the flanker task. The superior parietal cortex is responsible for deployment of attention to relevant spatial locations. Thus, posterior attentional areas such as the superior parietal cortex connect with anterior attentional systems including the ACC and the dlPFC to form an integrated neurofunctional network engaged in the flanker task. Certain flanker tasks show impaired behavioral performance in patients with schizophrenia but have not been studied using functional neuroimaging. Given the observed deficits in both the ACC and dlPFC accompanying schizophrenia, it is reasonable to hypothesize diminished task related activation in both regions on a flanker target detection task. We used a visual oddball task with flanker stimuli to examine the effects of stimuli presented in attended and unattended visual areas on brain activation. Target stimuli (circle), Standard stimuli (square), and task unrelated salient Novel stimuli (household object) were displayed in a central attended zone. Simultaneously both left and right flanker areas displayed Standards or Novels. Ten patients with schizophrenia and 14 healthy control subjects participated in a forced choice task during fMRI scanning. We observed greater target related activation in controls than patients in the ACC. Furthermore, consistent with the theory that the ACC is an action-selection area impaired in schizophrenia, we found differential activation between Targets and Flankers was reduced in patients. Middle frontal gyrus activation to Flanker objects was greater in patients than controls, suggesting increased processing resources devoted to task irrelevant distracters. Finally, interrogating posterior visuospatial attentional systems revealed that despite the bias to Targets in the anterior system of control subjects relative to patients, the intraparietal sulcus showed greater activation to Flanker objects in controls than patients. Thus, our results suggest the anterior system of patients is vulnerable to being subverted by task irrelevant stimuli (flankers) and the posterior system is insufficiently tuned to the detection of spatially peripheral stimuli.

VERBAL MEMORY ENCODING IN PATIENTS WITH SCHIZOPHRENIA: AN EVENT-RELATED FMRI-STUDY

B. W. Mueller,* G. Sartory, S. Heinze, A. Hesse, A. de Greiff, M. Forsting, M. Jueptner
Clinic for Psychiatry and Psychotherapy, University of Duisburg-Essen, Essen, Germany

Verbal memory deficits have been shown to be extant among cognitive deficits in schizophrenia. The Aim of our study was to investigate verbal memory encoding in healthy controls (study 1) and patients with schizophrenia (study 2) by means of event-related functional magnetic resonance tomografy (efMRI). While previous studies on verbal memory mainly focused on encoding success, we compared unsuccessful and successful encoding to a reading baseline condition. Methods Study 1: During efMRI-scanning, fifteen healthy controls (30.9 years; 8f, 7m) were presented with nine word lists consisting of 22 always new nouns. Seven word lists were to be learned and two lists were to be read (baseline condition). Immediately after presentation of each list subjects were asked to reproduce the words. Data acquisition was carried out on a 1.5 T Siemens Sonata Scanner; data were analysed with SPM99. Study 2: Eighteen patients with schizophrenia (35.6 years; 7f, 11m) and fifteen matched controls (30.5 years; 5f, 10m) took part in the efMRI-experiment described above. Word lists contained 19 nouns and stimulus duration was 2.7 sec (TR); data were analysed with SPM2. Results Study 1: Both, unsuccessful and successful encoding activated thalamic, cingulate and left premotor areas. Successful encoding was related specifically to bilateral prefrontal, bilateral parietal and left lateral temporal activation. Study 2: Memory performance in patients with schizophrenia was slightly lower than in healthy control subjects ($p = .049$). The specificity of parietal activation for encoding success was replicated in control subjects. In patients with schizophrenia, parietal activation emerged unspecifically during unsuccessful and successful encoding. Our results underline the impact of parietal involvement in successful verbal memory encoding. Patients with schizophrenia may have difficulties to effectively allocate parietal attention resources.

ALTERED NEURONAL ACTIVATION DURING A VERBAL FLUENCY TASK IN YOUNG AULTS WHO WERE BORN VERY PRETERM

C. Nosarti,* C. M. O'Carroll, P. K. McGuire, L. Rifkin, R. M. Murray
Psychological Medicine, Institute of Psychiatry, London, United Kingdom

BACKGROUND: Obstetric complications increase the risk of neurodevelopmental abnormalities and may predispose individuals to

develop schizophrenia. Several studies have suggested that patients with schizophrenia may exhibit deficits in executive function, which is subserved by neuronal networks in the frontal lobes. A widely used measure of executive function is the verbal fluency task. Neuroimaging studies have reported altered neuronal activation in the prefrontal cortices in patients with schizophrenia during performance of this type of task. Selective verbal fluency and executive-type deficits have been also observed in individuals who were born very preterm. This study investigated whether the patterns of neuronal activation during completion of an overt verbal fluency task in young adults born very preterm were indicative of abnormalities in prefrontal neuronal networks. METHODS: A group of 20 right handed young adults of both sexes who were born very preterm (< 33 weeks gestation) and 14 matched full-term controls were studied. Echo planar MR images demonstrating BOLD contrast were acquired using a 1.5 Tesla GE Signa Neurovascular MR system. Data were analysed with XBAMv3.3. The effect of group and task were examined in factorial analyses by fitting an ANCOVA model at each activated voxel. Hypothesis testing was carried out at cluster levels. RESULTS: There were no statistically significant differences in task performance between the two groups. During correct verbal fluency responses, relative to a baseline task, all subjects activated a fronto-stiatal-cerebellar network, predominantly but not exclusively in the left hemisphere. Preterm individuals showed additional responses in the hippocampus bilaterally and right parahippocampal gyrus. For the ANOVA analysis the number of positive clusters tested was 43 and <0.9 false positive activated clusters were expected at a p-value of < 0.005. Compared to controls, preterm individuals showed reduced BOLD signal response in left inferior frontal gyrus extending to insular cortex (BA 45/72). CONCLUSIONS: Our results suggested that despite good task performance, individuals who were born very preterm exhibited neuronal dysfunction in prefrontal circuits of the brain. These prefrontal neuronal alterations may form the neural basis of executive function impairments and constitute a vulnerability to the development of schizophrenia.

ALTERED NEURONAL ACTIVATION DURING PROCESSING OF VERBAL EPISODIC MEMORY IN PRETERM ADOLESCENTS

C. O'Carroll,* C. Nosarti, P. K. McGuire, L. Rifkin, R. M. Murray
Psychological Medicine, Institute of Psychiatry, London, United Kingdom

The general aim of the present research project was to investigate the ways in which the neuronal activation (as assessed with fMRI) of individuals born very preterm is altered in the presence of perinatal brain injury. In particular we were interested in identifying the neural correlates of selective aspects of memory functioning, with specific reference to episodic memory. This study involved comparing the generic brain activation of 21 right-handed male and female adolescents born very preterm (<33 weeks of gestation), and 22 matched controls during the performance of a paired-associate learning task. METHODS: Echo planar MR images demonstrating BOLD contrast were acquired using a 1.5 Tesla GE Signa Neurovascular MR system. Fourteen 7mm thick near axial slices were acquired parallel to the intercommisural plane with the addition of a high resolution inversion recovery EPI data-set with 3mm thick slices and an in-plane resolution of 1.5mm. Data were analysed with XBAMv3.3, which uses pseudo-generalised least squares fitting of the motion corrected time series at each voxel using a sinusoidal regression model with non-parametric inference using time series randomisation. The effect of group and task were examined in factorial analyses by fitting an ANCOVA model at each activated voxel. RESULTS: Task performance was similar in the two groups, i.e. there was no difference between groups in the number of correct or incorrect, recalled items. However, during encoding, preterm individuals showed reduced BOLD signal response compared to controls in the cerebellum and increased response in the hippocampus and surrounding parahippocampal gyrus. During cued recall, preterm subjects again showed reduced BOLD signal response in the cerebellum and increased response in the hippocampus. These results suggest that despite good task performance, individuals who were born very preterm may activate different neural networks and use alternative strategies when encoding and recalling previously learnt verbal information.

DYNAMIC STUDY OF SEQUENTIAL FEATURE PROCESSING IN SCHIZOPHRENIA

P. J. Pardo,* E. E. Dumas, A. P. Georgopoulos
Psychiatry, Univ. of Minnesota, Minneapolis, MN, USA

Schizophrenia patients exhibit difficulty in numerous attentional tasks requiring inhibitory brain mechanisms. An example of the lack of inhibitory processing is often illustrated in the pattern of reaction times in verbal priming studies. Schizophrenia patients, as compared to healthy control subjects, frequently exhibit more rapid automatic processing of the second word of identical/related words presented temporally close together and reduced inhibitory processing of the second word of these words presented temporally farther apart. The goal of this project is to identify the neural correlates of these behaviors in the case of pairs of sequential nonverbal visual stimuli. Presently, this paradigm is being refined with a group of control subjects and then will be applied in another study of schizophrenia patients and gender, age-matched matched control subjects. During whole-head magnetoencephalographic (MEG) recording, randomized pairs of minimally complex visual stimuli (low contrast, suprathreshold, gray Gabor function stimuli) are foveally presented at two different Stimulus Onset Asynchronies (SOAs). The subject's task is to push one button to indicate if the patterns of the stimulus pair are the 'same' and to push another button to indicate if the patterns of the stimulus pair are 'different.' Using co-registered MEG/MRI information, the timing and location of cortical regions recruited for the different task conditions can be determined for each subject. The time course and location of MEG neural responses, as well as the button press reaction times, will then compared across the four conditions of same, short SOA; different, short SOA; same, long SOA; and different, long SOA. We hypothesize (a) different patterns of dynamic brain activation between the same and different pairs of stimuli, (b) a systematic effect of SOA, mainly for "same" pairs, (c) an earlier and larger MEG signal for the second stimulus of the "same" (vs. "different") pairs in schizophrenia, as compared to controls, especially in the case of shorter SOAs, and (d) in patients, less dampening of the MEG response to the second stimulus in the "same" pair for the longer SOAs. Supported in part by the MIND Institute.

NEURAL NETWORKS SUPPORTING VISUAL MOTION PROCESSING

J. V. Pardo,* P. J. Pardo, E. E. Dumas, A. P. Georgopoulos
Psychiatry, University of Minnesota, Minneapolis, MN, USA

Schizophrenia patients have difficulty in processing rapidly moving, nonverbal, full-field, visual stimuli. They are inaccurate in predicting the trajectory of a motion. Such impairments have practical implications for everyday function. The neurophysiologic deficits are not

well-understood, particularly in the temporal domain. The goal of this project is to compare the timing and location of magnetoencephalographic (MEG) responses in schizophrenia and control subjects to low contrast, gray dots moving coherently. During MEG recordings, visual stimuli are briefly presented moving in one direction, which varies randomly across trials. Subjects undergo both MEG and MRI to optimize the magnetic source analysis of the neural responses. We hypothesize: (a) partially overlapping patterns of brain activation for the visual stimuli moving in different directions; and (b) significant differences between the activation patterns and the relations to stimulus parameters between schizophrenia and control subjects. Supported on part by the MIND Institute, NARSAD, and the Department of Veterans Affairs.

AN FMRI STUDY OF BODY POSTURE RECOGNITION IN SCHIZOPHRENIA

J. Park,* T. Ha, K. Kang, W. Moon, E. Chung, J. Kwon
Interdisciplinary Program in Cognitive Science, Seoul National University, Seoul, South Korea

Until recently, faces were the only class of objects processed differently and producing the inversion effect, in which inversion impairs recognition of faces more than nonface objects. Another class of objects that shares the abstract properties that are of importance in social interaction can be human body postures. In the present study, the alteration in brain activation patterns to posture in schizophrenia is explored, that has been reported to have social impairment. Eleven patients with schizophrenia diagnosed with DSM-IV criteria (SCID-IV) and 11 normal controls were recruited. We used functional magnetic resonance imaging (fMRI) to study the human body posture with body discrimination task. In fMRI paradigm, a stimulus is presented for 2s after 500ms ISI and 500ms "+" as a prompt, and subjects have to decide whether two photos in the stimulus are same or different. A run consists of 14 blocks each of which includes 7 stimuli, thus lasts for 21s, interleaved with 4 fixation blocks of 12 sec. Blood oxygen level dependent (BOLD) signal changes were measured at 1.5T Philips scanner and acquired functional images were preprocessed and analyzed using SPM99. As a preliminary result, human body postures elicit a strong activation in the superior temporal gyrus (STG) in the normal subjects and the schizophrenic patients showed the reduction of the STG activation compared to normal controls. These activation differences can be windows of neural bases for social cognition impairment in schizophrenic patients.

WORKING MEMORY DEFICITS AND ABERRANT PREFRONTAL CORTEX ACTIVATION IN FIRST-DEGREE RELATIVES OF SCHIZOPHRENIA PATIENTS: AN FMRI STUDY

G. Pearlson,* N. A. Morris, C. H. Kuzu, R. S. Astur, V. D. Calhoun, D. H. Mathalon, K. A. Kiehl
ONRC, Institute of Living, Hartford, CT, USA

We used functional magnetic resonance imaging (fMRI) to compare DLPFC activation during a modified Sternberg paradigm between nine unaffected relatives of schizophrenic individuals and nine matched healthy controls. We examined differences in DLPFC activation across task loads as an indicator of WM function in each group. fMRI statistical parametric maps imposed on the five-level Sternberg task were created for each participant and were used to compare DLPFC activation, behavioral performance, and WM load across groups. Healthy controls demonstrated a linear modulation of activation at the local maximum in the Left DLPFC (-45, 15, 19) when task load was increased ($p < 0.01$, uncorrected). The Pearson correlation was $r = 0.24$, $p < 0.04$, suggesting that controls dealt with increasing task load by activating more in the Left DLPFC. Non-affected relatives demonstrated aberrant DLPFC activation compared to healthy controls when matched on performance. Comparatively, relatives did not exhibit any significant linear modulation at the local maximum in the L-DLPFC (-53, 10, 30), found at the same threshold, with $r = -0.08$ and $p < 0.29$. These results imply that relatives' DLPFC activation does not increase with rising task difficulty during a WM task, indicating aberrant WM function. Furthermore, the abnormal DLPFC activation in relatives may be indicative of a genetic component in schizophrenia. Finally, because we compared relatives' activations averaged over task loads of four, five, and six to controls' activations averaged over task loads of six, seven, and eight target letters, we were able to match performance more closely than in some prior published reports. This may explain why we detected decreased, not increased DLPFC activation in relatives under these circumstances.

EXPLORING THE NEURAL SUBSTRATE OF VISUO-SPATIAL WORKING MEMORY USING A DELAYED MATCHING TO SAMPLE PARADIGM AND FMRI

M. M. Picchioni,* P. Matthiasson, S. Williams, P. K. McGuire
Section of Neuroimaging, Institute of Psychiatry, London, United Kingdom

Background: Working memory deficits are widely reported in schizophrenia. These deficits are evident from the earliest stages of illness. Methods: We explored the neural correlates of visuo-spatial working memory using a modified version of the Delayed Matching to Sample (DMTS) paradigm from the Cambridge Neuropsychological Test Automated Battery (CANTAB) in ten healthy controls using functional Magnetic Resonance Imaging. The paradigm engages three principle components of visuo-spatial working memory, encoding, maintenance and retrieval. We utilised two maintenance delays of 4 and 12 seconds in addition to a Simultaneous recall condition. All data were acquired at 1.5T and analysed using established non-parametric techniques. Results: Independent of the length of the preceding maintenance delay, successful recall was associated with activation of an extensive fronto-parieto-temporal network involving bilateral inferior and left middle frontal and cingulate gyri, bilateral superior parietal lobules, and the fusiform gyrus. As the length of the maintenance delay increased, activation at recall decreased in the right inferior frontal gyrus and bilateral superior parietal regions and increased in the right inferior temporal gyrus. Successful compared to unsuccessful recall was associated with greater activation in the inferior frontal gyrus bilaterally, the anterior cingulate, precuneus and right inferior temporal gyrus and uncus. Conclusions: Visuo-spatial working memory is mediated by a network of prefrontal, cingulate, parietal and temporal regions, with the pattern and extent of activation varying with both the demands on working memory and the accuracy of retrieval.

MAPPING LOCALIZED CEREBELLAR ACTIVITY IN MOTOR, EMOTIONAL AND COGNITIVE TASKS, AND RELATIVE DEFICITS IN SCHIZOPHRENIA

R. Pierson,* N. C. Andreasen, D. S. O'Leary
MHCRC, University of Iowa, Iowa City, IA, USA

Functional imaging studies are beginning to provide a rich source of information for creating an atlas of regional specialization within the cerebellum. In addition, if one is able to create a high-resolution mapping of cerebellar activations we may also provide insight into the nature of the temporal and associative processing tasks being completed in the cerebellar cortex. In this study we review data from numerous PET studies completed at our Center and create a composite atlas of the regions of activation in the cerebellum. Since many of our functional imaging studies of healthy controls have been completed in tandem with the study of patients with schizophrenia we are also able to create a composite atlas of the differences in cerebellar activations between these two groups. Analysis of the functional imaging data was performed using an implementation of the Montreal Method (Worsley analysis). For between-group comparisons, randomization analysis was performed to avoid assumptions of equal variance and normal distribution. Activities used in generating this atlas include a Theory of Mind task (empathetic narrative), verbal recall of stories and word lists, visual recall of faces, fingertapping, and acquisition of eyeblink conditioning. In general, motor tasks activated regions in the anterior lobe (lobes I-V) and in lobe VI. Tasks requiring verbal or auditory processing activated lobe VI, and memory tasks activated lobe VIIa in addtion to regions activated by the verbal processing. Theory of mind tasks activated regions throughout the cerebellum, but especially crus I of VIIa and vermis regions. There were numerous regions of significantly lower activity in patients compared to controls, but they were predominantly confined to the regions that were activated in controls.

SCHIZOPHRENIA WITH AN ADDICTION HISTORY DIFFER IN THE NEURAL PROCESSING OF AVERSIVE STIMULI: AN FMRI STUDY

S. Potvin,* A. Mancini-Marie, C. Fahim, B. Mensour, J. Roy, E. Stip
Centre de Recherche Fernand-Seguin, Hopital Louis-H Lafontaine, Universite de Montreal, Montreal, QC, Canada

The lifetime prevalence of substance use disorders among schizophrenia patients is close to 50%. According to the affect regulation model, schizophrenia patients would abuse drugs in order to cope with their negative affects. Supporting the model, clinical studies have shown that dual diagnosis patients have less emotional blunting, and that they are more prone to experience negative affects (NA). We hypothesized that patients with a history of addiction would have increased cerebral activations in response to aversive stimuli, when compared to abstinent ones. Schizophrenia patients (DSM-IV) were divided into two groups: patients with (n = 12) and without (n = 11) an addiction history (alcohol and/or cannabis). Using functional magnetic resonance imaging (fMRI), patients were scanned during the passive viewing of aversive pictures (International Affective System). Random effect (2-sample T-test) showed increased activations in the left medial prefrontal cortex (LMPFC BA 10) and the right parahippocampal gyrus (R BA 28) in the addiction group, which reported higher subjective emotional experience on a self-report scale (from 0 to 8). To our knowledge, this is the first fMRI study to assess the processing of aversive stimuli among addicted schizophrenia patients. Our results suggest that dual diagnosis patients would be more prone to experience NA, lending support to the affect regulation model. Drug consumption in schizophrenia could represent an active strategy to cope with NA Funding: The study was funded by AstraZeneca, the Fonds de Recherche en Sante du Quebec, and the University of Montreal Eli Lilly Chair of Schizophrenia.

RECOVERY OF RIGHT LATERAL FUSIFORM GYRUS FUNCTION IN RISPERDONE-TREATED SCHIZOPHRENIC PATIENTS DURING FACIAL INFORMATION PROCESSING

J. Quintana,* T. O. Wong, J. Osowsky
Psychiatry and Biobehavioral Sciences, UCLA School of Medicine, Los Angeles, CA, USA

Schizophrenic patients exhibit individual profiles of cognitive deficits. As a group, atypical antipsychotics improve cognitive deficits, yet each agent may have specific effects on different cognitive functions, a distinct cognitive therapeutic pattern which might be used to optimize individual treatments. Facial information processing deficits are well known in schizophrenia and predict functional outcomes. Recent reports indicate that right Lateral Fusiform Gyrus (rLFG) functional abnormalities may underlie those deficits. We are studying the effects of atypical antipsychotics on rLFG function during facial information processing. We have studied 15 stable schizophrenic outpatients (11 males, 4 females, age 37.9 14.3, length of illness 10.2 7.9), 7 treated with Risperidone (2-6 mg/day) and 8 with Olanzapine (10-20 mg/day). Both groups had similar age and gender distribution. Subjects underwent fMRI (GE or Allegra Siemens 3T, structural EPI and functional asymmetric spin echo or gradient echo) while performing a 5-min block-design task where series of facial affect and identity discrimination trials were interleaved with series of object discrimination control trials. Images were preprocessed and analyzed using AIR, a 6-mm FWHM Gaussian filter, and SPM99 (GE 3T data), or FEAT 5.1 (FSL; FLIRT for registration), a 5 mm filter, and FEAT 5.1 (FSL, FILM general linear model, Z>2.3 cluster threshold, corrected p=0.01)(Siemens 3T data). Performance data were analyzed using multiple or logistic regression models (SPSS). Both treatment groups showed statistically similar performance levels. We found significant rLFG activation in the Risperidone group but not in the Olanzapine one. Individually, all but one of the Risperidone-treated patients but only one of the Olanzapine-treated patients showed rLFG activation. Among patients who performed the task three consecutive times, those on Risperidone showed progressively increased rLFG activation whereas those on Olanzapine did not show any rLFG activation. These results suggest that Risperidone may have a specific restorative effect on neural systems critical for facial affect processing and thus important for social functioning. They support the fMRI assessment and monitoring of drug treatments in schizophrenia, and their selection based on neurocognitive and neurofunctional patient profiles. Supported by NARSAD, VA ARCD & Merit Review, and UCLA-HHMI awards (J.Q.), VA VSN22-MIRECC, and Janssen Pharmaceutica.

CONTROLLED VERSUS AUTOMATIC SEMANTIC RETRIEVAL IN SCHIZOPHRENIA: A COMPRESSED IMAGE ACQUISITION OVERT WORD PRODUCTION FMRI STUDY

J. Ragland,* S. T. Moelter, J. Valdez, M. Elliott, R. C. Gur, R. E. Gur
Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

Impaired semantic fluency (e.g., animal naming) in schizophrenia has been attributed to semantic retrieval problems rather than impaired semantic knowledge. Controlled aspects of semantic retrieval (e.g., semantic search) are also affected more than automatic processes such as generation of over-learned responses. The current functional magnetic resonance imaging (fMRI) study uses a previously established paradigm (1) to manipulate semantic search demands in 7 patients with schizophrenia and 8 healthy controls. Subjects alternated between generating words under high semantic category (SC) search demands (SC; e.g., furniture) and under low search demands using over-learned word sequences (OS; e.g., letters of alphabet). Compressed image acquisition (2) provided 3 sec. periods of silence to permit overt verbal responses. Images were acquired on a 3Tesla Siemens scanner using BOLD fMRI. Subjects alternated between 4 SC (vegetables, fruit, furniture, vehicles), 4 OS (numbers, alphabet, days of week, months), and 8 baseline (repeat word - REST) blocks lasting 42 sec. each. Images were pre-processed in SPM2 using standard motion correction, normalization and smoothing procedures, and conditions were modeled using a boxcar design. All subjects understood the task and there were no group differences in number of words generated. For the SC-OS contrast controls produced greater activation than patients in prefrontal cortex (left Brocas area, right dorsolateral and right frontal pole); bilateral thalamus, hippocampus, precuneus, and cerebellum; and left caudate and inferior temporal gyrus. Greater patient activation was restricted to right middle temporal, and superior parietal regions. Regional differences in activation despite unimpaired patient performance suggest different strategies during semantic search, with controls relying more on strategic control, semantic working memory, and episodic memory processes mediated by prefrontal and hippocampal networks. Work was supported by National Institutes of Health grants MH62103, NS045839, and M01RR0040. (1) Gurd JM, et al. (2002). Posterior parietal cortex is implicated in continuous switching between verbal fluency tasks: an fMRI study with clinical implications. *Brain*, 125;1024-1038. (2) Abrahams S, et al. (2003). Functional magnetic resonance imaging of verbal fluency and confrontation naming using compressed image acquisition to permit overt responses. *Human Brain Mapping*, 20:29-40.

NEURAL CORRELATES OF METAPHOR PROCESSING IN SCHIZOPHRENIA

A. M. Rapp,* D. T. Leube, M. Erb, M. Bartels, W. Grodd, T. T. Kircher
Department of Psychiatry, University of Tuebingen, Tuebingen, Germany

Patients with schizophrenia have deficits in understanding figurative aspects of language (e.g. metaphors). We wanted to investigate the pathophysiology of this phenomen. We studied 12 right handed patients with schizophrenia and 12 matched healthy controls with functional magnetic resonance imging while they read sentences with figurative or literal meaning. Patients and controls were matched for age, gender, education and verbal intelligency. During the experiment, volunteers read sentences silently and judged by button press whether the sentence had a positive or negative connotation. Each sentence was presented for 5 seconds with a 3 second interstimulus interval. 30 metaphors and 30 literal sentences in German language, constructed de novo, served as stimuli. Sentence pairs differed only in their last word and had half a metaphoric (e.g "Der Wecker ist ein Folterknecht" [the alarm clock is a torturer]) or a literal ("Der Wecker ist ein Elektroger?" [the alarm clock is an electrical appliance]) meaning. The stimuli were matched for comprehensibility, connotation (positive or negative), tense and frequency of the last word. Data was collected from the whole brain (22 slices, slice thickness 5mm, TR=2s, TE=40 ms) using a 1.5 T Siemens SONATA magnetic resonance system. Differences in brain activation during the task were measured using an event-related design and SPM 99 software (Wellcome Department, London) with a random effects model. During reading of metaphors, healthy control subjects activated the precuneus and superior temporal gyrus in the right hemisphere more than patients with schizophrenia. This difference in activation was not present in non-metaphoric control sentences. Dysfunction of this brain area may underly schizophrenic patients impaired ability to understand metaphoric expressions.

FMRI BOLD CEREBELLAR ACTIVATION OF FIRST-EPISODE SCHIZOPHRENIA PATIENTS DURING THE TOWER OF LONDON TASK

P. E. Rasser,* P. Johnston, G. Peck, P. M. Thompson, P. B. Ward, V. Carr, U. Schall
Neuroscience Institute of Schizophrenia and Allied Disorders, Sydney, NSW, Australia

Over the past decade there has been an increasing recognition that the cerebellum may play an important role in higher cognition. Above its traditionally accepted roles in gait and fine motor control, it has been suggested that the cortical-cerebellar-thalamic-cortical-circuit incorporates a neuronal loop that serves to integrate motor and cognitive functioning. In this study, sMRI and fMRI BOLD data have been used to examine the functional activation of the cerebellar cortex of 10 first-episode male schizophrenia patients with 10 healthy age and gender-matched control subjects during their performance of the Tower of London (TOL) task. A task that has previously been used to examine executive function/dysfunction in schizophrenia patients. The structural analysis for each subject involved alignment of their sMRI to a template, followed by masking and extraction of a 3D model of their cerebellar cortex. For the fMRI BOLD activation, each subject's data was processed using a regression model that took level of difficulty of the TOL task into account. Each subject's resultant z-scores were then mapped to their corresponding 3D cerebellum model. Finally, the individual cerebellum models and z-scores were group averaged, with the group average z-scores thresholded at $p<0.05$. In control subjects, the main cluster of activation was seen in left hemisphere lobules VI and Crus I, which receive direct cortical and indirect tectocerebellar visual input. A smaller cluster was seen in the right lobule VIIB and extending into VIIIA while the patients' main focus of activation was seen in the right peduncle with extension into lobules VIIIA and VIIIB. Suggesting a cerebellar contribution to higher level cognitive processing. The TOL paradigm used in this study increases the workload on spatial working memory by increasing the difficultly of the tasks. Increasing executive demands on spatial working memory are known to shift activation to the right frontal cortex. While the control subjects follow this pattern of right frontal cortical and contralateral cerebellar activation, first-episode schizophrenia patients exhibit a reversed pattern of BOLD

response in this circuitry. A higher level of left frontal cortex and predominantly right cerebellar activation may indicate that patients are more likely to rely on alternative strategies (e.g. verbalisation) due to impaired spatial working memory in order to perform the TOL at the same level as matched control subjects.

ASSESSING THE NEUROPHYSIOLOGIC CORRELATES OF CONTEXTUAL PROCESSING DEFECTS IN SCHIZOPHRENIA

J. L. Ritch,* D. C. Glahn, J. Barrett, D. I. Velligan, C. Franklyn, P. T. Fox
Psychology, University of Texas at Austin, Austin, TX, USA

Patients with schizophrenia are thought to be impaired in contextual processing, an aspect of working memory, to guide on-going behavior. We used functional magnetic resonance imaging (fMRI) to compare the neural activity of 20 clinically stable outpatients with schizophrenia and 19 demographically matched controls while engaged in a task in which the degree of contextual processing was manipulated across trials. The task required subjects to determine whether a probe stimulus was in the same or different location as a target seen prior to a fixed delay. Three stimulus probes were utilized and contained 1) no contextual information (single), 2) valid contextual information (anchor), or 3) invalid contextual information (fake anchor). Subjects underwent fMRI scanning using a 2 Tesla magnet whilst performing the spatial working memory task. Accuracy and reaction time data collected during scanning on the task were entered into 2x3 MANOVAs testing for main effects of diagnostic group and contextual condition. Results indicated that patients performed worse than controls on all conditions. The most pronounced difference between group performance was in the anchor condition where patients were less able to utilize valid contextual information to enhance performance. Although patient performance decreased in the fake anchor condition relative to the anchor condition, the decrement in performance was significantly less than that found in controls. Accessing fMRI signal from correct trials only, blocks of similar condition were averaged together and the time-course for functional regions of interest were entered into a ROIx3x11 mixed model MANOVA testing for main and interactive effects of brain region, contextual condition, and scan (11 time points). Results from control Ss suggest that a region of the right dorsolateral prefrontal cortex (DLPFC) is sensitive to spatial-contextual information. Significantly more activation was seen in the fake anchor condition relative to the anchor condition suggesting that this region is differentially engaged with invalid contextual information. Patients displayed less DLPFC activation across all conditions with the greatest reduction seen in the fake anchor condition. These results better typify the contextual processing deficit in schizophrenia and will help us plan more effective interventions as we improve our understanding of how these skills correlate with social and occupational functioning.

FUNCTIONAL MRI CORRELATES OF SOCIO-EMOTIONAL INTELLIGENCE IN ADOLESCENCE: IMPLICATIONS FOR THE STUDY OF SCHIZOPHRENIA

I. M. Rosso,* J. Rogowska, S. A. Gruber, D. A. Yurgelun-Todd
Cognitive Neuroimaging, McLean Hospital, Belmont, MA, USA

Schizophrenia is associated with multiple social and emotional deficits, including difficulties in discerning the emotions and intentions of others, which may, in part, be associated with abnormal brain development. Several prefrontal cortical areas that have been implicated in the processing and integration of emotional stimuli in adults and in the pathophysiology of schizophrenia, also undergo important maturational changes in childhood and adolescence. Thus, examining the functional neuroanatomy of socio-emotional processing abilities in healthy adolescents may have implications for understanding their disturbance in schizophrenia. We applied functional magnetic resonance imaging (fMRI) techniques to examine the neural correlates of socio-emotional intelligence (EQ), as measured by the Bar-On EQ-i. Fourteen healthy adolescents were presented with two stimulus conditions: viewing happy and fearful faces. fMRI data were acquired on a 1.5 Tesla GE LX MRI scanner equipped with a quadrature RF head coil (TR = 3 sec, TE = 40 msec, flip angle = 90 degrees). Twenty coronal images were acquired with an image matrix of 64 x 64 and an in-plane resolution of 3.125 x 3.125 x 7 mm. A statistical parametric map was generated for each subject using the general linear model within SPM99. To test whether EQ was associated with distinct patterns of activation the EQ Adaptability scale was regressed with brain activation maps within SPM99. Analysis of activation during the fear condition yielded significant ($p = .001$) activation in the rostral anterior cingulate cortex (ACC; T= 8.15; MNI coordinates: -6, 38, -2). A similar analysis completed for prefrontal activation during the viewing of happy faces and EQ Adaptability scores yielded no significant associations. These preliminary results indicate that higher scores on the EQ Adaptability scale (social problem-solving, reality testing, and flexibility) predict significantly greater activity of the rostral ACC during the viewing of fearful affect. This suggests that the so-called affective division of the ACC is involved in effectively processing and integrating socio-emotional stimuli in adolescence. These findings provide a foundation for examining maturational brain changes associated with social deficits in schizophrenia. In addition, they suggest that examining the neural correlates of socio-emotional intelligence in high-risk adolescents may yield insights into ACC abnormalities in schizophrenia.

FUNCTIONAL BRAIN IMAGING OF AUDITORY MISMATCH PROCESSING IN SCHIZOPHRENIA

U. Schall,* P. Johnston, J. Todd, P. B. Ward, P. Michie
Centre for Mental Health Studies, University of Newcastle, Newcastle, NSW, Australia

People with schizophrenia consistently demonstrate abnormalities in mismatch negativity (MMN), an ERP index of auditory sensory memory. With event-related fMRI we were able to demonstrate bilateral superior temporal gyrus and right-inferior and middle frontal gyri activation when using a MRI-adapted version of the MMN task (Schall et al 2003, *Neuroimage* 30: 729-736). The aim of the current study was to confirm this pattern of activation in healthy subjects using two variants of the MMN task, and to examine possible neural correlates of reduced MMN in schizophrenia. Ten patients with schizophrenia and ten age/gender-matched controls performed two variants of the MMN task whilst fMRI images were acquired in a 1.5 T scanner. In the first task subjects were presented with blocks of standard tones, in which low frequency duration deviant stimuli were interspersed. In the second version of the task subjects were presented with mini blocks of either 4, 8 or 16 standard tones, followed by either a single duration deviant, or a single standard tone. Preliminary results confirm more robust activation in the fronto-temporal network using mini-blocks when compared to blocked stimuli while patients show reduced activity in line with electrophysiological MMN data. Supported by NH&MRC Project Grant 252480.

ALTERED BRAIN ACTIVATION IN DORSOLATERAL PREFRONTAL AND PARIETAL CORTEX IN ADOLESCENTS AND YOUNG ADULTS AT GENETIC RISK FOR SCHIZOPHRENIA: A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY OF WORKING MEMORY

L. J. Seidman,* H. W. Thermenos, R. A. Poldrack, N. K. Peace, J. K. Koch, S. V. Faraone, M. T. Tsuang
Department of Psychiatry, Harvard Medical School, Boston, MA, USA

First-degree adult relatives of persons with schizophrenia carry elevated genetic risk for the illness, demonstrate working memory impairments, and manifest differences in prefrontal cortical function during working memory. However, there is far less research evaluating these parameters in adolescent and young adult high risk subjects. We used functional magnetic resonance imaging (MRI) to test whether young (age 13-28), non-psychotic relatives of persons with schizophrenia also show altered prefrontal and parietal lobe activation during working memory. A case-control design was used to compare blood oxygen level dependent signal in controls and young relatives of persons with schizophrenia performing a 2-back visual working memory task and a control, simple vigilance task. Participants were 21 non-psychotic, un-medicated relatives of persons with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, depressed type and 24 un-medicated controls. Blood oxygen level dependent signal changes were measured using two whole-brain gradient echo EPI pulse sequences (21 contiguous, 5 mm axial slices), acquired on a Siemens 1.5T full-body MR scanner while subjects performed the cognitive tasks. Data were analyzed using Statistical Parametric Mapping-99. Differences in working memory-related signal (relative to control task-related signal) were compared between the two groups. The groups did not differ on demographic, neuropsychological or working memory performance variables. Compared to controls, high-risk subjects had significantly higher Hopkins SCL-90-R Psychoticism and Phobic Anxiety scores and showed greater task-elicited activation in the right dorsolateral prefrontal cortex (BA 9/46) and right superior parietal lobule (BA 7). Although Psychoticism and Phobic Anxiety were significantly related to parietal lobe activity, they did not account for group differences in brain activation. Data replicate findings in adult relatives of schizophrenics, and add to the growing literature identifying neurobiological vulnerabilities to schizophrenia. Future studies of this population may be useful in studying the relationship of these abnormalities in predicting later onset of schizophrenia. Grant Support: Mental Illness and Neuroscience Discovery (MIND) Institute (LJS); MH- 43518 and MH65562 (MTT, LJS); MH 63951 (LJS); NIMH R25 MH 60485 Training in Psychiatric Genetics (HWT, PI: MTT).

CHARACTERISTICS OF CEREBRAL METABOLIC PATTERNS IN SCHIZOPHRENIA WITH INTRACTABLE AUDITORY HALLUCINATION: A PET STUDY

J. Seok,* J. J. Kim, J. W. Jeon, H. J. Park, J. D. Lee, H. S. Lee
Department of Psychiatry, Yonsei University College of Medicine, Seoul, South Korea

Introduction: Schizophrenia is a neuropsychiatric syndrome which has diverse and complex symptoms including auditory hallucination and delusion. In this study, we have investigated two distinct patient groups-one is the patients with schizophrenia who have intractable auditory hallucination and the other is the patients who have never experienced auditory hallucination since they have been ill-comparing to normal controls. We measured resting metabolic rate of brain using PET. We tried to discover the symptom-specific dysfunction of neural structures in patients with schizophrenia. Methods: Twelve patients with schizophrenia (6 men, 6 women) who had intractable auditory hallucination and the same number of patients with schizophrenia who had never experienced auditory hallucination and 22 healthy controls (11 men, 11 women) were scanned with [18F]FDG-PET in resting state. Severity of schizophrenic symptoms was assessed with PANSS. PET scans were analysed using statistical parametric mapping (SPM99). Results: Irrespective of the existence of auditory hallucination, all the patient groups showed increased regional cerebral blood flow(rCBF) in bilateral basal ganglia, temporal pole and premotor area compared with the control group. The patient group with intractable hallucination showed increased rCBF in diffuse bilateral cerebellar area and decreased rCBF in bilateral prefrontal area compared with the patient group without hallucination and the control group. The patient group without hallucination showed increased rCBF in bilateral orbitofrontal area but didn't show any decreased rCBF area compared with the control group. The patient group with intractable hallucination showed significantly higher positive symptom score but did not differ significantly in other dimensions of PANSS score compared with the patient group without hallucination. Conclusion: The patients with schizophrenia with intractable hallucination showed abnormal cerebral metabolic patterns in relatively larger area including cerebellum and prefrontal cortex. On the other hand, the patients with schizophrenia without hallucination showed abnormal metabolic patterns in relatively smaller area except for the increased rCBF area including basal ganglia and premotor area which had been reported to increase in medicated patients. Our study suggests that there may be differences in cerebral metabolic patterns of the patients with schizophrenia according to their symptom characteristics.

AUDITORY HALLUCINATIONS IN PSYCHOSIS: DYSFUNCTIONAL CORTICAL CONNECTIVITY IN NEURAL SUBSTRATES OF CENTRAL AUDITORY PROCESSING AND EPISODIC VERBAL MEMORY

A. A. Sergejew,* D. L. Copolov, G. F. Egan
Cognitive Neuroscience Group, Mental Health Research Institute of Victoria, Melbourne, VIC, Australia

Introduction: Theories of the neurobiological basis of auditory hallucinations (AHs) in psychosis mainly conceptualise these phenomena as "inner speech" which is misattributed to an external agency. However, the majority of neuroimaging studies of AHs report no evidence of activation of Broca's area, an otherwise reliable concommitant of "inner speech." We have previously reported behavioural evidence of impaired interhemispheric transfer in a hallucinating patient group (McKay et al, *American Journal of Psychiatry*, 157: 759-766). Method: Brain activation associated with self-reported AHs was measured using PET in patients with psychosis (n=8) compared to perception of transient random human speech in non-hallucinating patients (n=7) and normal controls (n=8). Effective connectivity is also compared using both EEG and fMRI measures in two other groups of patients with and without AHs. Results: Externally generated speech sounds elicited extensive bilateral activation

of auditory cortical regions (Brodmann areas 40, 41, 42 and 22). In contrast, hallucinations were associated with a network of activation including bilateral auditory association cortex, left limbic regions and hippocampus, right medial frontal and right prefrontal regions. Connectivity between left and right auditory association cortex appears to be lower in patients with hallucinations. Conclusions: The observed pattern of activation is most consistent with models of auditory hallucinations as mis-remembered episodic memory of speech (Copolov et al, *Psychiatry Research: Neuroimaging*, 122: 139-152). We formulate a new model of AHs in which AHs are related to reduced connectivity in neural substrates of episodic verbal memory and central auditory processing.

CONFLICT- AND ERROR-RELATED ACTIVITY OF THE ANTERIOR CINGULATE CORTEX IN MEDICATION-NAIVE FIRST-EPISODE SCHIZOPHRENIA

B. E. Snitz,* C. S. Carter, A. MacDonald, T. Becker, V. A. Stenger, J. D. Cohen
Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

The anterior cingulate cortex (ACC), on the medial surface of the frontal lobes, is increasingly recognized as an important element in the brain circuitry underlying performance monitoring impairments in schizophrenia. Recent fMRI evidence demonstrated decreased error-related activity and decreased conflict-related activity in ACC in chronic patients with schizophrenia. The present study examined ACC activity in never medicated first-episode patients, asking whether ACC dysfunction is present at illness onset. We used a slow event-related fMRI paradigm and a switching task which relies upon the Simon spatial incompatibility effect to elicit conflict-related ACC activity. Participants included nineteen first-episode, medication naïve schizophrenia patients and twenty-four controls. Subjects were instructed to respond to a left- or right-pointing arrow with either the ipsilateral hand (dominant stimulus-response [SR] mapping) or the contralateral hand (reversal of the dominant SR mapping), depending on the color of a cue presented at the beginning of each trial. Confirmatory data analysis was performed using mixed-effects ANOVA (subject as a random factor) with only correct trials included. Results show that modulation of ACC activity by degree of conflict (ipsilateral vs. contralateral responding) was only marginally reduced in first-episode patients compared to controls. A subset of participants (11 patients; 15 controls) were included in an analysis of error-related ACC activity. Results indicate no difference between patients and controls in modulation of ACC response by accuracy (correct vs. incorrect trials). These findings indicate that performance monitoring functions of the ACC are at most only marginally reduced in first-episode patients and suggest that ACC dysfunction may arise as the course of illness advances, whether related to age, illness duration and/or chronic medication use. Further analyses will be presented comparing ACC functioning in first-episode and chronic patients performing the same cognitive task to more directly evaluate the role of illness progression in ACC impairment in schizophrenia.

STIMULUS REPETITION CAN CAUSE PERFORMANCE DEFICITS EVEN IN A LOW LOAD N-BACK TASK IN SCHIZOPHRENIA

M. A. Tagamets,* C. R. Cortes
MPRC, Psychiatry, University of Maryland, Baltimore, MD, USA

A number of previous studies have shown that working memory deficits in schizophrenia are more evident in high load N-back tasks, while persons with schizophrenia usually show performance similar to healthy controls at low load N-back tasks (e.g. Carter et al. 1998). However, it is not clear whether the performance in low load N-back tasks will prevail under all conditions. We examined both the behavioral and brain activation effects of stimulus type in a one-back matching task. After IRB approval, we recruited two groups, 9 healthy controls and 9 stable DSM-IV diagnosed schizophrenic volunteers. Subjects were scanned with fMRI while performing a one-back visual matching task at a stimulus rate of one per second, with a 200 milliseconds stimulus duration. Three different stimulus types were examined: four-letter words, four-letter consonant strings, and simple single geometric shapes (● and ■). For the two string types (words and consonant letter strings) all stimuli were unique except for the repeated stimuli, whereas in the shapes task, only two geometric symbols were used repetitively. In all conditions, stimuli were presented in a random order, and one-back repeats constituted 30% of all stimuli. We found schizophrenia behavioral performance to be not significantly different in the two string conditions. A significant group difference was found only in accuracy during the condition of highly repetitive simple geometric stimuli ($t = 2.72$, $df = 16$, $p = 0.0153$). SPM analysis of both subtractions and correlations of the behavioral data with the mean task-related functional images showed between group differences in the three conditions for accuracy and reaction time. The neural correlates for these differences were found in visual areas, anterior cingulate, and prefrontal cortex. These preliminary results coincide with regions previously described in the literature, but with between-group differences primarily in high load N-back tasks. Our results suggest that in schizophrenia, task context can play a role even in a low load N-back task, and the data further suggest differences in the neural correlates of this phenomenon. We hypothesize that the repetitive stimuli may cause interference in schizophrenia even in a simple low load task. Reference Carter CS, Perlstein W, Ganguli R, Brar J, Mintun M, Cohen JD (1998) Functional hypofrontality and working memory dysfunction in schizophrenia. *Am. J. Psychiatry*, 155: 1285-1287.

HIPPOCAMPAL ACTIVATION PATTERNS DURING NOVELTY DETECTION WITH SUCCESSFUL MEMORY IN SCHIZOPHRENIA

C. A. Tamminga,* B. Thomas, R. B. Chin, K. Youens
Psychiatry, UTSW, Dallas, TX, USA

Several lines of evidence suggest alterations of hippocampal function in schizophrenia. The hippocampus is involved in aspects of learning and memory performance in human cognition. Its alteration may affect both the performance of these cognitive tasks and their representation during fMRI BOLD acquisitions. Novelty detection is known to activate regions of hippocampus; different stimuli show distinct activation patterns in hipppocampal subfields and along the long axis of the structure (Preston and Wagner, 2004). We are studying activation patterns in hippocampus during novelty detection with successful memory in persons with schizophrenia and matched control subjects. Initial studies have utilized a complex picture recognition task, using an event related design with subsequent memory evaluation. Scans are acquired during 5 blocks of 40 familiar and 40 novel interleaved pictures. Subsequent memory for the novel pictures is tested and the regional activation data evaluated for those pictures successfully encoded. Image analysis is carried out with SPM2. During the subsequent memory evaluation, persons with schizophrenia encoded significantly fewer complex pictures that the normal volunteers. In preliminary examination of the fMRI BOLD signals, each normal volunteer activated broad areas of hippocampus

during the successful encoding of complex images, whereas those persons with schizophrenia activated almost no regions of hippocampus during the successful encoding task. We will report a larger patient number and activations utilizing different stimuli.

A FMRI STUDY OF MAINTENANCE AND MANIPULATION PROCESSES WITHIN WORKING MEMORY IN FIRST-EPISODE SCHIZOPHRENIA

H. Tan,* W. C. Choo, S. Graham, C. S. Fones, M. W. Chee
Psychological Medicine, National University of Singapore, Singapore

Objective: Working memory is a critical cognitive capacity that is affected in schizophrenia. It can be fractionated into maintenance and manipulation processes. Behavioral work suggests that manipulation is more affected in patients with chronic schizophrenia. In this study, we studied first-episode schizophrenia patients to evaluate the extent to which the two processes are affected early in the course of schizophrenia. Methods: We studied 11 first-episode schizophrenia patients and 11 matched healthy controls. Each group performed two verbal working memory tasks while undergoing fMRI: one required maintenance of letters (LTR); the other required manipulation in addition to maintenance (PLUS). Results: Both patients and controls activated a predominantly left-sided frontal-parietal network, with PLUS eliciting activition of greater magnitude and spatial extent. With both tasks, patients showed less bilateral dorsolateral prefrontal cortex (DLPFC) activation, and greater ventrolateral prefrontal cortex (VLPFC) activation relative to controls. Additionally, a group by task interaction was observed at the left DLPFC and VLPFC. The increase in activation when patients engaged in the manipulation task was disproportionately less at DLPFC and greater at the VLPFC. Conclusions: These findings add functional neuroanatomical evidence to earlier suggestions that manipulation of information is selectively more affected than its maintenance in schizophrenia. They also suggest the presence of interacting regions of dysfunctional and compensatory prefrontal responses, at the DLPFC and VLPFC respectively, that are more prominent when information is manipulated. This disrupted prefrontal network is present relatively early in the course of schizophrenia at the first psychotic episode.

MEDIAL PREFRONTAL CORTEX DYSFUNCTION IN SCHIZOPHRENIA: A CLUE TO TREATMENT RESISTANCE?

S. F. Taylor,* R. C. Welsh, A. J. Velander, S. J. Mukherji, I. Liberzon
Psychiatry, University of Michigan, Ann Arbor, MI, USA

The medial prefrontal cortex, particularly the dorsal aspect (DMPFC) appears to play a key role in cognitive-emotional interaction, as well as the representation of self-relevant and social information. Using emotionally-salient stimuli, we have begun to probe the involvement of the DMPFC in schizophrenia. Specifically, we hypothesized that treatment-resistant positive psychotic symptoms would be associated with aberrant activation of the DMPFC. Treated schizophrenic/schizoaffective subjects were studied in two groups: with persistent positive symptoms (HiPos, 9 M, 3 F), and without significant positive symptoms (LoPos, 8 M, 4 F), plus a comparison group of healthy subjects (10 M, 5 F). All subjects viewed emotionally salient pictures (4 sec each) from the International Affective Picture System (aversive [AV] and non-aversive [NA] sets), plus a set of random geometric shapes (BLANK) in a block design. BOLD-sensitive fMRI scans were obtained using a reverse spiral sequence, while subjects made silent ratings of the pictures. Realigned and normalized images were analyzed in a standard, random effects model. Relative to the healthy subjects, the group of all patients showed less activation of the DMPFC (6, 63, 15; Z=3.01) in response to the salient NA stimuli (-BLANK), and failed to activate the left amygdala (-24, -6, -21, Z=3.30), replicating our previous work. There were no differences between the HiPos and LoPos patient groups for NA - BLANK in the DMPFC. To AV stimuli (-NA), the patients exhibited significantly greater activity of the DMPFC (15, 57, -9; Z=3.16; -6, 60, 18; Z=2.79), compared to control subjects. This difference occurred due to greater activation in the HiPos patients, relative to LoPos patients (15, 51, 15; Z=3.25; -15, 63, 0; Z=3.08). In summary, the results show that patients with schizophrenia/schizoaffective disorder exhibited reduced activation in networks which process salient, non-aversive information. However, in response to aversive stimuli, patients with persistent positive symptoms showed excessive activation of the DMPFC. If the DMPFC does play a role in cognitive-emotional interactions, these findings suggest that aberrant regulation of negative, aversive content may correlate with an incomplete response to antipsychotics.

ALTERED BRAIN ACTIVATION IN THE PARAHIPPOCAMPUS, CINGULATE GYRUS, AND NUCLEUS ACCUMBENS IN ADOLESCENTS AND YOUNG ADULTS AT GENETIC RISK FOR SCHIZOPHRENIA: A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY OF VERBAL ENCODING

H. W. Thermenos,* L. J. Seidman, R. A. Poldrack, N. K. Peace, L. Gabel, S. V. Faraone, M. T. Tsuang
Department of Psychiatry, Harvard Medical School, Boston, MA, USA

First-degree adult relatives of persons with schizophrenia are at elevated risk for the illness, demonstrate stable deficits on verbal encoding and memory tasks, and exhibit structural abnormalities in the medial temporal lobe. We used functional magnetic resonance imaging (fMRI) to test whether young (age 13-28), non-psychotic relatives of persons with schizophrenia show altered brain function in the medial temporal lobe memory system during verbal encoding. Participants were 21 young high-risk relatives (YHR) of persons with DSM-IV diagnosis of schizophrenia or schizoaffective disorder and 26 healthy control subjects. Blood oxygen level dependent signal was measured using two whole-brain gradient echo EPI pulse sequences acquired on a Siemens 1.5T MR scanner while subjects performed a word-pair encoding task. Word recognition was assessed immediately after the scans. FMRI data were analyzed using Statistical Parametric Mapping-99 software. The groups did not differ in demographic variables, intelligence or word-recognition after scanning. YHR scored higher than controls on the Hopkins SCL-90-R Phobic Anxiety, Paranoid Ideation and Psychoticism scales, and lower on the Miller Selfridge (MS) Memory test ($p<0.05$). MS scores were related word recognition after scanning. During performance of the word-pair encoding task, YHR exhibited greater activation in the anterior parahippocampus (PHP; bilaterally), the left posterior cingulate (PC; BA 31/23) and the left nucleus accumbens (NAC) com-

pared to controls (p< 0.05). Group differences in the PHP remained significant after the effects of the three SCL-90-R scores were controlled, but were attenuated when the effects of MS scores were controlled. Differences in the NAC remained significant after MS scores, word recognition, and Phobic Anxiety were controlled. Word-recognition and MS scores were related to activation in the left prefrontal cortex (PFC), and YHR with above-median MS performance showed more activation in left PFC compared to those with below-median performance (p<0.05). These data add to the growing literature identifying abnormalities in the limbic system as part of the neurobiological vulnerability to schizophrenia. Future studies of this population may prospectively identify abnormalities in brain function that predict later onset of schizophrenia. Grant Support: MIND Institute (LJS); MH43518, MH65562 (MTT, LJS); MH63951 (LJS); NIMH R25 MH60485 "Training in Psychiatric Genetics"(HWT, PI: MTT).

BRAIN ACTIVITIES ASSOCIATING WITH FACE MEMORY DEFICITS IN SCHIZOPHRENIA

M. Tomita,* J. Loughead, R. C. Gur, A. Brennan, W. Snyder, K. Lesko, R. E. Gur
Neuropsychiatry Section, University of Pennsylvania, Philadelphia, PA, USA

Event-related fMRI was employed to present study to investigating neural basis of relation between deficit in facial affect recognition and face memory dysfunction in patients with schizophrenia. Participants: Right-handed eight patients with schizophrenia (PT; 5 male, range 21-51 years) and 6 healthy controls (NC; 4 male, range 26-42 years) participated. Task and fMRI procedure: Their incidental face memory was tested during fMRI scan in seen/never seen recognition judgment made to a mixture of 30 faces which were showed in 10min preceded facial affect discrimination of face pictures (indicating neutral, happy, sad, fear, anger) and 30 new faces. A Siemens 3T MR scanner was used to acquire Echo-planner BOLD images with parameters of TE = 32ms; TR = 2000ms; 3x3x3mm resolution. All neutral faces were showed in pseudo randomized order with non-fixed inter stimulus onsets. fMRI analysis: Statistical analysis of individual fMRI data was carried out with FSL3.1 in a GLM approach. Group differences were analyzed with FLAME (a component of FSL). Behavioral results: PT averaged significantly poor accuracy in face recognition (NC; 55.6±3.4%, PT; 45.6±4.3% correct (Mean±SEM) P=0.05). NC scored significantly correct performance to faces of persons who showed a neutral face in encoding phase (Neutral-faces) than whom with other emotions (Emo-faces) (69.4% neutral, 41.7% to happy, 47.2% to sad, 27.8% to fair and 30.6% to anger in average; p=0.005, ANOVA, Fisher's PLSD). In contrast, Pt indicated no significant differences among emotions (37.5% neutral, 37.5% happy, 35.4% sad, 31.5% fear and 25% anger in average). fMRI results: Statistical parametric map by one-sample t-test showed that recognition for the Emo-faces in NC was associated with greater activation of amygdala (AMY), fusiform gyri, ventral lateral prefrontal and deactivation of anterior cingulate gyri (ACC). In contrast, lack of AMY activation was revealed in PT. Unpaired t-test showed greater activation of amygdala for Emo-faces and greater deactivation of ACC for both Emo-faces and Neutral-faces in NC compare with PT (thresholded p>0.005 uncorrected). Discussion: It is suggested that lack of activation of AMY and smaller deactivation of ACC might reflect different strategy in face recognition in patients with schizophrenia. Association of dysfunction in neural network including AMY and ACC with the deficit performance in face memory in schizophrenia was suggested.

THE EFFECT OF NICOTINE ON HEMODYNAMIC RESPONSE DURING A SMOOTH PURSUIT EYE MOVEMENT TASK IN SCHIZOPHRENIA

J. R. Tregellas,* J. L. Tanabe, L. F. Martin, R. Freedman
Psychiatry, University of Colorado Health Sciences Center, Denver, CO, USA

Deficits in performing a smooth pursuit eye movement task in patients with schizophrenia are temporarily normalized by nicotine. It is hypothesized that inhibitory dysfunction in the hippocampus contributes to the deficit and that nicotinic cholinergic stimulation normalizes performance by improving inhibitory function. Previous fMRI work has demonstrated increased activity in the hippocampus of schizophrenic subjects compared to controls. This study used fMRI to determine if nicotine alters activity in the hippocampus or other brain regions in schizophrenia subjects during a smooth pursuit eye movement task. fMRI data were acquired from nine schizophrenic subjects who performed two, four-minute trials of a smooth pursuit eye movement task. Subjects then received either 6 mg nicotine, or placebo, as chewing gum, then performed two more trials while being scanned. Subjects returned the following week to repeat the procedure, receiving the counterbalanced drug condition. The task was presented in a blocked design, consisting of four cycles of 25s smooth pursuit/25s rest per trial. The task consisted of following a small white target traversing back and forth across the screen at 16.7o /sec, pausing on the edges for 700 ms. For rest, subjects looked straight ahead at a blank screen. For each trial, 80 BOLD EPI volumes (TR=2500,TE=50, 642 matrix, 240 mm2 FOV, 20 axial slices, 6mm thick,1 mm gap, 1.5T) were acquired. After motion correction, spatial normalization, and smoothing, a random effects analysis of a priori brain regions of interest was performed using SPM99. The most significant observed response was decreased activity in the right hippocampus following nicotine administration, compared to placebo, during the task. Decreased activity was also observed in bilateral parietal eye fields. Nicotine administration was associated with increased activity in the cingulate gyrus, precuneus, and area MT/MST. Decreased hippocampal activation associated with nicotine may reflect improved inhibitory function in schizophrenia, consonant with behavioral studies showing reduced inappropriate intrusion of anticipatory saccades during the smooth pursuit task following nicotine administration. Greater activation in cingulate, parietal, and temporal lobes is consistent with increased attention to and tracking of visual stimuli following nicotine administration.

MULTI-CENTER FMRI METHODS AND DESIGN: FUNCTION BIRN

J. Turner,* S. G. Potkin, G. G. Brown, G. H. Glover, J. H. Fallon, G. McCarthy, K. O. Lim, R. L. Gollub, B. R. Rosen, A. W. Toga, R. Kikinis, S. Pieper, A. M. Dale, J. Lauriello, D. S. O'Leary, J. A. Lieberman, A. Belger, D. N. Greve, L. Friedman, T. D. Cannon, D. B. Keator, J. S. Grethe, I. Function BIRN
Psychiatry & Human Behavior, University of California, Irvine, Irvine, CA, USA

Background. Many fMRI studies of schizophrenia involve small and restricted samples. The combination of data across institutions allows

for rapid data collection, access to unique populations, and assessment of validity and generalizability of findings. Differences in imaging methods, analysis methods, and the methods for storing and retrieving data, all present challenges to sharing large imaging and clinical datasets. Previous multi-site imaging studies have not assessed intersite variability or reliability of the imaging data prior to data combination; or have avoided data combination in favor meta-analysis methods. *Methods.* The Function BIRN is a multi-site project funded by NCRR/NIH (www.nbirn.net) for the following goals: 1) Standardized calibration of equipment using geometric and human phantoms; 2) Developing a multi-site, standardized protocol for fMRI data collection on populations of persons with schizophrenia, including site-specific cognitive paradigms; 3) Creating a federated database to integrate multi-site data, for a deeper understanding of the functional neuroanatomy of schizophrenia than would be possible through meta-analysis. The eleven sites involved in the project are dedicated to collecting calibration fMRI data, developing experimental paradigms and analysis methods, populating a virtual data grid, and designing a searchable multi-site database of MRI and clinical data. *Results.* Using a set of geometric phantoms to measure spatial distortions and temporal drift across sites, the FBIRN has collected a unique dataset of machine characteristics in fMRI data, which have served to assess initial inter-site differences. Using a set of traveling human subjects repeatedly scanned at each site, the FBIRN has determined that inter-site variability in the BOLD signals can exceed inter-subject variability, thus limiting the usefulness of combining raw imaging data across sites. Initial assessements indicate that intersite variability can be decreased through use of a variety of calibration methods. *Conclusions.* The collaborative efforts of multiple researchers have resulted in novel approaches to human subject data sharing, experimental design, fMRI data standardization, and clinical and imaging database design. Correction algorithms can decrease the inter-site effects to allow the combination of multi-site data to identify differences between patient groups and treatments. Support Contributed By: NCRR (NIH), 5 MOI RR 000827, www.nbirn.net.

SYMPTOM DIMENSIONS AND REGIONAL CEREBRAL BLOOD FLOW RESPONSES TO ATTRIBUTION OF VALENCE TO VISUAL STIMULI IN SCHIZOPHRENIA

J. Vaidya,* S. Paradiso, D. O'Leary, L. Ponto, R. Hichwa, N. Andreasen
Psychiatry, University of Iowa Hospitals and Clinics, Iowa City, IA, USA

Background: Schizophrenia patients show reduced brain activation to affective stimuli. Furthermore, different symptoms have been differentially associated with measures of emotional processing. The present study systematically examined the association between psychotic, disorganized, and negative symptoms and brain activity elicited by the attribution of valence to pleasant, unpleasant, and neutral visual stimuli as well as a resting baseline condition. Methods: Regional cerebral blood flow was examined in 19 schizophrenia patients who had not received antipsychotic medication for at least 3 weeks prior to the study. Subjects were shown pleasant, unpleasant, and neutral pictures. Regional cerebral blood flow was measured in these 3 conditions as well as a fourth, resting baseline condition with the use of [^{15}O] water positron emission tomography. Subjects were asked to evaluate the emotional valence of the pictures. Correlations were computed between the 3 symptom dimensions and blood flow in each condition. Results: There were few significant correlations between Negative symptoms and blood flow across the four conditions. Disorganized symptoms (and to a lesser degree Psychotic symptoms) correlated with blood flow in the caudate, cerebellum, and hippocampus across all four conditions (rs > .60; volume > 1 mm^3). Disorganized symptoms were associated with greater activity in the ventral medial and ventral lateral prefrontal cortex in the pleasant condition. Conclusions: Disorganized symptoms correlated with greater blood flow in the caudate, cerebellum, and hippocampus in response to emotional pictures, neutral pictures, and during a resting baseline condition. This non-specific pattern of correlations may suggest that Disorganized symptoms are marked by elevated, tonic levels of activation in these brain regions. Future research should examine the factors that influence the increased activation in these areas as well as potential consequences of this enhanced, tonic activation.

FUNCTIONAL NEUROIMAGING OF WORKING MEMORY IN SCHIZOPHRENIA: TASK PERFORMANCE AS A MODERATING VARIABLE

J. X. Van Snellenberg,* I. J. Torres, A. E. Thornton
Human Neuropsychology Lab, Department of Psychology, Simon Fraser University, Burnaby, BC, Canada

Functional neuroimaging studies of patients with schizophrenia have revealed abnormal activation of dorsolateral prefrontal cortex (DLPFC) during the performance of working memory (WM) tasks. However, findings of both increased and decreased activity have been reported. The present study employed meta-analysis to examine whether divergent findings arise as a function of differential task performance between patients and controls. Across all cognitive activation studies investigating working memory in schizophrenia, patient and control subjects did not differ in prefrontal activity during the performance of WM tasks. However, the magnitude of the group difference in task performance (both accuracy and reaction time) was a moderator of DLPFC activation, supporting the notion that task performance plays a role in findings of patient hyper- or hypofrontality. Specifically, studies employing patient samples whose performance was more closely matched to that of control subjects were more likely to demonstrate patient hyperfrontality, whereas studies of poorly performing patients were more likely to exhibit patient hypofrontality. These results are consistent with the hypothesis presented by D. Manoach (2002, 2003) and others (J. Callicott et al., 2003) that patients exhibit a left-shift in an inverted-U relationship between working memory load and DLPFC activation.

ABNORMAL STRIATAL ACTIVITY IN SCHIZOPHRENIA AND FIRST-DEGREE RELATIVES

M. Vink,* M. Raemaekers, R. S. Kahn, M. P. van den Heuvel, N. F. Ramsey
Dept. of Psychiatry, Rudolf Magnus Institute of Neuroscience, Utrecht, Utrecht, Netherlands

Schizophrenia has been associated with abnormal activity in the fronto-striatal system. Raemaekers et al. (*Gen Arch Psych*, 59, 2002), for instance, have shown that patients fail to recruit the striatum during the inhibition of saccadic eye-movements. We recently presented preliminary findings that patients also display decreased striatal acti-

vation during anticipation of motor inhibition. In the present study we repeated the experiment with healthy siblings of schizophrenic patients, to assess whether abnormal striatal function is associated with the illness, or whether it could constitute a genetic predisposing factor. We also show the completed study with patients. Subjects were instructed to withhold their response to designated items (i.e. STOP trials) within a series of motor stimuli (i.e. GO trials). By varying the number of GO trials between two consecutive STOP trials, the likelihood of a STOP trial was parametrically varied. Brain responses (BOLD-fMRI) were measured during all trials, but we present activity data for the GO trials. We have shown previously that in healthy subjects activity in striatum increases at every GO trial until a STOP trial is presented, reflecting an anticipatory mechanism (Vink et al, *NeuroImage*, 19, 2003). Controls in the schizophrenia study (n=21) as well as controls in the sibling study (n=15) displayed linear increasing reaction times on GO trials as STOP likelihood increased. The striatal BOLD response also increased linearly with STOP likelihood in these groups. Schizophrenia patients (n=21) showed no such anticipation as their reaction times were not increased. Patients failed to recruit the striatum during the GO trials, and showed no anticipation related BOLD increase in the striatum. Accordingly, patients made more errors on STOP trials than their controls. Siblings (n=15) showed linear increasing reaction times similar to their controls, and also a general increased striatal activation level. However, like patients, they did not exhibit increasing striatal activity with increasing anticipation of a STOP trial. These data suggest that function of the striatum in inhibitory control is impaired in schizophrenia patients. Furthermore, striatal dysfunction is also present in healthy siblings, suggesting that it may constitute a genetic risk factor for the illness. The finding that siblings perform normally may be explained in terms of intact compensating cerebral mechanisms.

NEURAL CORRELATES OF PERSPECTIVE TAKING AND PREFERENCE ATTRIBUTION IN HEALTHY VOLUNTEERS AND SUBJECTS AT-RISK—A FMRI STUDY

K. Vogeley,* B. Bewernick, N. David, M. May, S. Lux, S. Ruhrmann, N. J. Shah, G. R. Fink, J. Klosterkoetter
Dept of Psychiatry, University of Cologne, Cologne, Germany

Social interaction is based on the ability to attribute more or less complex mental states to oneself and others mental state. On a basic level, perspective taking depends on the spatial position of a person, whereas specific knowledge about a particular character, e.g. personal preference, is required on a more complex level. To study the neural correlates of these two levels of complexity, three-dimensional scenes with different virtual characters (avatars) and different objects were presented to healthy, right-handed, male volunteers (n = 15) in a fMRI study. In the spatial condition (SPAT), subjects had to count the objects seen from their own "first-person-perspective" (1PP) or from the avatar's "third-person-perspective" (3PP). In the more complex preference condition (PREF), subjects had to count the objects in the respective visual field that corresponded to their own (1PP) or the avatar's preference (3PP). Factors Perspective (1PP versus 3PP) and Task (SPAT versus PREF) constituted a two-factorial design. Reaction times and errors were increased during 3PP and PREF compared to 1PP and SPAT. Neural activations were increased in medial cortical and superior temporal areas bilaterally and right insula during 1PP, in parietal cortex bilaterally and right premotor cortex during 3PP, in medial cortical and superior temporal areas bilaterally during SPAT, and in left dorsolateral prefrontal, left cingulate gyrus and right inferior parietal cortex during PREF. Thus, medial brain areas seem related to less complex and self-referential tasks, whereas dorsolateral, medial prefrontal and left inferior parietal brain regions are involved in the attribution of preferences to others. The experiment was additionally performed in a population of subjects at-risk (prodromal stage of schizophrenia, n = 10). Behavioral data showed no significant differences as compared to normal healthy volunteers. Neural correlates revealed a loss of activation in frontal brain areas under all key contrasts as mentioned above. These results support the hypothesis that prodromal stages of schizophrenia are associated with a neural activation pattern of hypofrontality during a perspective taking task without any significant changes in the behavioral domain.

A PARAMETRIC THEORY-OF-MIND DESIGN TO INVESTIGATE SOCIAL COGNITION IN SCHIZOPHRENIA

H. Walter,* A. Ciaramidaro, N. Vasic, M. Adenzato, B. G. Bara, S. Erk
Department of Psychiatry, University of Ulm, Ulm, Germany

Patients with schizophrenia show considerable deficits in social cognition. It has been postulated that their theory-of-mind abilities are impaired. We present a new design to study the neural correlates of theory-of-mind in a parametric design. 12 young healthy subjects (6 male, 6 female) and (up to now 8 patients with schizophrenia) were studied with fMRI. We used cartoons involving a sequence of three pictures followed by a selection of three pictures of which the subjects had to choose the correct ending of the cartoon. There were four conditions: (i) physical causality (only objects, no persons, no intentions = control condition), (ii) intention in action (one person, simple intentions), (iii) intention for future social interaction (one person intending to socially interact), (iv) intentions in social interaction (two persons interacting with gestures). Results are from second level random effect analysis (SPM99) with $p<0.001$ on the voxel and $p<0.05$ on the cluster level (both uncorrected).The results of the control group showed a parametric activation (ii < iii < iv) in the anterior paracingulate cortex, in the retrosplenial region and at the temporoparietal junction. The design is therefore well suited to study social cognition in patients with schizophrenia in a parametric fashion. We will present first data of the patient group. (1) Walter H, Adenzato M,, Ciaramidaro A, Enrici I, Pia L, Bara BG (2004) Understanding intentions in social interaction: The role of the anterior paracingulate cortex. *J Cog Neuroscience*, in press.

FUNCTIONAL MEDIATION OF THE ASSOCIATION BETWEEN STRUCTURAL ABNORMALITY AND SYMPTOM SEVERITY IN SCHIZOPHRENIA

S. Weinstein,* T. S. Woodward, J. F. Werker, E. T. Ngan
Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada

Thought disorder is associated with both structural and functional abnormalities in the left temporal lobe. Severity of thought disorder has been shown to correlate negatively with the volume of the left

posterior superior temporal gyrus and positively with the BOLD response in superior and middle temporal regions during performance of language tasks. We hypothesized that the association between severity of thought disorder and decreased left temporal lobe grey matter volume is mediated by the increased activation in this region during language processing. 11 patients with schizophrenia were assessed for thought disorder with the Thought and Language Index (TLI). fMRI images were acquired for each subject while they listened to English speech; a high resolution structural image was also collected. TLI scores were entered as a covariate in a functional analysis to identify brain regions within which the BOLD response during listening to English was positively correlated with thought disorder. Voxel based morphometry was used to calculate grey matter volume within identified regions for each subject. A mediation model was tested using a four-step multiple regression approach to assess the relationship between structure, function and symptom severity. A single cluster within the left temporal lobe showed a significant positive correlation between BOLD signal and thought disorder severity. Grey matter volume was found to correlate with a) the severity of thought disorder at r = -.46; and b) the BOLD response at r = -.51. Regressing thought disorder on grey matter volume and BOLD response simultaneously led to a partial correlation of grey matter volume with thought disorder of .02. This decrease from r = -.46 to partial r = .02 was significant at $p < .05$. These results provide evidence that the association between decreased grey matter volume in the left temporal lobe and severity of thought disorder in schizophrenia is mediated by activation in this region during language processing.

EVENT-RELATED OSCILLATORY RESPONSES TO AUDITORY ODDBALLS ARE DISTURBED IN THE DELTA AND THETA BANDWIDTHS IN PEOPLE WITH SCHIZOPHRENIA

T. P. White,* A. T. Bates, R. Jain, T. P. Patel, D. Das, P. F. Liddle
Division of Psychiatry, University of Nottingham, Nottingham, United Kingdom

Increasing evidence points towards oscillatory activity as an important mechanism in the coordination and integration of cognitive processes in the human brain. It has been proposed that impaired coordination of cerebral activity is a core feature of schizophrenia. To test this hypothesis, we compared event-related oscillatory activity in people with schizophrenia and healthy individuals utilising an auditory oddball target detection paradigm. Participants with schizophrenia were within the first five years of illness; at time of recording they were in a stable phase of illness and receiving antipsychotic medication. Digitalised electroencephalographic activity was recorded using a 128-electrode array, with additional electrodes monitoring eye movements and acting as external references. The experimental paradigm involved the repeated binaural presentation through headphones of sounds of two different frequencies, with low frequency non-target sounds being presented more frequently than higher frequency target sounds. Preliminary analysis (schizophrenic group n=12, control group n=3) reveals a statistically significant increase in the low frequency components of brain activity, between 0.5 Hz and 8 Hz, following targets compared to non-targets in both groups, over parietal cortex ($F(1,26)=12.9$, $p=0.001$). This increase of event-related delta and theta activity tended to be reduced in people with schizophrenia (mean power 13.2 microvolts squared plus/minus 5.3 standard error) in comparison with healthy individuals (mean power microvolts squared plus/minus 6.1 standard error). Our data demonstrate that target detection is associated with an increase in low frequency oscillatory activity, consistent with the hypothesis that oscillatory activity plays a role in information processing in the brain. Furthermore, although this preliminary analysis did not have sufficient power to detect a significant difference between patients and controls, the preliminary results reveal a trend consistent with the hypothesis that event-related low frequency oscillatory activity is diminished in schizophrenia.

BRAIN ACTIVATION DURING A VERBAL WORKING MEMORY TASK IN PATIENTS WITH SCHIZOPHRENIA AND DEPRESSION

R. C. Wolf,* N. Vasic, A. Hoese, A. Biller, K. Frasch, H. J. Brambs, T. Becker, M. Spitzer, H. Walter
Department of Psychiatry III, University of Ulm, Ulm, Germany

While frontal pathology is commonly considered to be a core feature in schizophrenia, evidence from functional magnetic resonance imaging (fMRI) studies seems to be less reliable in terms of demonstrating functional hypofrontality. Studies on working memory (WM) dysfunction in schizophrenia suggest that the magnitude of frontal activation may be related to a variety of factors, including experimental design issues and task-accuracy. Furthermore, only a few studies have addressed the question of diagnosis-specifity, compared with other major psychiatric disorders. In this study we assessed verbal WM-manipulation in patients with schizophrenia and major depression. Using event-related fMRI, we studied 17 healthy controls, 19 schizophrenic patients and 12 patients with major depression who met DSM-IV criteria for these disorders. WM-function was assessed by using a parametrically varied modified version of the Sternberg Item Recognition Paradigm. This task required the gradual manipulation of one to three letters during the delay period and an additional control condition. First and second level between-group analyses were carried out with SPM99. Compared with healthy controls, we found slower reaction times and a worse accuracy in both patient groups. Reaction times and task-accuracy did not differ between patients with schizophrenia and those with depression. In the group of schizophrenic patients, functional imaging results revealed a lack of bitemporal deactivation along with an increasing, load-dependent prefrontal activation. This pattern was specific for schizophrenia, being present when comparing these patients with both healthy control subjects and patients with depression. Furthermore, patients with schizophrenia showed less activation at high cognitive load in superior frontal and parietal areas, striatum and cerebellum, compared to controls. Less activation of left inferior frontal cortex and right cerebellum was present in the schizophrenic group when compared with patients with depression. Although this study could not replicate findings of functional hypofrontality in patients with schizophrenia, we could demonstrate an aberrant relationship between temporal and frontal areas within the context of an executive task. This result supports the concept of frontotemporal dysconnectivity in schizophrenia and may be suitable to differentiate between two major psychiatric disorders in terms of cerebral dysfunction.

SELF RECOGNITION PROCESS IN NORMAL AND SCHIZOPHRENIA BY USING [^{15}O]H_2O PET

T. Youn,* J. S. Kwon, J. J. Kim
Psychiatry, Chook Ryoung Evangelical Hospital, Namyangju City, Kyunggi-do, South Korea

The human self concept comprises essential features such as the experience of ownership of body-centered spatial perspectivity and

of a long term unity of beliefs and attitudes in accordance of the development. The neural circuitry that supports self recognition reflects the uniqueness of self processing in that it is distinct from object recognition. In the pathophysiology of schizophrenia, it is suggested that clinical subsyndromes like cognitive disorganization, derealization and hallucination reflect disorders of this self model in schizophrenia. These features can be neurobiologically instantiated as an episodically active complex of neural activation patterns, and can be mapped onto the brain given adequate operationalizations of self model features. Although the prefrontal cortex has been implicated in self processing, autobiographical memories, and the ability to infer mental states in others, the neural correlates of self?recognition have not been clearly elucidated even in normal persons as well as schizophrenics. In this study, we identified the neural circuitry involved in self recognition in both normal and schizophrenic groups using [^{15}O]H_2O PET with self face and famous face recognition tasks and compared the results of both groups to investigate the neural correlates related to the disorder of self model in schizophrenia. During a self-face recognition task in normal comparison groups, we observed increased activation of the left primary motor (M1) and sensory (S1) cortices corresponding to the face area of the homunculus, the premotor region that corresponds to the 'mirror-neuron' area in the nonhuman primates and the posterior part of Broca's area in humans. On the contrary, in schizophrenic groups, these areas were not activated anymore. On the other hand, during famous face recognition tasks in both groups, the right hippocampus and the posterior inferior temporal gyrus were activated, which suggests the involvement of memory system, only the intensity of activation was different between groups. These results suggest that disturbance of self model is play an importance role in the pathophysiology of schizophrenia. Moreover, besides hippocampus and temporal cortices, left prefrontal areas extended to the posterior part of Broca's area, caudate nucleus and right dorsolateral prefrontal cortices are related closely to the pathophysiology of schizophrenia from a disorder of self model of view.

PROCEDURAL LEARNING IN SCHIZOPHRENIA INVESTIGATED WITH FUNCTIONAL MAGNETIC RESONANCE IMAGING

L. Zedkova,* N. D. Woodward, E. M. Shih, P. Seres, S. E. Purdon, P. G. Tibbo
Psychiatry, University of Alberta, Edmonton, AB, Canada

Procedural learning (PL) involves skill acquisition without explicit awareness. The striatum appears to be critical for PL. In addition, frontal areas, the thalamus, cerebellum and visual cortex have been activated during PL in imaging studies. The neural correlates of PL deficits in schizophrenia shown in prior research are unclear. In a serial reaction time task (SRTT) subjects indicate a location of a target in 1 of 4 locations by pressing the corresponding key, unaware of repeated sequences of the target locations. With implicit sequence learning a reaction time (RT) advantage develops during blocks in which targets are presented in repeated sequences (PL blocks) compared to blocks with random target presentations. This study compared the performance on SRTT and corresponding brain activity between unmedicated patients with a first episode of psychosis (n=3), medicated patients with chronic schizophrenia (n=9) and healthy volunteers (HVs, n=7). Functional magnetic resonance imaging (fMRI) was performed during SRTT, in which 6 random blocks alternated with 6 PL blocks, each consisting of 60 target presentations (5 repeated sequences of 12 target locations in each PL block). Images were acquired with 1.5 Tesla Siemens scanner (TR = 3000, TE = 50 ms). Preliminary results showed that HVs and chronic patients developed a non-significantly greater RT advantage during PL blocks than the first psychotic episode patients (HVs: 10.4%; chronics: 8.8%; 1.episode: 4.4%). More brain areas were activated during PL in HVs than in patients, primarily the bilateral caudate, left visual cortex, left middle frontal gyrus, right insula and the right fusifom gyrus. Although first episode patients showed activation in the right caudate and left thalamus, these and other regions, such as the right cerebellum, left visual cortex, left postcentral gyrus and right midbrain, were activated significantly less than in HVs. First episode patients also activated fewer areas than chronic patients, with a significantly lower activity in the cerebellum and frontal and temporal areas. Surprisingly, chronic patients with RT advantage close to that of controls did not show any striatal activity; activation instead occurred in the sensory-motor area and bilateral medial and superior temporal gyri. The results suggest that chronic schizophrenic patients stable on atypical neuroleptics are capable of implicit learning during a simple task, but recruit different circuits than HVs.

15. Neuroimaging, Neurochemical

DIFFERENTIATING THE ROLES OF STRIATAL VS. EXTRASTRIATAL DOPAMINE D2 RECEPTORS IN ANTIPSYCHOTIC RESPONSE—A PET STUDY

O. Agid,* D. Mamo, R. B. Zipursky, I. Vitcu, P. Barsoum, S. Kapur
Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Introduction: Blockade of dopamine D2 receptors remains a common feature of all antipsychotics – however which particular D2 circuits are the most critical for antipsychotic response is still unclear. Most brain imaging studies examining antipsychotics have focused on 'striatal' dopamine D2 occupancy and have found a strong correlation to motor side effects and only a modest correlation to therapeutic response. The advent of extrastriatal tracers ([11C] FLB 457 and (18)F-fallypride makes it possible to examine the relationship of extrastriatal receptors to clinical response. Aim: We carried out the first double blind, randomized, controlled clinical-imaging study to examine the relationship between antipsychotic response and both striatal and extrastriatal D2 receptor occupancy. Methods: 14 patients early in the course of their psychosis were randomized to low vs. high doses of olanzapine or risperidone (2.5 vs. 15 mg/d; 1 vs. 4 mg/d respectively). Clinical conditions were assessed using rating instruments weekly for four weeks. At the end of this period, PET scanning were acquired to map out striatal ([11C] raclopride) and extrastriatal ([11C] FLB 457) dopamine D2 receptor occupancy. Results: The measured occupancies ranged from 49-95% in striatal and 4-95% in extrastriatal regions. Preliminary results show that extrastriatal and striatal binding are correlated: r=.77 (frontal vs. striatal occupancy), r=.82 (temporal vs. striatal occupancy). We do not find a significant difference in the degree of occupancy between striatal and extrastriatal regions (72%±17.7 vs. 61%±34.8; 58%±20.9; 61%±19 respectively for frontal, temporal and thalamus regions). Both striatal and extrastriatal regions were associated with antipsychotic response. Conclusions: This study represents the first controlled and randomized effort at characterizing the relationship between both striatal and extrastriatal D2 receptor occupancy and acute treatment response to antipsychotic medications. Further analyses are underway to examine if striatal vs. extrastriatal receptors contribute differentially to response.

RELEVANCE OF NMDA RECEPTORS FOR ANTIPSYCHOTIC DRUG ACTION—AN *IN VIVO* SPECT STUDY

R. A. Bressan,* K. Erlandsson, J. M. Stone, R. Mulligan, J. Owens, J. H. Krystal, P. J. Ell, L. S. Pilowsky
S Neuroreceptor Imaging, Institute of Psychiatry, London, United Kingdom

N-methyl-D-aspartate (NMDA) glutamate receptors have emerged as an important focus for studies of the pathophysiology and treatment of schizophrenia. Antipsychotic drugs modulate NMDA receptor function in animals. The novel SPET radiotracer [^{123}I]CNS-1261 binds to the PCP/MK-801 intrachannel site of the NMDA receptor allowing the non-invasive estimation of NMDA receptor activity in living humans. In this study we aimed to use [^{123}I]CNS-1261 to determine whether binding to the NMDA receptor intrachannel PCP/MK-801 site is affected by schizophrenia or by treatment with typical antipsychotics and clozapine in vivo. Three groups of schizophrenic patients: drug free (n=5), typical antipsychotic treated (n=7), and clozapine treated (n=9) and a control group of healthy normal volunteers (n=13) were submitted to [^{123}I]CNS-1261 SPET scans. Regional total volume of distribution was used to estimate [^{123}I]CNS-1261 binding. There was no apparent difference in total volume of distribution of [^{123}I]CNS-1261 in drug free patients relative to healthy controls. A non-significant reduction in total volume of distribution was observed in typical antipsychotic treated patients. A significant decline in total volume of distribution of [^{123}I]CNS-1261 was observed in all brain regions in the clozapine treated patient group relative to healthy controls ($p<0.005$). Conclusions: Clozapine treatment resulted in a global reduction in [^{123}I]CNS-1261 binding to the NMDA receptor intrachannel PCP/MK-801 site *in vivo*. This supports an effect of the drug on glutamatergic systems that could be exploited for future antipsychotic drug discovery.

MAGNETIC RESONANCE SPECTROSCOPY OF THE THALAMUS AT THE FIRST-EPISODE OF PSYCHOSIS IN SCHIZOPHRENIA

H. M. Emmerton,* D. J. Lang, W. MacEwan, A. L. MacKay, W. G. Honer
Psychiatry, University of British Columbia, Vancouver, BC, Canada

Previous studies have indicated several morphological and histological abnormalities in the thalamic nuclei in schizophrenia. Proton magnetic resonance spectroscopy (1H MRS) research indicates a possible decreases in N-acetylaspartate (NAA) in various brain regions in schizophrenia, including the thalamus, hippocampus and dorsolateral prefrontal cortex. The objective of this study is to investigate the concentrations of NAA, creatine and phosphocreatine (Cre), and choline-containing compounds (Cho) in the thalamus during the first-episode of psychosis in schizophrenia. In this ongoing study, single-voxel 1H MRS is used to measure concentrations of NAA, Cre, and Cho in the left thalamus of first-episode psychosis patients with eventual DSM-IV diagnoses of schizophrenia. Spectra from 3.24mL voxels, centered in the left thalamus, were acquired on a GE 1.5T scanner using a PRESS sequence. Metabolite signals were corrected for T1 and T2 relaxations, and CSF content. The subject group consisted of 12 patients (mean age=22.6, SD=5.9) as well as 23 controls (mean age=20.0, SD=4.2). Mean values of NAA concentrations and NAA/Cre ratios in the control group were similar to those reported in the literature for other healthy subjects. Analysis of variance using age as a covariate showed a significant reduction in thalamic absolute concentration of NAA in schizophrenia ($F(1,31)=8.13$, $p=0.008$). Additionally, there was a significant interaction effect between age and diagnosis ($F(1,31)=5.12$, $p=0.03$) for NAA concentration, with patients showing an increase and volunteers showing a decrease with age. One-year follow-up data is available for a subset of these patients, however time two shows no difference in thalamic NAA. These results support those of previous studies showing that there may be a reduction in thalamic NAA in schizophrenia. No differences were found in baseline concentrations of Cre ($F(1,31)=1.64$, $p=0.21$) or Cho ($F(1,31)=0.61$, $p=0.44$) between the patient and control groups. Our results support those of previous studies suggesting that NAA concentrations may be lower in thalamus in schizophrenia. Future integration of MRS data with high-resolution

structural data acquired concurrently may help to link neurochemical and structural abnormalities in the thalamus.

MAGNETIC RESONANCE SPECTROSCOPY: RECENT FINDINGS IN UNDERSTANDING THE NEUROCHEMISTRY OF SCHIZOPHRENIA

J. M. Gorman,* D. A. Yurgelun-Todd, L. Chang, C. Y. Tang, A. Bertolino
Psychiatry Department, Mount Sinai School of Medicine, New York, NY, USA

In this presentation, we review the use of magnetic resonance spectroscopy (MRS) to study the neurochemistry of schizophrenia by focusing on four new data sets. Proton MRS (1MRS) has been performed on a cohort of elderly patents with schizophrenia and matched normal volunteers. As expected, the patients with schizophrenia showed decreases in the neuronal marker N-acetyl aspartate (NAA) in the dorsolateral frontal white matter and the medial temporal white matter regions, bilaterally. The schizophrenia subjects also had decreases in the glial marker myoinositol (MI) and elevated glutamate+glutamine (GLX) in most brain regions. Age-associated decline in total creatine and in choline compounds (CHO) was observed only in the elderly schizophrenia patients. A series of 1MRS studies which have also shown regionally selective reduction of NAA in hippocampus and dorsolateral prefrontal cortex (DLPFC) will be presented. These effects were evident in both early onset and chronic cases and the DLPFC NAA findings were associated with striatal levels of dopamine, with working memory performance, and with negative symptoms. Data will be presented from studies utilizing two dimensional J resolved MRS (2D JMRS), which permits the simultaneous assessment of multiple neurochemical parameters that are relevant to the pathophysiology of schizophrenia. Compared to normal control subjects, cingulate values of transverse relaxation time (T2) for NAA were significantly reduced. Furthermore, NAA T2 values were found to correlate significantly with measures of PCr/Cr, which reflects local energy metabolism. Lower levels of GABA were also observed in this cohort. Finally, data will be presented on 1MRS and diffusion tensor imaging (DTIJ) in 31 patients with schizophrenia and 24 matched controls. Significant differences were found in the NAA/Cr ratios in the medial temporal regions. Relative anisotropy values from DTI in the same region were found to be significantly reduced in patients as well. Furthermore, the NAA/Cr rations from 1MRS and the relative anisotropy values from DTI were found to be significantly correlated.

IMAGING D1 RECEPTORS IN PATIENTS WTH SCHIZOTYPAL PERSONALITY DISORDER AND HEALTHY CONTROLS WITH [11C] NNC112

E. G. Iskander,* J. Ekelund, A. Abi-Dargham, H. Koenigsberg, V. Mitropoulou, M. Laruelle, L. J. Siever
Psychiatry, Mount Sinai Medical Center, New York, NY, USA

Background: While schizophrenic patients demonstrate dysregulated dopaminergic activity, imaging dopaminergic activity in vivo has been possible only recently. Schizophrenic patients demonstrate increased subcortical dopamine release associated with psychosis and increased D1 receptor density in the prefrontal cortex hypothesized to be associated with reduced prefrontal dopaminergic activity. On the other hand, patients with schizotypal personality disorder (SPD) - the prototypic schizophrenia spectrum disorder are spared the frank psychosis of schizophrenia. We have previously demonstrated that SPD patients are intermediate in their dopaminergic release between healthy controls and schizophrenic patients (Abi-Dargham et al, 2004). The dopamine (DA) D1 receptors in the brain of healthy subjects and patients with SPD were measured using radioactive drug [11C] NNC112 and a Positron Emission Tomography camera (PET), along with an MRI coregistration. 8 patients with SPD and 8 matched controls were studied in this paradigm. The results will be presented in relation to previous data using the same paradigm in schizophrenics suggesting upregulation of D1 receptors.

RELATIONSHIP OF AGE AND PATERNAL AGE TO NEURONAL FUNCTIONAL INTEGRITY IN THE PREFRONTAL CORTEX IN SCHIZOPHRENIA DETERMINED BY PROTON MAGNETIC RESONANCE SPECTROSCOPY

L. S. Kegeles,* D. C. Shungu, X. Mao, R. Goetz, C. B. Mikell, A. Abi-Dargham, M. Laruelle, D. Malaspina
Psychiatry, Columbia University, New York, NY, USA

Recent epidemiologic and genetic studies have shown that increasing paternal age is an independent risk factor for sporadic or nonfamilial schizophrenia, but the underlying neurobiology is unknown. Proton MRS provides a measure of neuronal functional integrity, the N-acetylaspartate to creatine ratio (NAA/Cr), with some but not all studies of NAA/Cr in the dorsolateral prefrontal cortex (DLPFC) in schizophrenia reporting deficits. In this study, we investigated the effects of paternal age and subject age on NAA/Cr (which has been reported to decline with age in healthy subjects) in a group of hospitalized schizophrenia patients. We studied 34 patients with DSM-IV schizophrenia and 34 group-matched healthy subjects to determine NAA/Cr in a left DLPFC region of interest (ROI). Twenty-five patients had sporadic illness. The acquisition protocol consisted of a multislice spin-echo sequence with outer volume suppression. We examined the effects of paternal age on the outcome measure, DLPFC NAA/Cr, controlling for maternal age and subject age, using multiple regression analysis within the sporadic and familial groups separately. We used regression analysis to examine the effects of subject age alone on DLPFC NAA/Cr in the pooled sample of patients and controls, in the full patient group, and in the sporadic patient group. The patients with sporadic illness (n=25) showed a significant decline in DLPFC NAA/Cr with increasing paternal age (df = (3,20), F=3.94, p=.017, after controlling for subject age (p=0.436) and maternal age (p=0.550)). The effect of paternal age was not significant in the familial group. The subjects showed a significant decline in NAA/Cr with age in this brain region (pooled controls and patients, n=68, r=0.30, p=0.013; patient group, n=34, r=0.45, p=.008), with a trend in the sporadic patient group (n=25, r=0.38, p=.058). DLPFC NAA/Cr did not differ between the patients and controls by 2-tailed t test. We found that advancing paternal age is associated with decreased DLPFC NAA/Cr in sporadic schizophrenia, after controlling for subject age and maternal age. In the full patient group, we found that DLPFC NAA/Cr declines with age, as previously shown in healthy subjects. The possibility that age dependence may be confounded by age-related atrophy will be addressed by volumetric analysis of the ROI. These data suggest that sporadic, paternal age-related schizophrenia may be a variant of the illness with distinct neurochemical alterations.

ASSESSMENT OF MYELIN INTEGRITY IN FIRST-EPISODE PSYCHOSIS USING A 48-ECHO MAGNETIC RESONANCE SEQUENCE

D. J. Lang,* H. M. Emmerton, G. W. MacEwan, A. L. Mackay, C. Laule, W. G. Honer
Radiology, University of British Columbia, Vancouver, BC, Canada

Introduction: A new, highly sensitive magnetic resonance (MR) methodology developed to assess the myelin-associated water fraction (MWF) in white matter has been successfully used to obtain index measures of frontal white matter integrity in chronic schizophrenia patients and normal volunteers. In healthy subjects, both age and education were found to have significant effects on measures of myelin integrity. These relationships were not seen in chronic schizophrenia patients. Both chronicity of illness and long-term exposure to medications may contribute to these observations. This current study of FEP patients was undertaken to address these issues. Subjects: 26 FEP patients (mean age 22.0 years) and 21 gender-matched volunteers (mean age 23.2 years) recruited as part of a larger longitudinal study were included in this assessment. Scanning: An axial 3D SPGR and single slice myelin water image was acquired using a 48 echo CPMG sequence. Region of Interest Assessments: A trained rater (DL) performed bilateral manual tracings of frontal, callosal and internal capsule- all anterior Analysis: Omnibus repeated measures ANOVAs were used to explore between-group, and between-side differences. Exploratory correlations and regression analyses of age, education (total yrs) and MWF scores were conducted. Results: Significant effects of diagnosis were seen in frontal white matter, with healthy volunteers having greater MWFs than FEP patients (Genu: $F(1,44)= 10.09$, p.=.003, frontal white: $F(1,44)=9.59$, p.=.003, Anterior Internal Capsule: $F(1,44)=6.74$, p.=.013). There were no diagnosis x side interactions. Frontal MWFs were also significantly correlated to age in healthy volunteers (but not FEP patients) and educational attainment in both volunteers and FEP patients (all p-values <.04). Subsequent ANOVAs covarying for age and education confirmed the effect of diagnosis on MWFs in the total (L R) Genu ($F(1,43)=5.76$, p.=.002) and the total frontal white ($F(1,43)=5.09$, p.=.03), but not in the total anterior internal capsule ($F(1,43)=2.04$, p. >0.10). Conclusions: As in chronic patients, minimally medicated first-episode psychosis patients appear to have reduced white matter integrity, particularly in bilateral frontal white matter. The loss of normal relationships of white matter integrity to age, but not education in psychosis are of interest and require further investigation. Follow-up data may provide further insight into these phenomena.

LONGITUDINAL ASSESSMENT OF BRAIN CHEMISTRY EARLY IN SCHIZOPHRENIA: A RANDOMIZED CONTROLLED TRIAL OF QUETIAPINE AND HALOPERIDOL

J. Lauriello,* L. Rowland, L. R. Hammond, W. Brooks, J. Bustillo
Department of Psychiatry, University of New Mexico, Albuquerque, NM, USA

Background: Proton magnetic resonance spectroscopy (H-MRS) permits the measurement of various brain metabolites in-vivo. One such metabolite, N-acetylaspartate (NAA), is readily measurable with H-MRS, is located primarily in neurons and is an index of their viability and function. NAA has been found to be reduced in frontal and temporal regions in chronically treated schizophrenia patients. The effects of antipsychotic medications on NAA in early schizophrenic patients is not clear. Methods: Single voxel proton magnetic resonance spectroscopy (H-MRS) of the left frontal and occipital lobes, left caudate and right cerebellum was acquired in minimally-treated (<3 weeks lifetime antipsychotic exposure) schizophrenia patients (n=34) and healthy controls (n=21). All spectra were acquired using a 1.5T GE MRI, with PRESS acquistion (TE=30 ms, TR=2000 ms, 128 averages). Metabolite concentration was corrected for voxel-csf proportion. Patients were randomized to treatment with haloperidol (2-12 mg/day) or quetiapine (100-600 mg/day) and re-scanned at 6 and 12 months. Results: NAA (corrected for voxel CSF proportion) was lower in the schizophrenia group at baseline (p=0.05) in the caudate, but not in the frontal, occipital or cerebellar regions. Longitudinal H-MRS data from the first year of treatment with quetiapine and haloperidol will also be presented. Conclusions: The initial results are suggestive of reduced caudate NAA before treatment with antipsychotic medications.

PEAK AND TROUGH DOPAMINE D2 RECEPTOR OCCUPANCY FOR LONG-ACTING INJECTABLE RISPERIDONE: A PET STUDY

G. Remington,* D. Mamo, A. Labelle, J. Reiss, C. Shammi, S. Mann, E. Mannaert, S. Kapur
University of Toronto, Toronto, ON, Canada

Long-acting injectable risperidone represents the first atypical slow-release intramuscular antipsychotic available for clinical use. The present study was designed to investigate its D2 occupancy over a range of 3 doses (25, 50 or 75 mg) administered every 2 weeks. After being stabilized on one of these three doses, D2 occupancy was measured using [11C] raclopride in nine patients with a diagnosis of schizophrenia or schizoaffective disorder. PET scanning was done at peak (mean 2.89 days post-injection, SD=0.3) and trough (mean 10.2 days post-injection, SD=1.5) levels in order to evaluate changes in D2 occupancy over the course of the injection interval. Nine participants (7 males and 2 females) completed the study. Mean D2 occupancy at peak and trough for each of the doses was as follows: 25 mg (N=2), 71% (SD=5.7) versus 54% (SD=1.4); 50 mg (N=5), 75.4% (SD=10.4) versus 65.4% (SD=2.1); 75 mg (N=2), 81.5% (SD=5.0) versus 75% (SD=5.7), respectively. Dose showed a significant correlation with plasma risperidone + 9-OH-risperidone levels, even controlling for time i.e., peak vs trough, as it did with D2 occupancy. The calculated ED50, or estimated risperidone + 9-OH-risperidone concentration associated with 50% maximal D2 occupancy, was 11.06 ng/ml. At peak, all 3 doses achieved D2 occupancy levels within the therapeutic range associated with optimal chance of clinical response i.e., 60-70%, with an increased likelihood of achieving > 80% occupancy, a threshold linked with increased risk of extrapyramidal symptoms (EPS), when using the 75 mg dose. The present findings support the use of long-acting risperidone in doses of 25-50 mg to optimize clinical response while diminishing risk of EPS, a finding in keeping with available clinical evidence.

THE EFFECTS OF NMDAR ANTAGONISM ON BEHAVIOR, COGNITION, AND GLUTAMATE ACTIVITY IN HEALTHY HUMANS

L. M. Rowland,* J. R. Bustillo, P. G. Mullins, R. Jung, R. Lenroot, J. Lauriello, R. Yeo, H. H. Holcomb, A. Lahti, W. Brooks
MPRC, University of Maryland, Baltimore, MD, USA

Objectives: (1) To test the hypothesis that N-methyl-D-aspartate receptor (NMDAR) antagonism results in increased cortical glutamate activity, as proposed by the NMDAR hypofunction model of schizophrenia. (2) To test whether NMDAR antagonism has a differential effect on encoding versus retrieval of verbal and spatial information. Methods: In-vivo 4T 1H spectra were acquired from bilateral anterior cingulate (AC) in 10 healthy subjects while being administered a subanesthetic dose of ketamine, an NMDAR antagonist. Subjects were tested with standard cognitive tests of attention, working memory, and declarative memory, and with a computerized Morris Water Task that assessed spatial learning and memory. Schizophrenia-like positive and negative symptoms were assessed with the BPRS, CADSS, and SANS. Results: As predicted, there was a significant increase in AC glutamine, a putative marker of glutamate neurotransmitter release, with ketamine administration. This increase was not related to schizophrenia-like positive and negative symptoms but was related to Stroop performance. Ketamine impaired encoding of new spatial and nonspatial information but retrieval of information learned prior to drug administration was preserved. Conclusions: In humans as in animals, an acute hypofunctional NMDAR state is associated with increased glutamatergic activity in the AC and impairs learning of verbal and spatial information. Increased cortical glutamatergic activity may be an adverse downstream effect of NMDAR hypofunction, and could be an important catalyst in the deteriorating course (cognitive and social functioning) of schizophrenia. To our knowledge, this is the first study in humans to suggest that NMDAR antagonism results in increased glutamate activity in the AC. This provides important evidence for a missing component of the NMDAR hypofunction model of schizophrenia.

1H-MRS STUDY OF INSIGHT DEFICITS IN FIRST EPISODE SCHIZOPHRENIA

M. U. Shad,* J. A. Stanely, M. S. Keshavan
Psychiatry, UT Southwestern at Dallas, Dallas, TX, USA

Few studies have investigated the neurobiological basis of impaired insight in antipsychotic naive schizophrenia subjects (1). However, the relationship between insight and specific prefrontally mediated cognitive functions suggests that insight deficits may be an expression of prefrontal cortical dysfunction. This study was designed to examine the relationship between insight and in vivo biochemical status of dorsolateral prefrontal cortex (DLPFC) in 19 antipsychotic naive first-episode schizophrenia subjects (Average age = 22.3; M/F = 14/5) based on single-voxel proton spectroscopy (1H-MRS). Spectroscopic assessments were conducted on a 1.5 T GE Signa Imaging System using a quadrature volume head coil by trained raters blind to clinical information. The gray matter, white matter, and cerebrospinal fluid content in the MRS voxels of interest were determined by performing segmentation with a semi-automated histogram method (2). Insight was assessed with a single question, derived from the insight item of the Hamilton Depression Rating Scale by a single well-trained clinician. Six subjects scored 0 (good insight) seven scored 1 (partial insight) and six scored 2 (poor insight). The group scoring 1 (partial insight) was added to the group scoring 0 (good insight), because of the non-normal distribution of data. This resulted in two insight groups, one (n = 13) with good insight and the other with poor insight. Based on ANOVA, we observed significantly lower DLPFC levels of N-acetylaspartate (NAA) in subjects with poor insight s compared to those with good insight (df = 17; F = 9.31; p = .007). However, no significant differences in any of the psychopathological or neuropsychological measures were observed in the two insight groups. Based on independent t-test, we found no association between DLPFC NAA levels and age, IQ, or GAF. Although preliminary, these findings suggest that insight deficits in first-episode schizophrenia may be a function of specific biochemical deficits in the DLPFC. References: 1) Shad MU, Muddasani S, Eklund KD, Keshavan MS. Prefrontal Sub-Regions and Dimensions of Insight in First-Episode Schizophrenia. Abstract Society of Biological Psychiatry in New York in April, 2004. 2) Keshavan MS, Anderson S, Beckwith C, Nash K, Pettegrew JW, Krishnan KR. A comparison of stereology and segmentation techniques for volumetric measurements of lateral ventricles in magnetic resonance imaging. *Psychiatry Res*. 1995 31;61(1):53-60.

STRESS-INDUCED DOPAMINE RELEASE IN THE STRIATUM OF HUMANS AT RISK OF SCHIZOPHRENIA: A [11C]-RACLOPRIDE PET STUDY

A. Soliman,* G. O'Driscoll, J. Pruessner, A. L. Wolff, I. Boileau, D. Gagnon, A. Dagher
Montreal Neurological Institute, McGill University, Montreal, QC, Canada

Background: The dopamine hypothesis focuses on the role of the dopamine (DA) in symptoms and treatment of schizophrenia. Drugs that increase DA release in the brain cause a psychological state in humans clinically indistinguishable from paranoid-type schizophrenia and worsen psychotic symptoms in schizophrenics. Exposure to psychological stressors also increases mesolimbic DA and increased sensitivity to stress is thought to play a role in susceptibility to schizophrenia. We hypothesized that schizotypal subjects, who are at increased risk of developing psychosis, would show greater stress-induced striatal DA release. We also proposed, that as in past studies, low parental bonding would predict higher DA release. Methods: Using the radiolabelled neuroreceptor ligand [11C]raclopride, we measured changes in synaptic DA concentrations in 10 controls and 16 psychometric schizotypes (9 perceptual aberration, PERAB, and 7 physical anhedonia, PHYSAN; Chapman and Chapman scales). Further, we measured their relationship with their parents during the first sixteen years of life. Raclopride binding potential (DA release) was obtained during two counter-balanced PET sessions on separate days: a sensory-motor control condition and a stress-reactivity paradigm (Trier Mental Challenge Test, Kirschbaum, 1999). Reports of stress and salivary cortisol were also monitored. Results: Voxel-wise t-maps were calculated; significant differences between the control and stress conditions showed both increases and decreases in DA release in the striatum. Group differences were observed; physical anhedonics had significantly greater DA release than the other two groups. Low maternal care predicted both classification in the PHYSAN group and magnitude of DA response to stress. A significant cortisol secretion accompanied the dopamine response. Conclusion: Thus, this stressful task was associated with greater DA release in subjects at risk for psychosis, albeit in a complex

manner that depends upon the type of schizotypal personality. The data suggest a possible role for early environment in the development of physical anhedonia and stress response, although the causal connections among these variables could not be determined here.

KETAMINE DISPLACEMENT OF THE NMDA ION CHANNEL SPET LIGAND [123I]CNS-1261 IN VIVO

J. Stone,* K. Erlandsson, E. Arstad, R. A. Bressan, V. Teneggi, P. J. Ell, L. S. Pilowsky
Institute of Psychiatry, London, United Kingdom

The novel single photon emission tomography ligand [123I]CNS-1261 binds with high selectivity and affinity to the NMDA intrachannel PCP/ketamine/MK-801 site in vitro (Owens et al., *Nucl Med Biol*. 2000; 27:557-64). We report the first in vivo validation of this ligand in humans following challenge with ketamine, a known competitor for the same site. A placebo controlled comparison was performed comparing the effects of ketamine and placebo delivered intravenously in a single blind fashion on two separate occasions. 9 healthy male volunteers (mean age=24(SD3) y) were recruited for the study. Subjects with substance misuse were excluded. Scans were performed with a triple headed Prism 3000XP (Phillips Medical Systems) SPET camera. The tracer was administered by a bolus/infusion protocol (Bressan et al., *Nucl Med Biol*. 2004; 31:155-64). Ketamine/placebo (saline) was delivered by intravenous infusion at tracer equilibrium. 0.3 mg/kg of S-ketamine was given as a slow bolus injection at 165 min p.i., and subsequently a constant infusion of ketamine was given over 70 min (170-240 min p.i.) with a rate of 0.7 mg/kg/hour. Data was acquired for 1h before and after the challenge started. Venous blood samples were taken during the scans and total volume of distribution (VT) was calculated. VT maps were transformed into standard brain space and analysed with predefined regions of interest. The post ketamine VT values were normalised to the pre-ketamine VT values. A brisk psychophysiological response was seen to ketamine in all cases. None was evident following placebo. A significant decline in normalised VT values was seen in ketamine cases relative to the placebo in thalamus, head of caudate, and in cortical regions (p=0.05). It appears from these data that [123I]CNS-1261 is displaceable in vivo by ketamine, a direct competitor for the same site. This supports its utility as a SPET probe for the NMDA intrachannel PCP/MK-801/ketamine site, and its application to clinical studies of neuropsychiatric disorders in which the NMDA system is implicated.

COMPARISON OF GLUTAMATE LEVELS IN AN OLDER GENETIC HIGH RISK SAMPLE: USEFUL PREDICTOR OR GENETIC MARKER?

P. Tibbo,* A. Valiakalayil, P. Seres, C. Hanstock
Deparment of Psychiatry, University of Alberta, Edmonton, AB, Canada

Siblings of individuals with schizophrenia have approximately the same genetic risk of developing the disorder as children of parents with the illness (8-10% compared to 10-12% respectively) (Gottesman & Shields, 1982). The aim of the current study was to examine brain metabolite differences in adult siblings of individuals with schizophrenia who have passed the age of onset risk compared to normal healthy controls and a psychiatric control group (siblings of individuals with non-psychotic affective disorders). Our previous work identified glutamate abnormalities in adolescents at high-risk for developing schizophrenia (Tibbo et al., 2004). By using a similar genetic high-risk sample that has passed the age of onset risk, it is possible to assess whether neurochemical differences reflect genetic liability or present a possible predictive marker of illness in the younger sample. Specificity to schizophrenia will be achieved by comparison to a psychiatric control group. 19 adult high risk for schizophrenia (HR) (mean age = 46.3 years), 16 normal adult controls (NC) (mean age = 44.5 years), and 6 psychiatric controls (PC) (mean age = 45.3 years) were subjected to 1H-MRS quantification of glutamate using a 3 Tesla scanner with a 2.5 cm^3 voxel placed over the right medial frontal lobe. Glutamate (Glu) was subjected to an ANOVA with group as a between subjects factor. No significant effect of group was seen in Glu levels $F(2,34)=1.97$, $p=.156$. The HR group showed a trend towards higher glutamate than the NC group $t(29)=1.779$, $p=.086$. The Glu elevations seen in HR adolescents are not seen in a HR adult sibling sample, reflecting the decreased risk in the older sample. This would suggest the Glu elevations are not simply a reflection of genetic liability. By following the younger cohort through time, it will be possible to track brain metabolite changes as this sample passes through the average age of risk. This will help determine the predictive ability of Glu levels in the development of schizophrenia. Gottesman II, Shields J. (1982). *Schizophrenia: The Epigenetic Puzzle*. Cambridge University Press. Tibbo P, Hanstock C, Valiakalayil A, Allen P. (2004). 3-T Proton MRS investigation of glutamate and glutamine in adolescents at high genetic risk for schizophrenia. *Am J Psychiatry*. 161: 1116-1118.

GLUTAMATE MODULATION OF PERSEVERATION IN FIRST EPISODE PSYCHOSIS

A. Valiakalayil,* P. Tibbo, S. Purdon
Department of Psychiatry, University of Alberta, Edmonton, AB, Canada

Glutamate dysfunction may relate to perseveration in schizophrenia, as suggested by pre-clinical studies linking the NMDA glutamate system to the inhibition of perseverative behavior. The relevance of glutamate to perseveration was examined in 6 patients in their first episode of psychosis, and 6 age and gender matched normal controls. Participants completed the Wisconsin Card Sorting Test (WCST) and 1H-MRS quantification of glutamate in the right and left frontal cortex. More WCST errors were observed in the psychosis group, $t(12)=1.78$, $p=.048$, but they did not exhibit more WCST perseverative errors (WCST PE) or abnormal concentrations of glutamate in the left (LHG) or right (RHG) hemispheres. WCST PE's in the psychosis group exhibited a trend towards a positive association with LHG ($r=0.74$, $p=.06$), and a negative association with RHG ($r=-0.78$, $p=.04$). The ratio of RHG to LHG accounted for 74% ($r=0.86$, $p=.013$) of the variance in WCST PE among patients, but only 8% among controls. Glutamate appears to be relevant to perseveration, even among first episode patients with psychosis exhibiting a minimal perseverative tendency. This may suggest a cerebral mechanism for novel pharmaco-therapeutic benefits.

LONGITUDINAL GRAY MATTER AND GLUTAMATERGIC CHANGES WITH HIGH FIELD 1H MRS IN FIRST EPISODE SCHIZOPHRENIC PATIENTS

P. C. Williamson,* J. Theberge, K. E. Williamson, R. Manchanda, A. K. Malla, R. Menon, R. W. Neufeld, N. Rajakumar, W. Pavlosky, M. Densmore, D. J. Drost
Neuropsychiatry Research Group, University of Western Ontario, London, ON, Canada

Reports of progressive volumetric changes in some schizophrenic patients have led to a renewed interest in neuronal degeneration in schizophrenia. However, these changes are not necessarily related to neuronal degeneration so it is important to examine other metabolic parameters in these patients over time. In this ongoing study, we hypothesized that 1) Cortical gray matter levels would decrease over the course of 30 months in first episode but not healthy subjects and 2) Gray matter losses would be associated with decreased levels of glutamatergic metabolites over 30 months in the same patients. Voxel-based statistical parametric mapping comparisons of gray matter were made between never-treated, first episode schizophrenic patients followed up after stabilization on medication at 10 months and at 30 months and comparable healthy volunteers studied at baseline and 30 months. Levels of glutamate (Glu), glutamine (Gln) and N-acetylaspartate (NAA) were quantified in these subjects with a 4 Tesla system using a STEAM sequence from 1.5 cc voxels in the left anterior cingulate and medial thalamus. Spectra were normalized to a water unsuppressed acquisition and were corrected for gray and white matter volumes. Preliminary analysis of 12 patients and 12 comparison subjects showed widespread ($p< 0.001$, corrected) loss of gray matter, particularly in prefrontal regions in first episode patients at 30 months. These same patients demonstrated decreased Gln levels and increased Glu/Gln ratios in the left anterior cingulate ($p<0.02$) and left medial thalamus ($p<0.06$). There were no differences in gray matter volumes or glutamatergic metabolites between the never-treated and stabilized on medication assessments suggesting little effect of clinical state or medications. Healthy volunteers did not show significant gray matter loss or glutamatergic changes at follow-up. No changes were seen in NAA over time in either group. The finding of gray matter loss in association with glutamatergic changes suggests neurodegeneration but this would not likely explain gray matter loss in other parts of the brain. It is of interest that many of the regions with progressive volumetric changes regulate the limbic basal ganglia-thalamocortical neuronal circuit. Thus, programmed loss of neuropil in these regions in the early years of illness could lead to a secondary neurodegenerative process reflected in the glutamatergic findings in this study. Further subjects are in follow-up.

EICOSAPENTANOIC ACID SUPPLEMENTATION ALTERS 1H MRS METABOLITE PROFILES IN FIRST EPISODE PSYCHOSIS

S. Wood,* R. M. Wellard, M. A. McConchie, G. D. Jackson, D. Velakoulis, P. D. McGorry, C. Pantelis, G. E. Berger
Melbourne Neuropsychiatry Centre, University of Melbourne, Carlton, VIC, Australia

Bioactive lipids are molecules that have both intra- and intercellular roles, including mediation, modulation and control of neurobiological processes, such as ion channel and receptor activity, neurotransmitter release, synaptic plasticity, second messenger pathways and neuronal gene expression. The essential fatty acid arachidonic acid (AA) and its metabolites, known collectively as eicosanoids, comprise a major fraction of bioactive lipids in the brain. Bioactive lipid metabolism has been implicated in the etiology of psychosis with depletion of bioactive lipids in cell membranes of patients with schizophrenia, independent of drug treatment. This study investigated the effect of EPA (eicosapentanoic acid) supplementation on the metabolite profile of the brain, in vivo, in first episode psychosis. Twenty-four patients in the first episode of a psychotic disorder were studied. After an initial 1H-MRS examination and in addition to standard treatment with atypical antipsychotics, 12 took a course of 2g oral EPA supplement and 12 patients placebo (mineral oil) for 12 weeks prior to a second MRS study. Short echo (30 ms) MRS was performed on a GE 3 T LX Horizon scanner using a PRESS sequence with two chemical shift selective imaging pulses for water suppression. A single voxel (2x2x2 cm) was placed in each temporal lobe. This region of interest included the hippocampus, amygdala and lateral aspect of the temporal lobe. Spectra were analysed with LCModel using a basis set of 15 metabolites acquired onsite, and data were rejected if the Cramer-Rao lower bounds were greater than 30%. Patients treated with EPA showed a significantly greater percentage increase for the combined glutamate/glutamine peak ($F1,22=6.4$, $p=0.021$) and for glutathione ($F1,12=7.9$, $p=0.018$) than did those treated with placebo. These changes were more pronounced in patients who showed a normal flush response to topical niacin (a measure of biolipid metabolism). Interestingly, n-acetyl aspartate levels increased equally in both groups, although this did not reach significance. The increase in glutathione in the EPA treated patients suggests that this agent may protect against oxidative stress accompanying the onset of the disorder, while the increase in glutamate/glutamine is likely to be part of the same metabolic pathway. The relationship of these changes to clinical features and structural imaging findings remains to be explored.

3-T PROTON MRS INVESTIGATION OF THE VENTRAL AND DORSAL ANTERIOR CINGULATE CORTEX IN SCHIZOPHRENIA AND OBSESSIVE COMPULSIVE DISORDER

M. Yucel,* S. J. Wood, K. Clarke, R. M. Wellard, M. L. Phillips, M. Kyrios, C. Pantelis
Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne, Melbourne, VIC, Australia

OBJECTIVE: Brain imaging studies have revealed abnormalities in multiple brain regions including the anterior cingulate cortex (ACC) in schizophrenia (SCZ) and obsessive-compulsive disorder (OCD). While it is clear that the ACC is involved in the underlying neurobiology of both disorders, the nature of its involvement is as yet unclear. This study used proton magnetic resonance spectroscopy (1H MRS) to identify potential similarities and differences in metabolic abnormalities in this region of patients with SCZ and OCD using 3-T proton magnetic resonance spectroscopy. METHOD: Spectra from the ventral and dorsal anterior cingulate cortices (bilaterally) of 5 patients with established SCZ, 8 patients with longstanding OCD (SCZ; mean age=38.3 years; OCD; mean age=32.2) were compared with spectra obtained from 17 healthy controls (HC) (mean age=29.9 years). Absolute levels of N-acetyl compounds (NAA), creatine plus phosphocreatine (Cr), choline compounds (Cho), myoinsotol (Mi) and Glutamine/Glutamate (Glx) were quantified using LCModel from basis sets obtained on site. RESULTS: Metabolites were compared

individually as a three way ANOVA with two repeated measures. The repreated measures were hemisphere (left and right) and position (ventral and dorsal). No group effect or interactions with group were found for NAA, Cr or Glx. However, a significant side by region by group effect for Cho ($p = 0.026$; a result of significantly elevated Cho in the left dorsal voxel of the SCZ group) and a side by group effect for Mi ($p = 0.004$; a result of significantly elevated levels in the right ACC of both patient groups) was identified. DISCUSSION: The finding of elevated Cho and Mi levels in this study suggests that both SCZ and OCD are associated with alterations in the membrane metabolic activity of the ACC. The pattern of membrane metabolic abnormalities within the ACC of the two patient groups raises the possibility that there is: (i) both overlapping and differential subregions of the ACC involved in the two disorders, and; (ii) a future role for MRS in differential diagnosis among psychiatric disorders. Finally, the normal levels of the neuronal marker NAA suggest that there is no concurrent neuronal loss in either disorder. This research was supported by the National Health & Medical Research Council (NH&MRC) of Australia (Project Grant I.D. 236175).

MICROGLIA ACTIVATION IN SCHIZOPHRENIA: AN (R)-[11C]-PK11195 POSITRON EMISSION TOMOGRAPHY STUDY

B. van Berckel,* R. Boellaard, E. Caspers, W. Cahn, A. Lammertsma, R. Kahn

Department of Nuclear Medicine and PET Research, VU University Medical Center, Amsterdam, Netherlands

Schizophrenia is a brain disease particularly involving decrement in gray matter as has been supported by findings from many imaging studies. The pathophysiology of these gray matter changes has not been clarified. Microglia activation is the consequence of virtually all conditions associated with neuronal injury. When activated following neuronal damage, microglia show a marked increase in the expression of peripheral type benzodiazepine binding sites which are particularly abundant on cells of the mononuclear macrophage. (R)-PK11195[1-(2-chlorophenyl)-N-methyl-N-1(1-methylpropyl]-3soquinolinecarboxamide) is a highly selective ligand for the peripheral benzodiazepine binding site. (R)-PK11195, labeled with the positron emitter carbon-11, can be used to monitor the peripheral type benzodiazepine receptors using Positron Emission Tomography (PET). In this currently ongoing protocol, 5 patients with paranoid schizophrenia (DSM-IV criteria) and 4 healthy controls have been included to date. PET scans were performed using an ECAT-EXACT HR+ scanner. A dynamic 3D scan, consisting of 22 frames over 60 minutes, was acquired following a bolus injection of 370 MBq (R)-[11C]-PK11195. Arterial whole blood concentration was monitored continiously using an online detection system. In addition, discrete samples were taken in order to derive a metabolite corrected plasma curve. Finally, for each subject a T1 weighted structural MRI scan was acquired using a Philips 1.5 Tesla scanner. Regions of interest were defined on the co-registered MRI. ROI were defined for frontal cortex, cerebellum and thalamus. These ROI were projected onto the dynamic (R)-[11C]-PK11195 scans, thereby generating time activity curves for each region. A two-tissue reversible compartment model (K1/k2 fixed to values obtained from whole brain) using a metabolite corrected plasma input function was fitted to the data. In addition, the simplified reference tissue model was used with the cerebellum as reference tissue. The primary outcome measure was binding potential (BP). Initial analyses indicate a moderate elevation in thalamus (R)-[11C]-PK11195 binding in this small sample. More subjects are currently being included.

16. Electrophysiology

P50 SUBCOMPONENT ABNORMALITIES IN SCHIZOPHRENIA: PHENOMENOLOGICAL CORRELATES

S. D. All,* S. Keedy, B. Beenken, A. Hartzell, R. E. Gur, R. J. Erwin
Psychology, Rosalind Franklin University of Medicine and Science, North Chicago, IL, USA

Efforts to uncover relationships between schizophrenia symptoms and sensory gating deficits as measured by the auditory evoked potential (AEP) P50 have been difficult with few conclusive relationships identified. Examination of subcomponents of P50 may reveal relationships between amplitude and suppression properties of P50 and symptom profiles previously undetected. This analysis examined the relationship between P50 subcomponents and schizophrenia phenomenology as measured by the observer symptom rating scales: BPRS, SAPS & SANS. AEP and clinical data were collected at the Mental Health Clinical Research Center at the University of Pennsylvania. AEPs were collected with at 32-channel recording array using a paired click paradigm (0.5 sec inter-click interval, 10 sec inter-pair interval). Spatial and temporal factor analyses performed on data from 37 control subjects revealed two spatial subcomponents of P50: a central midline component and a more frontally distributed bilateral component. Decreased amplitude of S1 on the midline subcomponent was related to increased BPRS positive symptoms ($r=-.34$, $p<.05$); whereas negative BPRS symptoms were related to decreased S1 amplitudes in the right frontal subcomponent ($r=-.31$, $p<.05$). BPRS disorganized symptoms correlated with poor suppression of S2 in the right frontal subcomponent ($r=.31$, $p<.05$); SANS global attention also correlated with poor suppression on this subcomponent ($r=.35$, $p<.05$) as well as poor suppression on the midline subcomponent ($r=.34$, $p.<05$). These findings are consistent with theories relating positive symptoms to impairments in midline limbic systems and decreased S1 amplitude, and negative and disorganized symptoms to more persistent fronto-temporal brain pathology. This research was supported by the following grants from the National Institute for Mental Health, MH43880 and MH50344, and by Scottish Rite Fellowships to S.D. All, B. Beenken, and S. Keedy.

NEURAL CORRELATES TO MORPHOLOGICAL AND LATENCY ABNORMALITIES OF THE MID-LATENCY AUDITORY EVOKED RESPONSES IN SCHIZOPHRENIA PATIENTS AND THEIR FIRST-DEGREE RELATIVES: A PRELIMINARY REPORT

T. G. Benios,* M. O. Pozdin, N. N. Boutros, O. Korzyuko, G. Pearlson
Neuropsychiatry, Olin Neuropsychiatry Research Center, Hartford, CT, USA

Auditory sensory gating deficits are trait attributes that seem to reflect very robust neurobiological substrates to psychosis and have a strong potential for serving as endophenotypes in genetic studies of schizophrenia. The ability to effectively screen out irrelevant sensory input is a fundamental protective mechanism that prevents an overabundance of sensory information in higher cortical centers and secondary cognitive fragmentation and disorganization. In this study, we explored whether morphological abnormalities of mid-latency auditory evoked responses (MLAERs) at P50 and N100 were associated with absolute whole-brain gray matter, white matter and cerebral spinal fluid (CSF) volumes in 14 schizophrenia patients, 9 first-degree relatives and 13 healthy controls. The morphology of the MLAER was considered abnormal if one or more of the components fell outside the expected latency range, if one or more of the components were missing or if a later occurring component was smaller in amplitude than an earlier occurring one, as described in Boutros et al. (in press). Of the 14 schizophrenia subjects, 50% had waveforms that were classified as atypical, compared to 33% of relatives and 23% of healthy controls. Significant prolongation of N100 S1 and S2 latencies, but not P50 S1 and S2 latencies, was observed in schizophrenia patients compared to first-degree relatives and healthy controls. First-degree relatives with abnormal N100 S1 and S2 latencies showed nonsignificantly smaller gray matter volumes (587.28 ml +/- 56.39 vs. 624.41 ml +/- 66.46) than age-matched relatives with normal N100 S1 and S2 latencies; while schizophrenia patients with abnormal N100 S1 and S2 latencies showed nonsignificantly lower CSF volumes (219.50 ml +/- 19.79 vs. 256.13 +/- 40.89) than age-matched patients with normal N100 S1 and S2 latencies. These results suggest that gating is a pervasive neurobiological deficit in schizophrenia patients that may extend further than the preattentive phase of information processing. The present study also helps to establish a relationship between morphological and latency abnormalities during the MLAERs phase of information processing and whole-brain tissue measures to better understand sensory gating as a vulnerability indicator for schizophrenia.

MISMATCH NEGATIVITY DEFICITS AND THEIR RELATIONSHIP TO FUNCTIONAL IMPAIRMENTS ARE STABLE IN SCHIZOPHRENIA PATIENTS

D. Braff,* G. A. Light, M. H. Hsieh, J. Sprock
Psychiatry, University of California San Diego, La Jolla, CA, USA

Schizophrenia patients have deficits in mismatch negativity that are associated with poor everyday functioning. In order to investigate the longitudinal stability of MMN deficits and the relationship of MMN deficits to poor functional status, 10 chronic schizophrenia patients underwent repeat testing over a 1-2 year period and were compared with 10 age-matched normal subjects. Schizophrenia patients had large effect-size MMN deficits that were stable (e.g., $r=0.79$, $p<0.01$, Fz) over time. MMN deficits were also significantly associated with poor functional status at both session 1 and session 2 ($r=-0.63$ to $r=-0.68$, $ps<0.05$). MMN deficits and their relationship to functional impairments are stable in schizophrenia patients, suggesting that MMN may be useful for assessing changes in auditory sensory processing in longitudinal studies. Future studies are needed to clarify possible medication related changes, as well as the time course, emergence, and progression of MMN deficits in schizophrenia patients.

CAN THE P300 WAVE HELP IN EARLY DETECTION OF PSYCHOSIS?

E. Bramon,* M. Broome, L. Johns, J. Woolley, P. Tabraham, C. Brett, L. Valmaggia, P. Sham, R. M. Murray, P. K. McGuire
Div. Psychological Medicine, Institute of Psychiatry, London, United Kingdom

The P300 wave is a change in the human EEG observed during tasks of stimuli discrimination. Our recent meta-analysis of the literature shows how the P300 wave has reduced amplitude and

delayed latency in schizophrenia as well as in unaffected relatives of patients. The P300 wave is thus thought to be a marker of genetic risk for psychosis. Could the P300 wave be deviant in other populations at risk? A group of 30 subjects meeting PACE criteria for the At Risk Mental State (ARMS) and 40 controls performed a P300 task. The latency and amplitude of the P300 wave were compared between groups using linear regression models adjusting by potential confounders. There was no difference in P300 latency between the cases at risk and the controls. We found a trend for the P300 amplitude to be reduced in the cases at risk [mean=8.7; sd=5.3 microVolts] compared to controls [mean=10.8; sd=4.5 microVolts] (p=0.06). These results suggest that the P300 amplitude may be a useful pre-morbid marker of vulnerability to develop psychosis. Since the P300 is a form of continuous performance task, its reduction in amplitude may reflect subtle cortical activation deficits during sustained attention in the prodrome. Neurophysiologic investigations of cognitive deficits in early psychosis require further study.

THE STABILITY OF PREPULSE INHIBITION OF THE STARTLE RESPONSE IN INDIVIDUALS AT-RISK FOR SCHIZOPHRENIA AND IN THE EARLY PHASES OF ILLNESS

K. Cadenhead
Psychiatry, University of California San Diego, La Jolla, CA, USA

Background: Prepulse inhibition (PPI) of the startle response is an operational model for sensorimotor gating that and has been shown to be stable in both normal subjects and patients with chronic schizophrenia. The findings of PPI deficits in schizophrenia spectrum populations and in unaffected first degree relatives of patients with schizophrenia suggest that PPI is a trait marker for schizophrenia and may have utility as an endophenotypic marker in genetic studies and a vulnerability marker in studies of the schizophrenia prodrome. Examining the stability of PPI in subjects at-risk for schizophrenia and individuals in the early stages of schizophrenia can potentially provide valuable insights into the progressive course of the illness. Method: Thirty-one individuals between the ages of 12 and 30 who met criteria for an at-risk state (AR) per the Structured Interview for Prodromal States (SIPS), 9 patients who had developed their first episode of schizophrenia (FE) within the last year and 10 normal comparison subjects (NC) were assessed in a PPI paradigm that included bilateral startle measurement at 3 interstimulus intervals (ISI) performed during 2 test sessions separated by 6 months to 1 year. Results: PPI was stable across all subject groups as assessed by Intraclass Correlation Coefficients (ICC) with the NC subjects demonstrating the most stability followed by the AR subjects and the FE subjects. The PPI of FE patients was stable only in one of the 6 PPI conditions. There were no differences between test sessions or group X test session interaction as assessed by omnibus ANOVA. The overall group difference ($p<0.07$) and gender difference ($P<0.06$) were short of significant but there was a significant group by gender interaction. There was also a significant age effect that was found to be present only in male subjects. Conclusion: PPI is a stable vulnerability marker in a population at-risk for schizophrenia. There appears to be less stability of PPI in the early stages of schizophrenia compared to chronic patients with schizophrenia, normal subjects and subjects at-risk for the illness.

REPLICATED ELECTROPHYSIOLOGICAL SUBTYPES OF SCHIZOPHRENIA

R. Cancro,* E. R. John, G. Winterer, W. M. Herrmann
Psychiatry, NYU School of Medicine, New York, NY, USA

Schizophrenia (SZ) is a heterogeneous disorder. Subtyping based upon clinical judgment, symptom scales, Structured Interview, lifetime symptoms or neuropsychological tests typically generate 4-5 clusters, but no criteria including DSM-IV subtypes reliably guide selection of treatment or agree with empirical clusters. Reliable subtyping of SZ patients is desirable. Quantitative EEG (QEEG) evaluations yield standard scores for a variety of brain measures, with high test-retest reliability, sensitivity and specificity, revealing profiles so distinctive for a variety of psychiatric diagnoses including SZ as to permit successful discrimination between groups of normals and patients. QEEG-identified clusters have been correlated with treatment outcome of OCD patients, crack-cocaine users, children with ADHD, mild cognitive impairment, and preferential response of SZ to risperidol or to haloperidol. This presentation proposes a procedure to develop a clinically credible and practical method for subtyping of SZ patients and reports some progress in this endeavor: 1. At New York University Medical Center, EEGs were collected from 3 groups of patients diagnosed with SZ using DSM criteria: [a] 15 first episode, never medicated; [b] 25 chronic SZ off medication for 3 months; [c] 94 chronic SZ currently medicated with various drugs; and [d] 134 age matched normal subjects; 2. Using standard scores of QEEG power spectral variables, a subset were selected that showed maximum heterogeneity of variance across the combined SZ + normal group and also spanned the signal space of 134 SZ EEG's defined by Principal Component Analysis; 3. The number of subtypes to be sought was objectively determined by seeking the minimum number which optimally separated SZ from normals, using sequential tests with SPSS K-Means, yielding 5 clusters, with A's, B's and C's in each; 4. Independent analysis of EEGs from 254 SZ from NYU plus 138 from Berlin replicated these subtypes, with members of each cluster from both sites. Brain images reveal that one set of brain regions displays the same type of underactivation in all 5 clusters, while a different set of regions displays 5 different types of hyperactivity. Collaborative endeavor are needed to learn whether membership of a SZ individual within a particular QEEG subtype is predictive of the outcome of treatment with different drugs, i.e., drugs that affect different neurotransmitter systems than those presently targeted.

IMPAIRMENTS IN GAMMA BAND SYNCHRONIZATION AND CONTEXT PROCESSING IN SCHIZOPHRENIA

R. Y. Cho,* R. O. Konecky, C. S. Carter
Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

Cognitive control disturbances lead schizophrenia patients to have impairments in the self-regulation of their behavior. An important aspect of cognitive control that is impaired in schizophrenia is the ability to actively maintain task context information. What are the neural substrates that might underlie such functional deficits? Gamma frequency range synchronization of cortical activation across brain regions has been shown to be associated with various types of information processing, including higher order cognitive processes. In a study of normal subjects employing a task that required cued, active maintenance of context information, wavelet analyses showed increases in gamma band activation in the frontal cortical areas in the condition that had greater demands for active context maintenance. Employing the same task in subjects with schizophrenia, the

present study found that in comparison with controls, schizophrenia subjects exhibited decreased gamma band oscillatory activity in frontal areas in association with their poorer behavioral performance in the condition with increased demand for context maintenance. Analyses of the predictability of behavioral performance by gamma band activity will be presented. These results suggest that deficits in gamma band synchrony in frontal areas may contribute to the impaired context processing in schizophrenia.

MOTION DETECTION IN RELATION TO MT FUNCTIONING IN SCHIZOPHRENIA

B. A. Clementz,* R. Brown, P. Buckley
Psychology, University of Georgia, Athens, GA, USA

Schizophrenia patients have abnormalities during smooth pursuit tasks. It is uncertain whether these abnormalities are related to deficits in motion detection or motor output. The present study used motion perception stimuli (achromatic sinusoidal gratings) to test MT function in schizophrenia. Whole-head (256-channel) EEG was used to record brain activity while subjects viewed the gratings. If there is no difference between schizophrenia (n=14) and normal (n=14) subjects in brain activity during early visual processing stages, through activation of MT, then it can be inferred that schizophrenia patients have no abnormalities in motion perception. Subjects fixated a center cross throughout testing. Gratings randomly appeared to the left or right of fixation moving at 5, 10, or 20 deg/sec. The gratings moved horizontally either toward or away from fixation. Subjects responded with a key press when the gratings moved away from fixation (25% of trials). No response was required when gratings moved toward fixation; these were the trials used to make group comparisons. Data were averaged, baseline adjusted, and time-locked to stimulus presentation using BESA. Minimum norm source estimates were conducted using the method of Dale and Sereno (1993) with a four shell ellipsoidal model. Initial processing of the stimuli began with approximately 90 ms latency, and was contralateral to hemifield of presentation in both groups. Normal subjects had stronger activity in the vicinity of MT both during the initial (170-200 ms after stimulus onset) and later reentrant (310-350ms post-stimulus) activation of this region. Schizophrenia patients had stronger activity in posterior parietal cortex (both laterally and medially) than normal from 300-350ms after stimulus onset. Normal subjects had stronger activity in the vicinity of frontal eye fields beginning about 200 ms after stimulus onset. Normal subjects had stronger activation of MT than schizophrenia patients, indicating that poor smooth pursuit performance in schizophrenia may be associated with deficient activation of motion processing units in extrastriate cortex. Schizophrenia patients, however, had greater activation of posterior parietal cortex than normal, indicating that they may be devoting additional attentional resources to the task and/or using complimentary neural mechanisms to compensate for deficient activation of motion sensitive neurons in response to moving stimuli.

ALTERED AUDITORY RECOVERY CYCLE FUNCTION IN SCHIZOPHRENIA AND BIPOLAR DISORDER: AN EVENT-RELATED POTENTIAL STUDY

N. J. Clunas,* P. B. Ward
Schizophrenia Research Unit, Liverpool Hospital, Liverpool, NSW, Australia

The present study measured the recovery cycle of the auditory N100 event related potential (ERP) component in patients with schizophrenia, patients with bipolar disorder and age- and sex-matched healthy volunteers. Converging evidence from ERP and behavioural studies demonstrates that patients with schizophrenia display deficits in early stages of auditory information processing. It has been suggested that such deficits may reflect altered inhibitory processing. Patients performed a simple visual distraction task while listening to 80 dB SPL, 1000 Hz tones presented via headphones. Tone pairs were presented with an intra-pair (S1-S2) interval of 1, 3, 5 or 7 seconds, with a pseudorandom interpair interval ranging from 9-13 seconds. We previously reported that patients with schizophrenia had significantly reduced N1 amplitudes for S1 stimuli compared to healthy volunteers. For healthy volunteers, N1 amplitudes were reduced for S2 stimuli in 1 s, 3 s and 5 s, but not 7 s, pairs, compared to S1 N1 amplitudes. We also reported abnormal N100 recovery cycles in patients with schizophrenia, characterized by larger N100 amplitudes elicited by S2 stimuli presented at 5 and 7 second intrapair intervals. Preliminary analysis suggests that patients with bipolar disorder also demonstrate altered recovery cycles, with enhanced N100 amplitudes also found in this patient group for longer intrapair intervals. This research was supported by the Australian Rotary Health Research Fund (Ian Scott Fellowship) and the Neuroscience Institute of Schizophrenia and Allied Disorders (NISAD).

EFFECTS OF NICOTINE ON MISMATCH NEGATIVITY IN SCHIZOPHRENIA

D. B. Davalos,* L. F. Martin, R. Freedman
Psychiatry, University of Colorado Health Sciences Center, Denver, CO, USA

Abnormalities of the nicotinic cholinergic system in the brain have been noted in a number of clinical disorders. The higher than average rate of smoking in clinical populations has been theorized as being related to abnormalities in this system. In schizophrenia, the rate of smoking surpasses that of other clinical populations (approximately 80-90% compared to 45-70%). The high rate of smoking, evidence of genetic linkage of schizophrenia to specific nicotinic receptors, and evidence for positive neuropsychological effects of nicotine, all suggest that nicotinic cholinergic mechanisms may play a pathophysiological role in schizophrenia. To assess whether nicotine could normalize early neurophysiological processing in schizophrenia, we studied a measure that has repeatedly been shown to be impaired in this population. The mismatch negativity (MMN) paradigm is an electrophysiological index that has gained interest in recent years as an endophenotype of schizophrenia. MMN measures "preattentive" physiological processes and is elicited by an infrequent change in a repetitive sound. The utility of MMN to assess change in response to pharmacological challenge has been identified by other researchers. However, MMN deficits do not appear to improve with the use of either conventional or atypical medications. Improvements associated with nicotine would suggest a novel change in physiological processing that is unique to nicotinic agonists. To assess the effects of nicotine challenge on MMN amplitude and latency, controls and individuals diagnosed with schizophrenia were administered nicotine gum versus placebo gum during two visits. Subjects underwent a baseline recording on each of the two visits and an additional recording following administration of either nicotine or placebo. Participants were played a series of tones (standard ISI between tones was 500 ms, deviant ISI of 250 ms occurred on average every 20th interval). The average amplitude of MMN waveform elicited by the deviant interval was significantly larger following nicotine administration compared to placebo condition in both the controls and the schizophrenia patients ($p<.02$). In addition, a

significantly greater improvement was noted in the schizophrenia group compared to the controls ($p<.05$). These results are consistent with the idea that pharmacological agents targeting nicotinic receptors may provide unique physiological benefits that are not addressed by current medications.

AUDITORY ATTENTION EVENT-RELATED POTENTIAL ABNORMALITIES AND SCHIZOTYPAL SIGNS IN RELATIVES OF SCHIZOPHRENIA PATIENTS: DO THEY CO-OCCUR IN IMPLICATING GENETIC LIABILITY FOR SCHIZOPHRENIA?

R. B. Force,* N. C. Venables, S. R. Sponheim
Psychology, University of Minnesota, Minneapolis, MN, USA

Electrophysiological abnormalities during processing of auditory stimuli have been considered markers of genetic liability for schizophrenia. If auditory processing anomalies serve as indicators of genetic vulnerability for schizophrenia, one would predict that they covary with subclinical signs of schizophrenia in individuals carrying genetic liability for the disorder. In other words, it is expected that first-degree relatives of schizophrenia patients who exhibit schizotypal symptoms will show evidence of greater event-related potential (ERP) abnormalities during auditory processing than relatives who are without schizotypy symptoms. To test auditory processing abnormalities against this endophenotypic criterion, we administered a dichotic listening task to schizophrenia patients, their first-degree biological relatives, and nonpsychiatric control participants. Tones of four different pitches were presented binaurally to participants. Subjects were instructed to attend to one ear and to press a button whenever they heard the higher pitch of the two tones in the attended ear. Ten percent of all stimuli were targets. Electroencephalography data were recorded from 27 scalp sites with tin electrodes affixed in an elastic cap and referenced to the left ear lobe. Results indicated that first-degree biological relatives of schizophrenia patients did not differ significantly from normal controls in regard to behavioral performance. However, a significant difference was found in the amplitude of the N100 ERP component. The N100, a negative wave occurring approximately 100 ms after the onset of the auditory stimulus, is thought to reflect early attentional processing. Further analyses will test whether N100 amplitude is associated with measures of schizotypy. We will also examine relatives identified as having high schizotypy scores for evidence of early and late electrophysiological abnormalities during auditory attention. Association of electrophysiological abnormalities during auditory processing with schizotypal signs would lend further support for auditory attention dysfunction as being a endophenotype for schizophrenia.

FAILURES OF AFFECT REGULATION IN SCHIZOPHRENIA: ERPS TO EMOTIONALLY EVOCATIVE PICTURES

J. M. Ford,* D. H. Mathalon, T. Rinderknecht, M. B. Johnson, E. M. Gray
Psychiatry, Yale University, West Haven, CT, USA

Patients with schizophrenia often exhibit a narrow range of affective response and are described as having blunted affect. Whether this reflects differences in emotional experience or simply a limited ability to express emotion was addressed directly by assessing brain responses to affectively-laden pictures from the International Affective Picture System (IAPS) using event-related brain potentials (ERPs), in a task-free paradigm. ERPs were collected while patients (DSM-IV schizophrenia) and healthy controls passively viewed 144 pictures drawn from IAPS pictures chosen to represent 6 picture types: high and low arousal images that were positive (e.g., romantic embrace), negative (e.g., baby with facial tumor) and neutral (e.g., cupcake). Each picture was presented for 6 secs. Half of the pictures (72) were presented in the Random condition, in which the 6 picture types were randomly intermixed. The other half of the pictures (72) were presented in the Blocked condition, in which pictures were blocked by valence. No picture was presented twice. The Random condition always preceded the Blocked condition. The Late Positive Component (LPC) to pictures was measured as the average voltage between 500 and 1000 msec post-onset. For the LPC to pictures, there was a significant interaction between Arousal x Valence x Group. In controls, LPC was affected by Arousal x Valence, such that high arousing pictures elicited larger LPCs than low arousing pictures, especially for negative and positive valence pictures. In patients, although there was a main effect of Arousal, the Arousal x Valence interaction was not significant ($p=.27$). Nevertheless, comparison of means revealed that there was an arousal effect for the neutral pictures, with high arousal neutral pictures (e.g., fighter jets) eliciting a larger LPC than low arousal neutral pictures (e.g., cupcakes). There was a Condition x Valence interaction that did not differ by Group, suggesting that the Valence effect was stronger when valence varied randomly, rather than being blocked. These data suggest that patients with schizophrenia have a qualitatively and quantitatively different affective response from healthy controls. While patients are less sensitive to arousal differences among positive and negative pictures, they are more sensitive to arousal differences in neutral pictures.

A COMPUTATIONAL MODEL OF DEVELOPING SCHIZOPHRENIA: PROGRESSIVE DISCONNECTIVITY AND THE LIMITS OF COMPENSATORY MESOSTRIATAL DOPAMINE

K. Garcia,* E. Niebur
Krieger Mind-Brain Institute, Johns Hopkins, Baltimore, MD, USA

Several inherited, developmental, and acquired central nervous system disorders, each a unique combination of neurocytoskeletal, neurochemical, and neurophysiological effects, have in common the progressive incremental corruption of processes that facilitate interneuronal spike train efficiencies critical for oscillatory synchrony of discrete neuronal ensembles. A core feature of these disorders is an increasing dependence on compensatory mechanisms to maintain network synchronization. Specifically, mesostriatal dopamine release kinetics rise towards the upper limit of the functional inverted-U curve (where the apex represents the ideal for optimal function). We propose that schizophrenia represents the increasing reliance on such compensatory mechanisms to an extent that eventually undermines the probabilistic learning rules that guide the linkage between contributing network subprocesses. Long-term potentiation and long-term depression, and therefore inclusion within any neuronal ensemble, becomes less shaped by increasing adaptive efficiencies (through feedback from behavior-response couplings) and, instead, the result of over-driven processes, which become increasingly unstable and chaotic. We are in the process of developing a detailed computational model of our theory. The finished model will include simplified parallel subprocesses represent-

ing the thalamus, areas of cortical integration (sensory, motor, and dorsolateral prefrontal cortex), amygdala, dorsal and ventral basal ganglia, cerebellum, substantia nigra, and the ventral tegmental area. The connectivity of the model will be based on the known anatomy and physiology of the normal system in order to study the effect of connectivity degradation and resultant compensatory mechanisms, in particular, dopamine gating. Conduction-degradation function values are initially set such that spike trains from contributing parallel processes reach neural nodes (populations of integrate-and-fire neurons) with optimal synchrony, resulting in neural ensembles showing robust gamma synchrony. By degrading inter-area communication functions along connecting pathways, increasing interference results in lower outputs, which the system attempts to normalize by boosting the signal-to-noise via elevated striatal dopamine release. With further degradation of the connectivity, a point is reached where further dopamine will not correct for the interference.

AUDITORY INTEGRATION IN SCHIZOPHRENIA

C. Gilmore,* B. Clementz, P. Buckley
Psychology Dept., University of Georgia, Athens, GA, USA

The amplitude of the N1 auditory evoked potential can normally be increased by presenting bursts of steady-state stimuli with frequencies greater than 30-40 Hz, suggesting that N1 indexes information integration over time. However, it is unknown if schizophrenia patients' lower than normal N1 amplitude is a function of a deficit in auditory integration, or whether their N1 response can be altered by increasing information density. The present study tested the hypothesis that schizophrenia-normal differences on the N1 could be reduced/eliminated using bursts of steady-state stimuli below 40 Hz, but due to schizophrenia patients' inability to sustain 40 Hz neural synchronization, a paradoxical decrease in N1 amplitude for rates at or above 40 Hz would occur. Dense-array (256 channel) EEG was recorded while 15 schizophrenia patients and 15 normal subjects were presented 1 kHz tones amplitude modulated at 10, 20, 40, or 80 Hz. Spectral power across time was compared between the schizophrenia and normal subjects. Results showed: 1) increased N1 latency in schizophrenia patients regardless of burst rate, 2) the typical lower N1 amplitude in schizophrenia at the 10 Hz burst rate, 3) a greater increase in spectral power going from the 10- to the 20-Hz burst rate in schizophrenia patients, which essentially eliminated the N1 amplitude difference between groups, and 4) a large increase in spectral power going from 40- to 80 Hz burst rates in normal subjects, while schizophrenia patients showed a drop in spectral power going from 40- to 80-Hz burst rates. These results suggest that a single transient stimulus conveys insufficient information for efficient processing by schizophrenia subjects' neuronal circuitry, but that steady-state stimuli, up to a point, can provide the extra information needed for patients to more normally integrate auditory information. This work was supported by grants from the United States Public Health Service.

CORRELATION OF CLOZAPINE INDUCED QEEG CHANGES WITH CLINICAL RESPONSE IN SCHIZOPHRENIC PATIENTS—A PROSPECTIVE, LONGITUDINAL STUDY

A. Gross,* S. L. Joutsiniemi, R. Rimon, B. Appelberg
Tammiharju Mental Hospital, Tammisaari, Finland

The changes of theta activity (3.5-7 Hz) in the quantitative electroencephalography (QEEG), serum clozapine (CLO) levels, and their correlation with clinical response, measured by the Positive and Negative Syndrome Rating Scale for schizophrenia (PANSS), were examined prospectively in 16 patients suffering from schizophrenia during 18 weeks of CLO treatment. Evaluations were performed in 5 occasions: before commencing of the CLO treatment as the baseline and after one, 3, 10, and 18 weeks of treatment. Doses of CLO starting from 50 mg/day were determined on the basis of clinical response. In the PANSS subscales for positive and for negative symptoms a significant ($p<0.05$) improvement was observed after the first week and in the subscale for general symptoms after three weeks of treatment with CLO. A significant increase in the absolute theta power ($p<0.01$) was found after 3 weeks of CLO treatment in the electrodes over fronto-central scalp area, most distinctly in the midline (FpZ, Fz, Cz). After 3 weeks there were significant inverse correlations between the theta power increase and the changes in PANSS subscales for negative ($p<0.01$) and positive ($p<0.05$) symptoms and after 10 weeks between the absolute theta power increase and the change in PANSS subscales for general ($p<0.05$) and positive ($p<0.05$) symptoms observed. After 18 weeks a trend of inverse correlation between the PANSS subscales of general and negative symptoms and the theta power increase in the right frontocentral and in the midline areas was observed, but not with regard to positive symptoms. There were trends but no significant correlations between CLO treatment response and serum CLO levels. These findings indicate that the change in the absolute theta power in the QEEG fronto-central midline electrodes might be a more sensitive and specific indicator for the CLO treatment efficacy evaluation than the serum CLO level.

DURATION MISMATCH NEGATIVITY IN TWINS WITH SCHIZOPHRENIA

M. Hall,* M. Picchioni, K. Schulze, F. Rijsdijk, U. Ettinger, E. Bramon, R. Murray, P. Sham
Social, Genetic and Developmental Psychiatry, Institute of Psychiatry, KCL, London, United Kingdom

A reduction in the amplitude of an auditory event-related brain potential, mismatch negativity (MMN), have been proposed to underlie the pathophysiology of schizophrenia. In addition, some studies have found a similar decrease in duration MMN amplitude in their biological relatives. Here we report preliminary results from an ongoing investigation of genetic bases of the ERPs in monozygotic (MZ) twins with schizophrenia. We measured MMN to duration increments (deviants 50 msec vs. standards 25 msec). Participants include 14 pairs (11 male, 3 female) of MZ twins concordant for schizophrenia (age mean=42.65, SD=11.94); 5 pairs (3 male, 2 female) of MZ twins discordant for schizophrenia (age mean=28.37, SD=5.87); and 20 pairs (8 male, 12 female) of non-schizophrenic MZ control twins (age mean=33.63, SD=10.17). Linear regression with robust standard errors was used to assess the effect of group on the MMN amplitude, accounting for the correlations within twin pairs. Age, gender were also included in the model. Preliminary analyses indicate that MMN amplitude at FZ, F3 and F4 was significantly smaller in both concordant and discordant twin groups compared with control twins. Affected MZ discordant members had the smallest MMN amplitude (mean= -2.5; SD= 0.27), followed by their unaffected co-twins (mean= -2.54; SD= 0.78) and the MZ concordant pairs (mean= -2.8; SD= 1.12). Control twin pairs have the largest MMN amplitude (mean= -3.62; SD=1.46). There was no significant difference in MMN amplitude between subjects with schizophrenia and unaffected co-twins. These findings support the hypothesis that

reduction in MMN amplitude constitutes a genetic predisposition for schizophrenia.

EVEN RELATED POTENTIALS DURING THE MENSTRUAL CYCLE: IMPLICATIONS FOR SCHIZOPHRENIA

B. C. Heasman,* A. L. Sumich, V. Kumari, N. R. Tunstall, E. Gordon, M. J. Brammer
GKT School of Medicine, London, United Kingdom

Sexual dimorphism is commonly observed in schizophrenia. Men show an earlier age of onset and a preponderance of negative symptoms; women frequently present with coexisting symptoms of depression. Furthermore, schizophrenia symptoms vary according to menstrual cycle phase, with a significant increase in hospital admissions during the premenstrual phase. Some of these differences may be due to the effects of neurosteroids on brain function that have a complex interaction with central brain neurotransmitters implicated in schizophrenia, such as serotonin and dopamine. Identification of changes in brain function across the menstrual cycle (and during menopause) has implications for understanding the aetiology of schizophrenia in women. Event Related Potentials (ERPs) have been used to study brain function in healthy controls across the menstrual cycle and in patients with schizophrenia. The current study employed an international brain function database (www.brainresource.com) to explore the effect of menstrual phase on controlled attention processing, as measured by P3b and N2b ERP components. A visual continuous performance task was performed by 125 women at different phases of the menstrual cycle (n=22 menses days 1-3; n=31 days 4-15; n=26 days 16-22; n=21 days 23-25; n=25 days 26+), 52 postmenopausal women and 306 age-matched men. Significantly higher N2b amplitude was seen during the premenstrual compared to the postmenstrual phase. P3b amplitude dropped towards the end of the cycle. However, differences did not reach conventional levels of significance. Results are compatible with previous studies showing increased N2b in depression and in healthy controls with high levels of paranoia. Reduced P300 amplitude is a common finding in schizophrenia. Future studies should investigate the effects of menstrual phase on ERPs in patient groups.

RECOGNITION OF AFFECTIVE CONTENT: AN EXAMINATION OF EVENT-RELATED POTENTIALS IN SCHIZOPHRENIC PATIENTS

G. F. Heinz,* M. Rubly, C. Leitnaker, F. Jessen, P. Falkai
Psychiatry and Psychotherapy, University of Saarland, Homburg, Saarland, Germany

Recognition and evaluation of affective content in pictures or events is disturbed in schizophrenic patients. But little is known about the basal processes involved: disturbance of information processing in general, or processing of affective information in particular? The aim of this ERP-study was to differentiate between these processes. We examined 24 schizophrenic patients (F20.xx ICD-10, f=12, m=12), and 20 controls (f=10, m=10). All schizophrenics were partially remitted patients of a day-clinic and were on a constant neuroleptic medication for months. As visual stimuli, we gave 12 affective pictures from IAPS: 3 neutral (7010, 7050, 7150), 3 positive (2260, 4610, 5830), 3 negative (3000, 3130, 3140), and as non-affective stimulus a b/w-checkerboard. ERP were collected from Fz, Cz, Pz and from C3, C4, P3, P4. Recording was 500 ms pre- and 1500 ms post-stimulus; bandpass was 0.03 - 70 Hz, digital sampling at 256 Hz. In both groups, the ERP of different affective contents were significantly different ($p<.05$). The differences were correlated with arousal rather than with valence values: higher arousal made larger areas under the curve. These effects occurred in all leads in the time range from 300 to over 1500 ms. Effects were similar in both groups. In contrast to expectation from literature, we found the ERP of schizophrenic patients significantly larger than those of controls (i.e. 12uV vs. 8uV for negative affect). In addition, we found two further differences: i) controls only, but not schizophrenics showed a significant difference between left and right hemispheric ERP (C3, P3 vs. C4, P4); ii) the area between central and frontal leads was significantly larger in patients for all stimuli, and vice versa, the area between central and parietal leads was significantly smaller in patients for all stimuli. These results reveal a more general disturbance in information processing in schizophrenics, rather than a selective disturbance of the processing of affects. This general disturbance of information processing results in a topographic alteration of the ERP for all stimuli: a flatter gradient from central to parietal areas and a lost gradient between left and right hemisphere compared to controls. Granted by Deutsche Forschungsgemeinschaft, He1732/3.

THE EFFECT OF BACKGROUND NOISE AND PREPULSE CHARACTERISTICS ON PREPULSE INHIBITION AND PREPULSE FACILITATION IN NORMAL MALE SUBJECTS: IMPLICATIONS FOR NEUROPSYCHIATRIC RESEARCH

M. H. Hsieh,* N. R. Swerdlow, J. Sprock, D. L. Braff
Psychiatry, National Taiwan University Hospital, Taipei, Taiwan

Both prepulse inhibition (PPI) and prepulse facilitation (PPF) deficits have been reported in schizophrenia patients. However, different laboratories have used different experimental parameters making direct comparison of results difficult. The major aims of this study were to assess in normal subjects the relative contributions of (1) ambient versus 70 dB background noise in assessing PPI and PPF, (2) the effects of continuous versus discrete prepulses in assessing PPF. Nineteen healthy right-handed male subjects were tested for PPI and PPF of the eyeblink component of the startle reflex measured by electromyographic (EMG) recording from the orbicularis oculi muscle. The pulse-alone stimulus was a 40-msec presentation of 115-dB SPL white noise and the prepulses were 86 dB. The primary assessments included the effects of 1) ambient (54 dB) versus 70 dB background noise, 2) continuous versus discrete prepulses in the the PPF condition. Secondarily, other factors were also assessed, including the effect of tones versus white noise prepulses, right versus left eye effects and different interstimulus intervals (ISI) for the PPF condition. Prepulses arising from a lower level 54 dB ambient background noise level versus the 70 dB background induced greater levels of PPI but did not affect PPF. Sessions with continuous prepulses induced higher levels of PPF than those with discrete prepulses. The effect of ISI (4500 msec condition more effective than 2000 msec condition) and a number of interactions were observed for PPF. There was no significant right versus left eye effects across all the measurements. These observations have relevance for studying PPI and PPF deficits in psychopharmacological challenged subjects and in psychiatric disorder patients. It is hoped that these data will help to guide investigators in the selection of optimized parameters in PPI and PPF research in both control and neuropsychiatric patient groups, in order to create maximal useful information and comparability of results from different laboratories.

EVENT-RELATED POTENTIALS IN SCHIZOPHRENIA: SPATIOTEMPORAL FACTOR STRUCTURE IN EMOTION RECOGNITION

T. Indersmitten,* C. G. Kohler, R. C. Gur, R. E. Gur, B. I. Turetsky
Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

Emotion recognition deficits are well established in schizophrenia. However, few studies exist that examine brain related processing of emotional stimuli in schizophrenia. 20 schizophrenia subjects (6 female, 14 male) and 10 healthy controls (4 female, 6 male) had to recognize faces with happy, sad and neutral emotional expressions in mild and extreme intensities. Electrophysiological data was obtained using a 64-channel EEG. Principal Component Analyses were performed yielding 2 spatial and 4 temporal factors. Repeated measures ANOVAs were performed between patient and control groups for behavioral and electrophysiological data. Schizophrenia subjects performed worse on recognition of emotions. During emotion recognition, principal components analyses found fronto-central activations at 120 ms, 240 ms and 540 ms and a posterior activation at 410 ms. Patients had lower activations frontally at 240 ms, specifically for sad faces, and posterior at 410 ms. At 410 ms and 540 ms, emotion specific activations could be found. In addition, severity of negative symptoms, in particular alogia and anhedonia, were negatively correlated with recognition of happy faces and with activation at 410 ms. In schizophrenia subjects compared to controls, we found lower brain activations associated with emotion processing, suggesting a dysfunctional linkage between anterior and posterior areas. Emotion recognition performance and brain activation patterns at 540 ms were related to negative symptoms, suggestive of associations between brain based processing, emotion recognition and experience. NIMH MH01839.

RESTING FRONTAL BRAIN ACTIVATION ASYMMETRY AND SHYNESS AND SOCIABILITY IN SCHIZOPHRENIA

M. K. Jetha,* L. A. Schmidt, J. O. Goldberg
Psychology, McMaster University, Hamilton, ON, Canada

A number of recent studies have shown that the pattern of resting frontal EEG alpha (8 to 13 Hz) asymmetry is predictive of individual differences in affective style in healthy adults and children and some clinically depressed and anxious populations even when their symptoms are in remission. Individuals who exhibit stable patterns of greater relative right frontal EEG activity at rest are known to be at risk for depression and anxiety-related disorders, while individuals who exhibit stable left frontal EEG activity at rest are more successful in regulating stress and are sociable and outgoing. Using recent frontal activation/affective style models as a theoretical platform, we attempted to extend these findings to adults with schizophrenia. The relations among the pattern of resting regional EEG alpha activity, Cheek and Buss trait shyness and sociability, and positive and negative symptoms scores (PANSS) were examined in 20 adults with schizophrenia who attend a community-based treatment and rehabilitation center. Baseline regional EEG was measured continuously for 2 min (1 min eye-open, 1 min eye-closed) using a lycra stretchable cap from the left and right mid-frontal (F3, F4), central (C3, C4), parietal (P3, P4), and occipital (O1, O2) sites. We found that high trait shyness was related to greater relative resting right frontal EEG activity ($p < .05$), whereas high trait sociability was related to greater relative resting left frontal EEG activity ($p < .05$), only in those adults with schizophrenia who were classified as having low positive symptoms. These findings were specific to the mid-frontal asymmetry measure. The relations with posterior asymmetry measures and trait personality measures were not significant. The present findings extend earlier work noting relations between the pattern of resting frontal EEG alpha asymmetry and personality in healthy individuals to a clinical population characterized by major psychosis. Findings are discussed in terms of the use of frontal EEG asymmetry as a metric for personality in schizophrenia.

ALPHA EEG SELECTIVITY PREDICTS EFFICACY OF RTMS IN SCHIZOPHRENIA

Y. Jin,* S. G. Potkin, S. Huerta, A. Kemp, G. Alva, J. Sievers, W. E. Bunney
Psychiatry, University of California Irvine, Irvine, CA, USA

Human alpha EEG has a strong resonant feature. Changes in the EEG activity in schizophrenia have been found to be associated with negative symptoms. The present study showed that individualized rTMS could tune the alpha EEG and improve the negative symptoms. The selectivity of a resonant system can be described by quality factor, Q. For small damping it can be identified with $Q = fp/(f1-f2)$, where fp is the resonant frequency, and f1-f2 is a half-power bandwidth (HPB) around the resonance. Eight first-break drug-naive schizophrenic patients in a separate study showed a significant reduction in alpha EEG slectivity as compared with age and gender matched controls. In this rTMS study, 16 schizophrenic patients with predominantly negative symptoms were included. rTMS rate was set at the alpha EEG resonant frequency. Magnetic pulses (80% motor threshold) were delivered bilaterally through a 9cm circular coil at prefrontal area. Treatment was consisted of 10 daily sessions for active or sham condition followed by a 2-week washout between treatments. During each session, rTMS was given 2 seconds per minute for a total of 20 minutes. Sham stimulation was conducted in the similar manner except that the coil was not plugged into the electricity. A separate coil placed 2 ft away was charged to simulate the acoustic effect of the active stimulation. Clinical symptoms and EEG were evaluated at baseline and after 10 treatments at each condition. Analysis of EEG at Fz revealed a significant increase in alpha EEG selectivity ($Q = 2.60$, $sd = 0.61$; $t14 = 19$, $p = 0.001$) after the active rTMS as compared with baseline ($Q = 2.17$, $sd = 0.42$). Power density at peak frequency was also increased ($p = 0.07$). No significant changes in EEG selectivity and power were found with sham. Using 11 cases who had completed both EEG and clinical evaluations, we found that the clinical improvement in negative symptoms was significantly correlated with the degree of increase in Q factor ($R = 0.61$, $p = 0.04$; $n=11$). These data provide evidence that human alpha EEG can be tuned by direct electromagnetic stimulation. The association between changes in the alpha selectivity and clinical symptoms suggests that the timing (purity and persistence) of rhythmic brain activity may play a critical role in cognitive process. The potential role of EEG tuning in symptom improvement will be discussed in light of other supportive materials.

RELATIONSHIPS BETWEEN N100 AND M100 SENSORY GATING DEFICITS IN SCHIZOPHRENIA

A. P. Jones,* F. M. Hanlon, R. J. Thoma, M. P. Weisend, M. X. Huang, K. Martin, A. Smith, R. A. Yeo, G. A. Miller, J. M. Canive
Psychiatry, New Mexico VA Healthcare System, Albuquerque, NM, USA

A failure to filter out redundant auditory sensory stimuli is a hallmark deficit in schizophrenia. This sensory gating deficit has been

studied in relation to 50 ms and 100 ms responses, extensively with electroencephalography (EEG) at electrode Cz and more recently, and to a lesser degree, with magnetoencephalography (MEG) at superior temporal gyri (STG) sources. Sensory gating of the EEG 50 ms component, P50, and the left-hemisphere MEG 50 ms component, M50, are correlated (Thoma et al., 2003). With simulated and real data, variations in latency, orientation, and strength of the two MEG STG sources have been shown to affect the amplitude of P50 measured at Cz (Edgar et al., 2003). The relationship between the 100 ms sensory gating components for EEG (N100) and MEG (M100) has yet to be thoroughly explored, however. The aim of the present study was to investigate the contributions of gating in each hemisphere using MEG, which has the advantage of localizing dipolar sources, to the gating deficit measured at Cz for N100. 25 controls and 28 schizophrenia patients underwent simultaneous EEG and MEG recording during a standard paradigm utilized to assess sensory gating. Binaural auditory stimuli were presented as pairs of clicks, and a sensory gating ratio was obtained by dividing the response to the second click (S2) by the response to the first (S1). N100 amplitude for S1, S2, and their gating ratio (S2/S1) were calculated. M100 STG dipolar sources were fit to obtain: S1 source strength, angle, projected amount of source strength measured at Cz, S2 source strength, and gating ratio (S2/S1). There were group differences in both sensory gating measures with schizophrenia patients showing an N100 gating deficit as well as a bilateral M100 gating deficit. Gating ratios for N100 correlated with right hemisphere M100 gating ratios, and a trend was found for the left. Thus, poor M100 gating was associated with poor N100 gating. M100 dipoles oriented more towards Cz in controls than in patients, an overall difference across hemispheres for both projected source strength at Cz and dipolar angle. Interestingly, when M100 source strength was projected more towards Cz in either hemisphere, N100 S1 amplitude was higher. M100 dipole orientation at STG may be affecting N100 measurement at Cz. These data suggest that there is a relationship between N100 and bilateral M100 gating deficits in schizophrenia and that further study into this complicated phenomenon is warranted.

P50 SUBCOMPONENT ABNORMALITIES IN SCHIZOPHRENIA: NEUROPSYCHOLOGICAL CORRELATES

S. Keedy,* B. Beenken, M. Marlow-O'Connor, S. D. All, P. Moberg, R. C. Gur, R. J. Erwin
Psychology, Rosalind Franklin University of Medicine and Science, North Chicago, IL, USA

Several studies have reported abnormal suppression of the P50 component of the auditory evoked potential (AEP) in individuals with schizophrenia. Recent work has indicated that P50 is comprised of both bilateral frontal and midline subcomponents (Erwin et al., Biol Psychiatry, 1996; Weisser et al., Neuroreport, 2001). As several studies have linked P50 abnormalities to deficits in attention, the relationship between P50 subcomponent suppression abnormalities and performance on neuropsychological tests of attention was examined. It was hypothesized that greater suppression abnormalities for a midline P50 subcomponent would predict poorer performance on measures of sustained attention (Gordon Diagnostic System Vigilance test). It was also hypothesized that greater suppression abnormalities in bilateral subcomponents would predict poor performance on attention tests that involve, in part, frontal regions (Trailmaking tests, Digit Symbol Coding, and Digit Span). Neuropsychological and AEP data were collected at the Mental Health Clinical Research Center at the University of Pennsylvania. A 32-channel recording array and a paired auditory click paradigm (0.5 sec inter-click interval, 10 sec inter-pair interval) were presented for the AEPs. Spatial and temporal factor analyses performed on AEP data from 37 control subjects confirmed the presence of two spatial subcomponents of P50: a midline component and a bilateral component of frontal regions, as has been reported in previous studies. Integrated amplitudes from these subcomponents were calculated for a sample of 33 individuals with schizophrenia and 35 healthy controls and examined in relationship to neuropsychological measures. The results revealed that the midline subcomponent did not predict any of the sustained attention measures. Abnormalities of the left frontal subcomponent were more strongly related to poor performance on the hypothesized attention measures compared with the right. These relationships were found for Trails B (Pearson r = .37), Digit Symbol Coding (-.70), and Digit Span (-.59) in schizophrenia. The results of this study suggest that abnormalities in a specific subcomponent of P50 may be more strongly linked with observed attention deficits in the disorder. This research was supported by the following grants from the National Institute for Mental Health, MH43880 and MH50344, and by Scottish Rite Fellowships to B. Beenken, S. Keedy and M. Marlow-O'Connor.

AN EVENT-RELATED POTENTIAL STUDY OF THE RELATIONSHIP BETWEEN SCHIZOTYPAL PERSONALITY AND SEMANTIC PROCESSING IN A CATEGORY-VERIFICATION TASK

M. Kiang,* M. Kutas
Dept. of Cognitive Science, University of California, San Diego, La Jolla, CA, USA

To determine whether schizotypy is associated with differences in how categories activate their exemplars during semantic processing, we examined the N400 component of the event-related brain potential (ERP) elicited during a category-verification task. ERPs of 24 healthy volunteers were recorded while they viewed category definitions (e.g. "A type of fruit"), each followed by a target noun that was either a high-typicality exemplar ("apple"), a low-typicality exemplar ("cherry"), or a non-exemplar ("clamp"). Participants indicated whether the target was or was not an exemplar of the category. Schizotypy was assessed via the Schizotypal Personality Questionnaire (SPQ). Overall, N400 amplitude was largest for non-exemplars, smallest for high-typicality exemplars, and intermediate for low-typicality exemplars. SPQ score was associated with decreased N400 amplitude to non-exemplars, and increased N400 amplitude to both high- and low-typicality exemplars. SPQ score was negatively correlated with the differences in N400 amplitude between non-exemplars and both types of exemplars (i.e. N400 category effects), but was not correlated with the N400 amplitude difference between low- and high-typicality exemplars (i.e. the N400 typicality effect). The size of the N400 category effects was negatively correlated with the SPQ Interpersonal factor, but not the Disorganized factor. The results are consistent with an association of higher schizotypy with decreased use of context to activate related items and inhibit unrelated items. The reliable correlation of N400 effects with the SPQ Interpersonal factor but not the Disorganized factor calls into question hypotheses that they reflect semantic processing differences causing disorganized speech, but raises the possibility that such differences may be mediated by suspiciousness. This study was supported by grant HD22614 to M. Kutas from the National Institutes of Health. M. Kiang is supported by a Canadian Institutes of Health Research Postdoctoral Fellowship.

DEFICITS IN PREPULSE INHIBITION OF ACOUSTIC STARTLE ARE ASSOCIATED WITH POSITIVE SYMPTOMS IN JAPANESE PATIENTS WITH SCHIZOPHRENIA

H. Kunugi,* R. Hashimoto, M. Tanaka, H. Hori, T. Nakabayashi, O. Saitoh, N. Hironaka
Departmnet of Mental Disorder Research, National Institute of Neuroscience, NCNP, Tokyo, Japan

Prepulse inhibition (PPI) of acoustic startle response is a measure of sensorimotor gating. Weakened PPI is a well replicated finding in schizophrenics and their unaffected relatives, leading to the use of PPI as an endophenotype in genetic studies. An advantageous of PPI is that it can be studied across species (e.g., rodents, primates, and humans). However, the measure of PPI depends substantially on parameters such as sound pressure levels of pulse and prepulse and prepulse-to-pulse interval. Little information is available on such parametric influences on PPI measure in Asian populations. Furthermore, relationships between PPI and clinical correlates have not well been studied. We examined 21 Japanese patients with chronic schizophrenia (DSM-IV) who received maintenance treatment with antipsychotic medication (mainly typical antipsychotics) and 27 controls matched for age and gender. PPI was obtained by Startle Reflex Test Instrument for humans (Ohara Medical Co., Tokyo, Japan) with interstimulus interval (ISI) of 30, 60, 120 msec, background white noise of 70dB, prepulse of 82, 86 and 90dB for 20 msec, and pulse of 115dB for 40 msec. We obtained 6 recordings for each condition with inter-trial interval of 15 sec. Psychopathology was assessed with Positive and Negative Syndrome Scale (PANSS). Schizophrenics showed a significantly reduced startle response to pulse alone trial, compared to controls. Significantly weakened PPI was observed in schizophrenics compared to controls when ISI was set at 120 msec and prepulse 90dB. Multiple regression analysis controlling for age and gender revealed a highly significant relationship of PPI with positive ($p<0.001$), but not negative, syndrome score assessed with PANSS. Our results suggest that deficits in PPI are detectable in Japanese chronic schizophrenics when appropriate parameters were employed. Such deficits in PPI were suggested to be associated with pathophysiology of positive symptoms in schizophrenia, which is consistent with a few previous studies. The weakened startle response to pulse alone trial observed in the present study has not well been described in the literature, which warrants further investigations.

HIGH DENSITY MAPPING OF VISUAL P300 DEFICITS IN SCHIZOPHRENIA

D. I. Leitman,* J. J. Foxe, V. Leavitt, P. Sehatpour, J. Piesco, D. I. Javitt
Prog in Cog Neuroscience and Schizophrenia, Nathan Kline Institute, Orangeburg, NY, USA

Schizophrenia is an illness that has been characterized by impaired cognitive and emotional functioning as well as profound deficits in sensory perception. Previous research in the illness has shown deficits in basic visual perception as reflected in visual evoked potentials. While a number of auditory studies show P300 deficits, previous studies have yielded mixed results regarding visual P300 deficits with some showing deficits and others not. In this study, 22 patients with schizophrenia and 16 age matched healthy controls performed a standard target detection task in which targets were schematic pictures of animals and standards were check squares. Behavioral data collected included hit and miss rate as well as reaction time. Electrophysiological data was collected using, a high density array consisting of 168 electrodes. These data were subjected to inverse modeling and source analysis. Our results show significant deficits in visual P300 generation in patients relative to controls. Further, source analysis revealed distinct topographic differences in P300 generation between groups. The use of high-density techniques combined with source localization further characterizes the nature of P300 deficits in patients with schizophrenia and provide novel information about higher order visual cognitive deficits in schizophrenia.

MISMATCH NEGATIVITY DEFICITS ARE ASSOCIATED WITH COGNITIVE, CLINICAL, AND FUNCTIONAL IMPAIRMENTS IN SCHIZOPHRENIA PATIENTS

G. A. Light,* N. R. Swerdlow, J. Sprock, M. H. Hsieh, D. L. Braff
Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA

Schizophrenia patients have widespread information processing deficits ranging from abnormalities in sensory registration to impairments in cognition and everyday functioning. Mismatch Negativity (MMN) is an EEG waveform that is automatically elicited by infrequent, oddball stimuli (P=10%) that occur during the presentation of frequent (P=90%) stimuli. MMN can be elicited in the absence of directed attention. It is presumed to represent a largely preattentive probe of the earliest stages of cognition. We have previously demonstrated that MMN deficits in schizophrenia: 1) have high 1-2 year retest reliability; and 2) are associated (e.g., r=-0.65) with impairments in everyday functioning. MMN deficits have also been reported in relatives of schizophrenia patients. The aims of the present study were to determine if MMN deficits are associated with downstream impairments in cognition, clinical symptoms, and everyday functioning. Schizophrenia Patients (n=100) and normal comparison subjects (NCS, n=75) were tested on MMN, cognitive, clinical, and functional measures. Relative to the NCS, schizophrenia patients had significantly reduced MMN ($F=113.7$, $p<0.0001$). Indeed, 99 of the 100 schizophrenia patients had MMN amplitudes that were below the mean amplitude of the NCS. Patients were then classified into subgroups on the basis of the magnitude of their MMN deficits (Fz). The subgroup with moderate-to-severe MMN deficits were significantly older ($p<0.01$), had a longer illness duration ($p<0.05$), and performed worse on tests of working memory ($p<0.001$) and verbal learning ($p<0.05$) relative to the subgroup of patients with mild to moderate MMN deficits. Similarly, the most MMN-impaired schizophrenia patients also had relatively higher levels of negative symptoms ($p<0.05$), performed worse on measures of functional capacity ($p<0.05$), had lower global functional status ($p<0.001$), and were less likely to live independently ($p<0.001$). No significant differences were observed between the MMN-derived subgroups of schizophrenia patients on other demographic, cognitive, or clinical variables. These results support the view that deficits at the earliest stages of sensory preattentive information processing reflect a core neural substrate dysfunction that is associated with cognitive, clinical, and functional deficits of schizophrenia patients. These MMN deficits may also play a role in assessing medication response and the genetic architecture of schizophrenia.

EFFECTS OF PRENATAL EXPOSURE TO NICOTINE ON MISMATCH NEGATIVITY IN YOUNG INFANTS

R. Lipmanson,* D. B. Davalos, R. Hood, R. Freedman, R. G. Ross
University of Colorado Health Sciences Center, Denver, CO, USA

Schizophrenia is closely associated with increased tobacco use and with an abnormal mismatch negativity (MMN) response. While prenatal exposure to nicotine is linked to a constellation of negative cognitive and behavioral outcomes in children and adults, its effect on brain structure and function in infants is unclear. In this study, sensory gating in young infants who had been exposed to nicotine in utero was compared to those of unexposed infants; it was hypothesized that the nicotine-exposed group would exhibit a diminished MMN response. 25 infants (4 of whose mothers smoked and 21 of whose mothers did not smoke during their pregnancy) heard two series of tones in which the standard-interval series was randomly interrupted by tones at set deviant intervals, either "easy-to-detect" (50% temporal deviance) or "hard-to-detect" (15% temporal deviance). Evoked response potentials for the deviants were analyzed using the MMN paradigm. For the "easy-to-detect" interval duration deviant, the mean MMN amplitude at Pz was significantly smaller for infants who were exposed to nicotine in utero than for those who were not, and this trend was observed at Cz for the "easy" deviant (Pz: $t = -2.91$, $p = 0.014$; Cz: $t = -2.02$, $p = 0.074$). Preliminary findings indicate that fetal nicotine exposure impairs auditory temporal processing in young infants, and support the involvement of nicotinic mechanisms in physiological abnormalities associated with risk for schizophrenia. Further investigation with a larger sample size of infants whose mothers smoked during their pregnancy is recommended to verify these results. Grant Support: Grant support from the Department of Health and Human Services (5 T35 DK07496, 1 R21 MH67382, 2 R01 MH56539) and the Department of Veterans Affairs.

P50 SENSORY GATING IN SCHIZOPHRENIA AND SECOND GENERATION ANTIPSYCHOTICS

B. Lu,* F. M. Hanlon, R. J. Thoma, M. P. Weisend, M. X. Huang, K. Martin, J. C. Edgar, G. A. Miller, J. M. Canive
Psychiatry, University of New Mexico Health Sciences Center, Albuquerque, NM, USA

Introduction: P50 gating is the most common paradigm used to assess sensory gating or filtering of auditory stimuli. In schizophrenia patients, the P50 amplitude to the second of a paired-click stimulus exhibits little reduction, compared to controls. Such gating deficit is described as an increase in the ratio of second click (S2) amplitude over that of the first click (S1). Studies have shown that conventional antipsychotics do not alter the gating ratio, whereas clozapine and other atypical antipsychotics may normalize it to some degree. However, sample size and range of medications in these studies have been relatively small. Methods: To explore whether modulation of the gating deficit is medication-specific, P50 gating data from 48 controls and 37 schizophrenia patients (10 haloperidol, 3 olanzapine, 10 clozapine, 8 risperidone, 6 quetiapine). All the patients had been treated with the same medication for at least 3 months. Subjects were run on a standard auditory paired-click paradigm (ISI = 500ms) during EEG. Results: As a group, schizophrenia patients had worse sensory gating (higher gating ratios) than controls: average control=.41, patient=.58, p=.023. Schizophrenia patients were divided into medication groups resulting in the following averages: haloperidol=.65, olanzapine=.65, clozapine=.63, risperidone=.56, quetiapine=.40. Each medication group was then compared separately to the control group: haloperidol p=.022, olanzapine p=.125, clozapine p=.055, risperidone p=.217, quetiapine p=.909. Conclusions: As expected, patients on conventional antipsychotics (haloperidol) gated significantly worse than controls. In agreement with past reports, olanzapine and risperidone are not effective in restoring gating. Contrary to previous studies showing normalized gating subsequent to effective clozapine treatment, the high gating ratio in the clozapine group is puzzling but may be accounted by not controlling for treatment response. Finally and most intriguingly, quetiapine (not previously studied) is associated with sensory gating ratios essentially indistinguishable from the controls, albeit the small number of subjects. Larger scale studies on the effects of antipsychotic medications on sensory gating are likely to provide additional insight into the neurotransmitters involved in the gating machinery as well as neurophysiological phenomena in schizophrenia. This work has been supported by NIH and AstraZeneca.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) INCREASES GAMMA DRIVING IN HALLUCINATING SCHIZOPHRENIC PATIENTS

D. H. Mathalon,* R. S. Hoffman, J. M. Ford
Psychiatry, Yale University, West Haven, CT, USA

When stimulated with periodic sounds, neural circuits involving thalamus and auditory cortex behave like tuned oscillators synchronized to input frequency. Patients with schizophrenia are specifically deficient at synchronizing EEG frequency at ~40 Hz in the gamma band (20-80Hz), perhaps reflecting deficient auditory system recurrent inhibition, and computational inflexibility. We asked whether this would be affected by rTMS therapy in patients with treatment resistant auditory hallucinations. We recorded EEG from 38 patients with DSM-IV schizophrenia (SZ) and 13 normal comparison subjects (NC). Of the 38 SZ patients, 11 were non-hallucinators and 27 had chronic, treatment-resistant hallucinations. Of these, 15 underwent a course of 1Hz rTMS delivered to one or more cortical regions underlying speech processing and were retested with EEG. EEG data were recorded while subjects listened to 3 sequences (20, 30, 40Hz) of pulsed click trains. EEG power from 1 to 50Hz was calculated for each 1Hz bin using a Fast Fourier Transform. The power in the entire EEG band (1-50Hz) was normalized, so that power in each bin was calculated relative to all the others. For each click sequence, there was a significant effect of Bin, revealing that the 20, 30 and 40Hz stimulation resulted in the greatest power in the EEG spectrum around 20, 30 and 40Hz, respectively. For the 30 and 40Hz driving conditions, there was a significant NC/SZ x Bin interaction revealing that controls had greater relative power than patients in the ~30Hz ($p<.0001$) and ~40Hz ($p<.0001$) bins, respectively. Treatment with rTMS significantly improved the severity of auditory hallucinations in these patients, ($p<.05$). In addition, treatment with rTMS, increased the EEG power in the 30Hz and 40Hz ranges during 30Hz and 40Hz sequences, respectively ($p<.05$, one-tailed), although the amount of improvement was not related to increased EEG power. Gamma may reflect computational flexibility of neural circuits that emerges from local resonance of inhibitory networks. If auditory hallucinations express a "locked-in" activation state of a distributed neural network then neural resources available for gamma-resonant

processes could be reduced. "Suppressive" 1Hz rTMS delivered to receptive language areas might disrupt this state, thereby allowing more fluid and flexible responses to both internal and external inputs to these areas.

ABNORMAL GAMMA BAND NEURAL SYNCHRONY INDEXES DISORDERED PERCEPTION AND COGNITION IN SCHIZOPHRENIA

R. W. McCarley,* K. M. Spencer, P. G. Nestor, R. Perlmutter, M. A. Niznikiewicz, M. C. Klump, M. Frumin, M. E. Shenton
Psychiatry, VAMC/Harvard, Brockton, MA, USA

Many current views of schizophrenia, including our own, suggest that it results from abnormalities in neural circuitry, but empirical evidence in the millisecond range of neural activity has been difficult to obtain. We previously demonstrated that schizophrenia is associated with abnormal patterns of stimulus-evoked phase-locking of the EEG in the gamma band (30-100 Hz; Spencer et al., *J. Neurosci*., 2003). These patterns may reflect impairments in neural assemblies, which have been proposed to use gamma band oscillations as a mechanism for synchronization. In the present study we used a visual gestalt stimulus in 20 chronic schizophrenia patients (SZ) and 20 healthy control subjects (NC), who pressed separate buttons to indicate perception of an illusory square or its absence. Phase-locking was used as a measure of neural synchrony in the EEG, and was computed separately on stimulus-locked and response-locked single trials. The Morlet wavelet transform was applied to the 20-100 Hz frequency range of the EEG on correct-response trials for stimulus-locked epochs and response-locked epochs (response onset was start of the epoch). Confirming our previous study, SZ failed to show a stimulus-locked gamma oscillation in occipital electrodes. In what we believe to be a novel finding of the present study, both NC and SZ showed an oscillation that was phase-locked to reaction time. However, the frequency band of this oscillation was significantly lower in SZ (22-24Hz) than in NC (31-44Hz). Furthermore, the stronger this abnormal frequency band of phase-locking, the more SANS/SAPS/PANSS visual hallucinations, thought disorder, and disorganization in the SZ. There were no correlations with medication. The RT-locked oscillation may reflect processes associated with conscious perception and feature binding of the stimuli prior to response. These data suggest that, while synchronization must occur for perception of the Gestalt, it occurs at a lower frequency in SZ due to a reduced capability of neural networks to support high-frequency synchronization, an abnormality strongly associated with fundamental SZ symptoms. These data support our hypothesis of a fundamental deficit in SZ neural circuitry supporting synchronization, which we suggest may be related to abnormalities in NMDA neurotransmission and inhibitory interneurons (Grunze et al., *J. Neurosci*., 1996; McCarley et al., *Eur.Arch.Psych.Clin.Neurosci*., 1999).

A COMPARISON OF AUDITORY CONTINUOUS PERFORMANCE AND ATTENTIONAL MODULATION OF PREPULSE INHIBITION IN SCHIZOPHRENIA: A PILOT STUDY

A. F. Moates,* L. E. Hong, G. K. Thaker
Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD, USA

Prepulse inhibition (PPI) of the startle reflex is thought to be an important biological marker for the liability for schizophrenia. Several studies have shown attentional modulation of PPI. However, it is unclear whether the effect is due to an abnormality in sustained attention in the patients or their inability to modulate the PPI during increased attentional loads, or both. In this study we tested attentional modulation of PPI as well as sustained attention using a modified version of the auditory continuous performance task (CPT). We hypothesized that patients would show deficits in attentional modulation of PPI compared to healthy controls. We further hypothesized that attentional modulation of PPI is correlated to ability to sustain attention in the auditory domain as measured by the auditory CPT. During the auditory CPT task subjects were asked to respond to one of three tones subtly differing in pitch. The level of sustained attention was evaluated by d′, calculated by hit and false alarm rates. The PPI paradigm included auditory stimuli presented in 120 ms, 240 ms, and 4500ms prepulse-pulse inter-stimulus intervals (ISI), intermixed with pairs of prepulse-prepulse sounds. Participants were tested in two sessions, 3-7 days apart. In the attended condition they were asked to respond to the pairs of prepulse sounds by button pushing, and in the relax condition were asked simply to relax. The presentation of experimental conditions was randomized across subjects. A preliminary analysis in the first five healthy controls and five patients with schizophrenia showed that suppression of startle response was less in patients in 120 ms ISI (p=0.68, ns, effect size = 0.52), 240 ms ISI (p=0.02, statistically significant, effect size = 0.71) compared to healthy controls. The two groups were similar in 4500 ms ISI (effect size = 0.1). There was no significant group differences in attentional effect (condition by group interaction)in this small sample of subjects. Attentional modulation of PPI (the difference between attended and relaxed conditions) appeared to be correlated to the level of sustained attention (d′ of auditory CPT) in 4500 ms ISI (Pearson's r=0.83, p=0.03), suggesting sustained attention may help the facilitation of startle response in 4500 ms of ISI. Data collection is on-going and larger sample sizes are necessary to determine the effect of attention on prepulse inhibition in patients and healthy controls.

INTERACTION OF DRIVEN OSCILLATORY NEURAL ACTIVITY AND VISUAL EVOKED POTENTIALS IN SCHIZOPHRENIC PATIENTS

S. Moratti,* A. Gao, B. A. Clementz, P. Buckley
Clinical Psychology, University of Konstanz, Konstanz, Germany

Event related brain potential studies in schizophrenia research often report later and smaller responses to transient stimuli compared to normal subjects. A possible explanation for this effect is that excitatory drive on and/or coordination between neurons firing in relation to a transient stimulus is suboptimal among schizophrenia subjects. Another possibility is that differences in background EEG activity account for reduced evoked responses in patients since higher background brain activity results in smaller response amplitudes. The aim of the present work, therefore, was to induce similar background neural firing in schizophrenia (n=15) and normal (n=15) groups by using visual steady-state evoked potentials. A 12.5Hz luminance modulated checkerboard was presented simultaneously in the left and right visual fields for a period of 2sec to induce the steady-state response. A transient stimulus was presented centrally either 240ms before or 240ms, 480ms or 720ms after offset of the flickering checkerboard. Dense array (256-channel) EEG data were used to quantify subjects' neural responses to steady-state and transient stimulus presentation. Patients and controls exhibited the same steady-state response indicating that we successfully induced equal neural background activity in the visual system. The reduction of the N1 amplitude of the

transient stimulus during and after the steady-state stimulus decreased with increasing distance in time. The recovery slope was faster for controls than for patients. The P2 also recovered over time but schizophrenic patients did not show such a strong reduction during and shortly after the steady-state offset as did normal subjects. These data indicate that recovery from stimulation is a major determinant of evoked response amplitudes, and schizophrenia and normal subjects recover at different rates from visual stimulation. Differences between-groups in evoked response amplitudes, therefore, must be considered within the context of ongoing brain activity.

AN ERROR-RELATED NEGATIVITY STUDY OF REINFORCEMENT LEARNING IN SCHIZOPHRENIA

S. E. Morris,* E. A. Heerey, B. M. Robinson, J. M. Gold
VA Maryland Health Care System, VISN 5 Mental Illness Research, Education and Clinical Center (MIRECC), Baltimore, MD, USA

The purpose of this study was to examine changes in brain activity that accompany learning in schizophrenia using the error-related negativity (ERN) component of the event-related brain potential and an innovative probabilistic learning task developed by Holroyd and Coles (2002). We recorded response- and feedback-related ERNs while participants performed a task in which they learned picture-response pairs via trial-by-trial feedback consisting of a small financial reward or penalty. The stimuli varied in the consistency with which they were mapped to a response. For stimuli in the 100% condition, correct responses were invariantly rewarded. In the 80% condition, correct responses were rewarded on 80% of trials and penalized on the remaining trials. In the 50% condition, rewards and penalties were given on a random basis. Preliminary analyses suggest that schizophrenia patients and normal comparison subjects differ in their patterns of ERN amplitude in these conditions. Consistent with previous reports, normal comparison subjects exhibited a feedback-related ERN when response accuracy was uncertain (i.e., in the 50% condition) and when negative feedback was unexpected (i.e., following invalid error feedback in the 80% condition). Schizophrenia patients' ERN was reduced in amplitude compared to normal comparison subjects and did not show differentiation between positive and negative feedback. Interpreted in the context of the reinforcement learning theory of the ERN, these findings may reflect impairment in schizophrenia patients' ability to monitor and predict the success and failure of ongoing events, possibly due to disturbance in the function of the midbrain dopamine system.

P50 GATING IN SCHIZOPHRENIA AT 500 AND 100 MSEC INTERVALS IN TYPICAL ANTIPSYCHOTICS VERSUS CLOZAPINE

H. T. Nagamoto,* L. E. Adler, M. A. Kisley, R. A. Hea, E. Cawthra, J. M. Griffith, K. A. McRae, R. Freedman
MHS and VISN 19 MIRECC, Denver VA Medical Center, Denver, CO, USA

Sensory gating as measured by the vertex P50 auditory evoked potential has been shown to be abnormal in schizophrenic patients, whether acutely ill and unmedicated or clinically stable and treated with typical antipsychotic medications. This finding has been shown to be most robust at a 500 msec interstimulus interval (ISI) between the conditioning (S1) and testing (S2) stimuli in a paired stimulus paradigm. In previous studies (1), clinically stable schizophrenic patients who demonstrated abnormal P50 gating at a 500 msec ISI showed gating in the normal range at a 100 msec ISI. P50 evoked potentials were recorded in 11 acutely ill and 15 clinically stable schizophrenic patients (all treated with conventional antipsychotics) and 22 normal controls without any family history of mental illness. At the 500 msec interval, both groups of schizophrenic patients showed deficient sensory gating as measured by P50 ratios [(S2/S1) X 100] that were significantly higher than the normal controls (ANOVA P50 ratio by group, Tukey HSD multiple comparisons, $F=11.926, df(2), p<0.01$). At the 100 msec interval, the acutely ill schizophrenic patients showed deficient P50 gating with higher P50 ratios than the clinically stable schizophrenic patients and normal controls (ANOVA P50 ratio by group, Tukey HSD multiple comparisons, $F=6.472, df(2), p<0.01$). These findings in patients treated with typical neuroleptics are in contrast to those with clozapine (2,3), which has been shown to improve P50 gating in schizophrenic patients to normal levels at the 500 msec interval but have variable effects at the 100 msec interval. 1. Nagamoto HT, Adler LE, Waldo MC, Griffith J, Freedman R (1991): Gating of auditory response in schizophrenics and normal controls: Effects of recording site and stimulation interval on the P50 wave- *Schizophrenia Research* 4:31-40. 2. Nagamoto HT, Adler LE, Hea RA, Griffith JM, McRae KA, Freedman R (1996): Gating of auditory P50 in schizophrenics: Unique effects of clozapine- *Biological Psychiatry* 40:181-188. 3. Nagamoto HT, Adler LE, McRae KA, Huettl P, Cawthra E, Gerhardt G, Hea R, and Griffith J. (1999): Auditory P50 in schizophrenics on Clozapine: Improved gating parallels clinical improvement and changes in plasma 3-methoxy-4-hydroxyphenylglycol- *Neuropsychobiology*, 39:1, 10-17.

HYPER-PRIMING IN FIRST EPISODE SCHIZOPHRENIA

M. A. Niznikiewicz,* V. Paytner, L. Lucia, P. Nestor, M. Shenton, R. W. Mccarley
Psychiatry, Harvard Medical School, Boston, MA, USA

It has been hypothesized that schizophrenia (SZ) is associated with abnormal activation in semantic networks. Word-pair priming paradigms have been used to probe processes in semantic networks in schizophrenia, with those employing short (under 500 msec) stimulus onset asynchrony (SOA) tapping initial processes of activation. More recently, they are often used in conjunction with event related potentials. The N400 component peaking about 400 msec, post-stimulus, associated with the ease of forming a semantic link between words, have been used in such paradigms as a dependent measure. In this study, we used a short SOA word pair paradigm to study processes of activation in semantic networks. Stimuli consisted of 140 word pairs. The first word of a word-pair was always an English word, the second was either related (35 words), unrelated (35 words) relative to the first word, a non-word (35 items), or a random letter string (35 items). The SOA was 450 msec. Subjects indicated if the second word was an English word or not. To date, we studied 8 first episode patients, and 8 normal control subjects. More data are being collected. All subjects were male, right handed with English as their first language. The EEG was recorded to a second word in a word pair using 64-channel electrocap. Individual averages to four word types were constructed off-line over -100 to 900 msec, post-stimulus epoch. N400 amplitude was less negative to both related and unrelated words in the chronic and first episode patients relative to NCs (for both related and unrelated condition FE vs NC $p < .01$); at Cz: related condition: NC: -.5 microV, FE: 4.4 microV; unrelated condi-

tion:NC:-.8 microV, FE:3.5 microV. Thus, less effort, as indexed by N400, was necessary for the patients to form a semantic link with the preceding word, consistent with the hypothesis of overactivation in semantic networks in schizophrenia. These data suggest that this dysfunction exists at the illness onset and, in conjunction with our earlier findings of semantic overactivation in SPD (Niznikiewicz et al., 2002), indicate that abnormal spread of activation may characterize schizophrenia spectrum and is not related to frank psychosis.

NO ABNORMAL SENSORY GATING IN CHRONIC USERS OF CANNABIS

B. Oranje,* S. Bijl, C. C. Gispen-de Wied, M. N. Verbaten
Psychiatry, Bispebjerg University Hospital, Copenhagen, Denmark

Cannabis is used in a growing group of teenagers and young adults worldwide. A causal relationship between Cannabis use and schizophrenia is often suggested, but remains still controversial. The aim of this study was to investigate whether similar attentional anomalies are present in a group of chronic users of Cannabis, as are commonly found in patients with schizophrenia. In this respect, the sensory and sensorimotor gating of a group of 16 (male) heavy and chronic users of Cannabis was compared to that of a group of age and gender matched Cannabis naive controls. The mean use of Cannabis among the heavy users was 2.65 grams per week, spread over an average of 6 days, for an average period of 7 years. No differences in any of the parameters of P50 suppression (sensory gating) and prepulse inhibition of the startle reflex (sensorimotor gating) were found between the two groups. These results indicate that heavy and chronic use of Cannabis does not automatically lead to a deterioration of cognitive processes towards schizophrenia.

EFFECTS OF RIVASTIGMINE ON REM SLEEP EEG SPECTRAL ANALYSIS IN PATIENTS WITH SCHIZOPHRENIA: PRELIMINARY RESULTS

J. Poulin,* S. Chouinard, E. Stip, F. Guillem, R. Godbout
Psychiatry, University of Montreal, Montreal, QC, Canada

Objective: Previous results show that rivastigmine, an acetylcholinestrerase inhibitor, added to atypical neuroleptics treatment in patients with schizophrenia increases waking during sleep, a marker of increased cholinergic activity (Poulin et al., 2004). The present study aims to evaluate the effects of rivastigmine on REM sleep EEG spectral analysis in patients with schizophrenia. Methods: The sleep of 13 patients with schizophrenia stabilized with atypical neuroleptics (11M, 2W, 29.7 +/- 6.3 years old) was recorded for two consecutive nights in a sleep laboratory and for a third night following 12 weeks of rivastigmine treatment. Posology of rivastigmine increased from 3mg/day to 6 mg/day during the first month to progressively increase at 9mg/day, taken at mealtime. Medication was generally well tolerated. All participants had a 19-electrodes EEG montage referenced to linked earlobes. Night two (baseline) and night 3 (rivastigmine) were visually scored according to Rechtschaffen and Kales (1968). Fifteen four-seconds epochs (60 sec) of artefact-free EEG were selected from the first three REM sleep periods of both nights. Spectral analysis was performed using Fast Fourier Transform with a cosine window smoothing and a resolution of 0.25 Hz. Absolute and relative ([Band power/total power] * 100) power amplitude of five EEG bands were extracted: Delta (0.75-3.74Hz), Theta (4.00-7.75Hz), Alpha (8.00-12.75Hz), Beta1 (13.00-19.75Hz) and Beta2 (20.00-30.00Hz). EEG bands were compared between night 2 (baseline) and night 3 (rivastigmine) using paired T-tests. Results: After rivastigmine treatment, relative and absolute alpha EEG activity increased for Fp2, F4, F7, and T3 and relative delta activity decreased for F8 and T3. Conclusion: The presents results show that rivastigmine treatment increases alpha activity and decreases delta activity in anterior derivations during REM sleep. It have been proposed that REM-alpha activity reflect micro-arousals during REM sleep (Cantero et al., 2000) and that cholinergic release blocks the hyperpolarisation underlying delta activity (Steriade et al., 1990). Thus, as for increased waking during sleep previously demonstrated, increased alpha activity and decreased delta activity during REM sleep could be a marker of increased cholinergic activity. Further research will evaluate the relationships between REM sleep EEG spectral analysis and cognitive performance after rivastigmine treatment.

SEXUAL DIMORPHISM OF P3B IN DEPRESSED PATIENTS WITH SCHIZOPHRENIA

M. Rodriguez,* A. L. Sumich, B. C. Heasman, M. J. Brammer, T. Sharma, V. Kumari
Psychological Therapy Services, New Ham Trust, London, United Kingdom

Reduced amplitude of the P300 event-related potential (ERP) evoked in an auditory oddball task is reliably found in schizophrenia. However, differences in topography and asymmetry may depend on the sex and syndrome. For instance depression, which is reported more often in women, is associated with reduced frontal P300 amplitude. Withdrawn syndrome is seen predominantly in men, however, and is associated with reduced right parietal P300 amplitude. Furthermore, reduced frontal and right temporo-parietal amplitude are associated with affective symptoms in major depression. However, findings reported in the literature are apparently conflicting. For example, neuroimaging findings suggest temporal lobe volumes are larger in depressed schizophrenia patients. This supports findings of increased posterior P300 amplitude in major and subclinical depression, which is reliably reported in women. Sexual dimorphism in major depression suggests there may be distinct aetiologies for men and women. However, sex differences associated with depressive symptoms in schizophrenia patients have not been studied. The current study investigated sexual dimorphism of P3b amplitude in 13 depressed schizophrenia patients (scoring greater than 2 on the Calgary Depression Scale (8 men) compared to 16 non-depressed patients (scoring less than or equal to 2 on CDS) (n=9 men). P3b amplitude was measured in response to target stimuli in an auditory oddball task which also included novel stimuli. Only the response to target stimuli is reported here. Groups did not differ significantly in mean age or years of education. Sex specific analysis was performed using repeated measures analysis of variance (within subject variables = hemisphere (left, right) and coronal site (anterior, central, posterior) to test for differences in P3b amplitude between depressed groups. There was a significant main effect of group and coronal site*group interaction in women but not in men. Depressed women had higher amplitudes at central and posterior sites than non-depressed women. There was a significant hemisphere*coronal*group interaction in men. Depressed men had lower P300 amplitudes at right temporal (T3) sites than non-depressed men. Results support studies showing sexual dimorphism for P3b amplitude in major depression. Understanding sex differences in the aetiology of depression may lead to more effective treatments, tailored to the gender of the patient.

AUDITORY N1 AND HESCHL'S GYRUS IN FIRST HOSPITALIZED AND CHRONIC SCHIZOPHRENIA

D. F. Salisbury,* K. C. Collins, N. Kuroki, M. E. Shenton, R. W. McCarley
Cognitive Neuroscience, McLean Hospital Harvard Medical School, Belmont, MA, USA

The mismatch negativity event-related potential (ERP) reflects the preattentive detection of auditory stimulus deviance through an automatic comparison process. Recent data reveal associations between mismatch negativity amplitude and the cortical gray matter volume of left hemisphere primary auditory cortex (Heschl's gyrus, HG) in first hospitalized schizophrenia patients. Further, both measures show highly correlated progressive reductions during the first few years of the disease. To assess whether such relationships were present for endogenous auditory potentials directly reflecting sensory characteristics of the stimuli, the N1 ERP and HG volumes were examined in first hospitalized patients, chronic patients, and younger- and older-matched controls. 55 first hospitalized schizophrenia patients and 55 age-, sex-, and parental socioeconomic status-matched controls, and 56 chronic schizophrenia patients and 53 matched controls underwent ERP testing. N1 was measured in response to standard 1 kHz tones in an auditory oddball paradigm from 28 scalp electrodes, but only the midline sites (Fz, Cz, Pz) are reported here. Between group factors were illness, chronicity, and stimulus (over the 10 years of data collection the auditory stimulator changed once). N1 was reduced in schizophrenia ($p < .001$). It was smaller in first-episode patients relative to their controls ($p < .04$) and chronic patients ($p < .001$). Patients, however, did not differ from each other ($p > .24$). 25 first hospitalized patients and 29 younger-matched controls were followed longitudinally to assess any time-related changes. N1 did not show time-related changes in either group. Finally, there were no significant correlations between N1 amplitude and HG volume at first hospitalization, or at retest. Changes in N1 amplitude did not correlate with changes in HG over time. N1 is reduced at first hospitalization for schizophrenia, but is not correlated with underlying primary auditory cortex volume. Though HG shows time-related reductions, N1 does not. Hence, N1 is abnormal in schizophrenia, and reduced at first hospitalization, but does not serve as a index of underlying structural integrity of primary auditory cortex.

AUDITORY P300 IN BIPOLAR DISORDER: A FAMILY STUDY

K. Schulze,* M. Hall, E. Bramon, N. Marshall, C. McDonald, R. M. Murray
Psychological Medicine, Institute of Psychiatry, London, United Kingdom

Auditory event related potential (ERP) measures, including the P300 wave, are promising potential endophenotypic markers of schizophrenia. Patients with schizophrenia show P300 delay and amplitude reduction with robust effect sizes of -0.57 and 0.85 respectively (Bramon et al., 2004). Similar deviances can be observed in unaffected relatives of patients with schizophrenia. Family, twin, and adoption studies suggest that schizophrenia and bipolar disorder may share susceptibility genes, but to date ERPs have been far less studied in samples of patients with bipolar disorder. In this ongoing investigation, we collected P300 using an auditory oddball paradigm in patients with BPI disorder (N=22) from families with multiple cases of BPI or other functional psychotic illness, unaffected first degree relatives of patients (N=22) and unrelated controls (N=29) without personal or family history of bipolar or psychotic disorders. Patients were tested outside of acute episodes when stable. Linear regression analyses with robust standard errors controlling for the effects of age and gender were used to test differences in P300 (at Pz) amplitude and latency between the groups. Non-independence of observations from within families was accounted for in the analyses. Preliminary results indicate that there were no significant differences in P300 amplitude between patients or relatives and controls. There was a trend for both patients ($p < .10$) and relatives ($p < .14$) to show prolonged P300 latency. If these results are borne out in the total sample, this would suggest that while P300 amplitude reductions may be vulnerability markers for schizophrenia, such deviances may not be shared to the same extent by non-acute patients with bipolar illness. Prolonged P300 latency on the other hand may be characteristic of both patient groups. Bramon, E., Rabe-Hesketh S., Sham P., Murray R. M., Frangou S., 2004. Meta-analysis of the P300 and P50 waveforms in schizophrenia. *Schizophr Res.* 70, 315-329.

EARLY AND LATE GAMMA BAND ABNORMALITIES IN SCHIZOPHRENIA PATIENTS AND THEIR FIRST-DEGREE BIOLOGICAL RELATIVES DURING VISUAL SUSTAINED ATTENTION

S. R. Sponheim,* E. M. Bernat
Minneapolis VA Medical Center, Minneapolis, MN, USA

Researchers using tasks requiring the identification of difficult to perceive stimuli have revealed visual sustained attention deficits in schizophrenia patients and their first-degree relatives. Thus, electrophysiological activity associated with discerning degraded objects may provide important evidence for the neural expression of genetic liability for schizophrenia. Several studies have shown gamma band activity increases in power and synchrony when humans perceive the gestalt of an object. To determine whether abnormal gamma band responses during object perception may serve as a marker of genetically influenced brain abnormalities associated with schizophrenia, we studied the electrophysiological activity of schizophrenia patients, their first-degree biological relatives, and control subjects collected during a degraded-stimulus continuous performance task (DS-CPT). The DS-CPT consisted of subjects watching a series of large single numerals presented on a computer monitor and pressing a response button whenever they saw the number 0 displayed. Targets (0) occurred in 25% of the trials while nontargets (numbers 1 to 9) composed the remaining trials. To make stimuli difficult to perceive white numerals and black background were visually degraded by 40% and presented for 29 msec every 1000 msec. Electroencephalogram (EEG) data were collected from 27 scalp sites with tin electrodes referenced to the left earlobe. Re-referenced and preprocessed EEG data for correctly responded to target trials were subjected to time-frequency analyses of the 20 to 60 Hz frequency range. In response to target stimuli control subjects exhibited early gamma activity prior to 175 ms post stimulus at 30 and 45 Hz, and a wide band of gamma activity (35 to 55 Hz) between 400 and 600 ms post stimulus. Both early and late gamma band events were maximal over lateral frontal and posterior brain regions. Schizophrenia patients exhibited diminished late gamma activity. These findings suggest that in schizophrenia gamma band anomalies over frontal and posterior brain regions during visual sustained attention reflect cortical neural mechanisms that underlie aspects of attentional dys-

function in the disorder. Findings for gamma band abnormalities associated with genetic liability for schizophrenia in first-degree biological relatives will also be presented.

A SELECTIVE FAILURE TO SUPPORT SYNCHRONIZED STIMULUS-DRIVEN GAMMA RANGE OSCILLATIONS IN SCHIZOPHRENIA PATIENTS

J. Sprock,* G. A. Light, M. H. Hsieh, J. Hsu, D. L. Braff
Department of Psychiatry, University of California, San Diego, La Jolla, CA, USA

Schizophrenia patients often have large-effect size deficits in the routine processing of repetitive sensory stimuli. These information processing deficits have been observed in the support of synchronized gamma band (i.e., ~40 Hz) oscillations in response to steady-state (i.e., entrained) stimulation. Thus entrained gamma band activity is a key electrophysiological measure of early sensory information processing. Gamma band activity accompanies many basic sensory and cognitive operations and is thought to be important for relatively long-distance transmission of information across neural networks. The aim of the present study was to characterize the extent of gamma band entrainment deficits which have been observed in schizophrenia patients and their unaffected relatives. A large cohort of patients with schizophrenia (n=100) and normal comparison subjects (n=75) were tested following established methods. Stimuli consisted of 1-millisecond duration clicks, presented in 500 msec trains varying in rate of presentation (20, 30 and 40 Hz) in each of 3 blocks. Topographic analyses revealed maximal entrainment at frontocentral electrodes. In normal subjects, maximal amplitude occurred to 40 Hz stimulation, with 30 Hz and 20 Hz responses showing progressively lower amplitudes. Schizophrenia patients had normal responsivity to 20 Hz stimulation ($t=-1.1$, $p>0.25$) but reduced synchronization to 30 Hz ($t=2.4$, $p<0.05$) and 40 Hz ($t=2.9$, $p<0.01$) stimulation. Thus, in the non-gamma 20 Hz range, normal entrainment was observed in schizophrenia patients. In conclusion, this pattern of results indicates that information processing deficits represented by gamma band activity are selectively present in schizophrenia patients. These selective deficits in supporting synchronized gamma band information processing may form part of the substrate of cognitive, and functional deficits of schizophrenia patients and their unaffected relatives. Future studies will examine the role of gamma range synchronization dysfunction in sensory, cognitive, functional and neural netwok disturbances characteristic of schizophrenia patients. In addition, future studies will also begin to examine the genetic basis of these gamma synchronization deficits in schizophrenia patients.

SPECIFICITY OF ELECTROPHYSIOLOGICAL ABNORMALITIES DURING VISUAL SEARCH TO SCHIZOPHRENIA: A FIVE GROUP COMPARISON

J. Stanwyck,* S. R. Sponheim
Veterans Affairs Medical Center, Minneapolis, MN, USA

Studies have shown that performance deficits on visual search tasks may be specific to genetic risk for schizophrenia (Asarnow et al., 1991). Further examination of brain function underlying visual search is needed to understand the basis of these anomalies. If functioning brain abnormalities prove to be specific to the vulnerability of schizophrenia, the anomalies potentially could help detail the expression of genetic risk for schizophrenia in brain function. To investigate the diagnostic specificity of visual search performance deficits and to study associated functional brain abnormalities, we analyzed electroencephalogram (EEG) recordings made during the Span of Apprehension (SPAN) task to study clinically diagnosed schizophrenia and bipolar disorder patients, first-degree biological relatives of the patient groups, and non-psychiatric control subjects. EEGs were recorded using tin electrodes from 28 scalp sites referenced to A1. Data were corrected with electrooculogram, filtered, and re-referenced to linked-earlobes. Averaged waveforms were individually computed for each condition of the attention task. We have found schizophrenia patients and their biological siblings exhibit differences in their event related potential (ERP) components compared to non-psychiatric controls during the SPAN task. Based on previous ERP and performance findings, we predict schizophrenia patients and their first-degree relatives will show a diminished P300 component and augmented parietal N1 component compared to bipolar patients, their first degree-relatives and non-psychiatric control subjects. Full results of group comparisons and association with SPAN task performance will be reported.

MAGNETOENCEPHALOGRAPHY OF LANGUAGE IN SCHIZOPHRENIA

M. Stephane,* C. R. Fletcher, G. Pellizzer, A. Leuthold, K. McClannahan, A. Georgopoulos
Psychiatry, University of Minnesota, Minneapolis, MN, USA

Introduction: Both speech aberrations and auditory verbal hallucinations reflect a language disorder in schizophrenia. Speech abnormalities are found at the lexical, sentencial, and discourse levels of language. Also patients report hearing voices with different linguistic complexity (words, sentences, or conversation). Thus, language disorder in schizophrenia could occur at multiple levels of language processing. In this study, we examine the neural correlates of these levels of language processing using magnetoencephalography (MEG). Method: MEG data were obtained on one healthy control and two schizophrenia patients during the performance of tasks designed to explore sublexical-discourse levels of language processing. Event related synchronization/ desynchronization was used to analyze the data. This method was used as 1) it accounts for phase locked and phase unlocked evoked activity. 2) It allows to investigate the differential contributions of different frequency bands to the measured brain signal. Results: At this stage of analysis, we observed: 1) The power of frequency bands behaved differently according to the levels of language processing. These differences were location and time specific, and were predominantly in the left hemisphere. 2) For any given level of language processing, there were differential contributions of frequency bands to the measured signal. These differences were also dependent on the location of the detector and the time dimension. 3) For all levels of language processing, there were differences in the power of specific frequency bands between the patients and the control. They include: abnormal laterality of synchronization, desynchronization instead of synchronization, and failure of activation (no difference from baseline). Conclusion: These preliminary findings indicate: 1) The linguistic procedure described briefly above elicits MEG correlates specific to each level of language processing. 2) Different aspects of language processing call upon neural activities that oscillate at specific frequencies, which are location and time dependant. Therefore, temporospatial investigation of language in the frequency domain could further our knowledge of the neural mechanisms of language. 3)

Schizophrenia patients have anomalous neural correlates in the frequency, spatial and temporal domains for all the investigated levels of language processing.

SEXUAL DIMORPHISM FOR EVENT-RELATED POTENTIALS IN SUBCLINICAL DEPRESSION

A. L. Sumich,* V. Kumari, B. C. Heasman, N. R. Tunstall, E. Gordon, M. J. Brammer
BIAU, Biostatistics and Computing, Institute of Psychiatry, London, United Kingdom

Depression is a common symptom in schizophrenia, and has a greater preponderance in women. Sexual dimorphism in the prevalence and symptom profile associated with depression in schizophrenia may be due to sex-specific differences in brain function associated with depression. Changes in brain function in schizophrenia have been studied using event-related potentials (ERPs). ERP abnormalities for amplitude, latency and asymmetry have been reported. These may be syndrome- and sex- dependent. Subclinical forms of psychosis such as schizotypal personality disorder are associated with similar abnormalities. Study of subclinical groups has the advantage of being free from the effects of long-term medication use and enables recruitment to be balanced across the genders. Moreover, compensatory and vulnerability markers may be investigated simultaneously. Sexual dimorphism of controlled attention as measured by P300 and N200 ERP components was studied in subclinical depression (SCD). One hundred and forty healthy, right-handed participants (aged 20-60 yrs; screened for clinical depression and psychosis) from an international database completed an auditory oddball task and the Depression Anxiety and Stress scale (DASS). Seventy (n=35 men) SCD (ie. scoring >2 for depression on DASS) participants were matched for age and education with 70 (n=35 men) participants showing no signs of depression (ND). Repeated measures was used to test for differences in N200 and P300 latency and amplitude at midline, medial and lateral sites between SCD and ND groups, whilst covarying for stress and anxiety. Sex-specific analysis was also performed. Independent of sex, earlier P300 latencies were seen at lateral sites. SCD men showed earlier P300 latencies at medial sites. SCD men, but not women, had abnormal asymmetry of N200 amplitude which may reflect executive functions of the anterior cingulate. SCD women demonstrated abnormal asymmetry (L>R) and enhancement of bilateral posterior temporal P300 amplitude. This is compatible with studies demonstrating increased temporal lobe volume in depressed patients with schizophrenia. Changes in asymmetry and increased posterior temporal P300 amplitude may reflect trait characteristics for depression in schizophrenia. The results suggest sexual dimorphism in the aetiology of depression exists at a subclinical level. Implications for more effective treatment of male and female schizophrenia patients with depression are discussed.

THE EFFECTS OF GLYCINE AND D-CYCLOSERINE ON SENSORY GATING IN PATIENTS WITH SCHIZOPHRENIA

A. Summerfelt,* G. Francis, P. Ball, W. T. Carpenter, R. W. Buchanan
Maryland Psychiatric Research Center, University of Maryland, Baltimore, MD, USA

NMDA receptor dysfunction has been proposed as a modulator of negative symptoms and cognitive impairments in schizophrenia. Agents that bind to the glycine site of the NMDA receptor, such as glycine (full agonist), or d-cycloserine (partial agonist), have shown promise as potential therapeutic agents. Patients with schizophrenia are characterized by sensory gating impairments, which are manifest in abnormal P50 event-related potentials obtained during paired click stimulation. P50 reflects the effects of multiple neurotransmitters. Ketamine, an NMDA-receptor antagonist, has been shown to disrupt sensory gating in animals, but for humans, results have been equivocal. It is not known, however, whether glycine agonists improve sensory gating in schizophrenia. In this study, P50 sensory gating was evaluated in the context of a double-blind, placebo-controlled, parallel groups clinical trial of glycine and d-cycloserine in schizophrenia. Schizophrenia patients with persistent negative symptoms were randomly assigned to receive either 60gm glycine (n = 14), 50 mg d-cycloserine (n = 13), or placebo (n = 15) during the 16-week trial. P50 was assessed at baseline and end-of-study. P50 was obtained from Cz during a paired-click procedure to yield measures of gating (TC ratio) and S1 and S2 amplitude and latency. Gating did not differ as a function of treatment condition or time. At baseline, 50% of the subjects had abnormal gating (TC ratio >= 60), which did not improve differentially for either active treatment relative to placebo. P50 latency was also consistent among groups at both measurement occasions. P50 amplitude was enhanced following glycine, but not d-cycloserine treatment, relative to placebo. Neither glycine nor d-cycloserine enhanced gating in our study. Although glycine was associated with increased p50 amplitude, gating was not affected because both S1 and S2 amplitudes increased. Results will be discussed in the context of associated clinical findings.

THE CONSORTIUM ON THE GENETICS OF SCHIZOPHRENIA (COGS): INITIAL FINDINGS OF REDUCED PREPULSE INHIBITION OF ACOUSTIC STARTLE (PPI) IN SCHIZOPHRENIA PATIENTS IN A MULTISITE STUDY

N. R. Swerdlow,* G. A. Light, K. S. Cadenhead, J. Sprock, D. L. Braff
Consortium on the Genetics of Schizophrenia, La Jolla, CA, USA

COGS is a 7-site (Harvard, Mt. Sinai, PENN, UCHSC, UCLA, UCSD, U WA) consortium studying schizophrenia genetics using multiple endophenotypes, including PPI, P50 suppression, and antisaccade measures. Data herein were collected across all 7 sites. Carefully screened probands (PRO), relatives (REL) and normal comparison subjects (NCS) are assessed by structured clinical and neuropsychological instruments. In total, COGS will test 420 schizophrenia pedigrees (1680 subjects) and 525 NCS over 5 years. Due to the complexity and scope of this project, interim analyses of endophenotypes will be used to identify expected response patterns as well as potential site specific anomalies in data collection. Five months of consortium-wide training and quality assurance (QA) efforts, standardization of equipment and test protocols and database development, preceded 10 months of data collection. Startle testing and DNA collection were completed on 314 subjects across 7 COGS sites (66 PRO, 142 REL and 106 NCS). Bilateral EMG startle blink recordings were made (70 dB(A) background; 115 dB(A) 40 ms pulses; 85 dB(A) 20 ms prepulses; 30, 60 or 120 ms prepulse intervals; all stimuli white noise). The COGS QA process, including on-site inspections, detected and corrected several relatively minor methodological differences across sites. Initial comparisons examined startle and PPI in NCS vs. PRO groups. Nine (5.2%) subjects were omitted from analyses due to low startle magnitude (<10 units).

ANOVA of startle magnitude revealed a significant effect of sex (F>M; p<0.035) but not diagnostic group, nor sex x group interaction. ANOVA of PPI revealed a significant effect of sex (M>F; p=0.02) and prepulse interval, and a significant interaction of group x interval (p<0.025). Post-hoc comparison at the 60 ms interval revealed PPI deficits in PRO vs. NCS subjects (p=0.01), and sex differences (M>F; p<0.03) but no sex x group interaction. There were no differences across the 7 COGS sites in 60 ms PPI. These findings demonstrate the feasibility of testing startle and PPI in schizophrenia patients and NCS across 7 laboratories, to detect schizophrenia-linked gating deficits as well as known sex differences (M>F) in PPI. This initial experience also revealed challenges of standardizing methods across multiple test sites, and successful strategies for addressing them. Additional analyses in PRO and REL groups are ongoing, across all of the COGS endophenotypes. Supported by MH 65571.

RESTING EEG POWER IN SCHIZOPHRENIA PATIENTS, THEIR NON-SCHIZOPHRENIC CO-TWINS, AND CONTROL TWINS

D. Tran,* P. Bachman, J. Kim, D. C. Glahn, S. Therman, M. Manninen, M. Huttunen, J. Lonnqvist, J. Kaprio, R. Naatanen, T. Konotchick, M. Quintero, T. D. Cannon
Psychology, UCLA, Los Angeles, CA, USA

We examined resting state EEG power in an electrophysiological data set collected from nine twin pairs discordant for a diagnosis of schizophrenia and nine demographically matched control twin pairs. Initial analyses indicate that the directions of patient-control differences are consistent with those reported in the literature: patients show greater mean power levels within the 0-8 Hz range, lower mean power within the 8-12 Hz range, and higher mean power within the 12-70 Hz range. The magnitudes of these frequency band specific differences, however, do not appear to be statistically significant. Interestingly, patients' non-schizophrenic cotwins appear to show band power abnormalities (with respect to controls) qualitatively different from the patient-control differences. Specifically, patients' cotwins' mean power levels are significantly lower than patients' mean power levels within the 4-10 Hz and 12-70 Hz ranges, but only differ significantly from controls' mean power levels in the 8-10 Hz band. Also, several significant associations exist between measures of band power and relevant clinical variables. The overall pattern of findings suggests that schizophrenia patients' band power levels are elevated above controls' levels (non-significantly) and above their cotwins' levels (significantly) in all frequency bands studied except for the "Delta" (0-4 Hz) and "slow Alpha" (8-10 Hz) ranges, the latter of the two including a predictable resting state increase for controls, which is unmatched by patients and their cotwins. Collectively, these results carry at least two important implications. First, although absolute resting power levels are low, significant differences in mean resting "Gamma band" (30-70 Hz) power can be demonstrated between groups. Additionally, non-schizophrenic subjects thought to be at increased genetic risk for developing schizophrenia display broadband EEG abnormalities that are different in extent and nature from possible abnormalities demonstrated by patients manifesting the full syndrome. Should further examination indicate more conclusively that patients' cotwins' resting EEG power differences are indeed related to genetic vulnerability, these differences may ultimately serve as a valuable phenotype in the search for genes contributing to schizophrenia vulnerability.

SEXUAL DIMORPHISM FOR ERPS ASSOCIATED WITH POSITIVE DIMENSIONS OF SCHIZOTYPY

N. R. Tunstall,* S. L. Sumich, V. Kumari, B. Heasman, E. Gordon, M. J. Brammer
Psychological Medicine, Institute of Psychiatry, London, United Kingdom

Schizotypy, which lies on the spectrum of genetic liability to schizophrenia (schizotaxia), shares some abnormalities of brain function with schizophrenia, and may have utility as a subclinical model of psychosis. Studying samples of individuals with schizotypy circumvents the problems of medication and hospitalization effects, and facilitates balanced recruitment across genders. It may also allow simultaneous investigation of both compensatory and vulnerability mechanisms. Event-related potential (ERP) components N200 and P300 have been used to study controlled attention and emotion processes in schizophrenia and at-risk groups. ERP abnormalities may be modified by symptom profile: increased posterior N200 amplitude is seen in subjects with the paranoid subtype, frontal and left temporal attenuation in P300 amplitude is associated with positive symptomotology, while right hemisphere deficits are seen in subjects with prominent negative symptoms. The identified ERP abnormalities also show sexual dimorphism: women demonstrate greater frontal and left temporal P300 amplitude reductions, while men show right temporoparietal amplitude reductions. Sexual dimorphism for ERPs in schizotypy has hitherto not been reported. Forty-two individuals (men=22) with no previous psychiatric history performed an auditory oddball task and completed self-report personality questionnaires to measure aspects of schizotypy including mystic experiences (ME), paranormal ideation (PI) and paranoia/suspiciousness. P300 and N200 amplitudes were measured at 21 electrode sites. High paranoia scores were associated in men only with increased N200 amplitude. Independent of gender, high ME individuals demonstrated reduced left temporal (T3, T5) amplitude. Men with high ME scores also demonstrated a trend towards increased right frontal amplitude leading to a significant hemisphere*ME*sex interaction. High PI was associated with reduced P300 amplitude at frontal sites in women and centro-parietal sites in men. The results are consistent with findings from schizophrenia studies, and provide further evidence for the existence of sexual dimorphism for brain abnormalities associated with liability to psychosis, and for the construct of schizotaxia.

OLFACTORY DYSFUNCTION IN SCHIZOPHRENIA BEGINS AT THE NOSE

B. I. Turetsky,* K. Owzar, D. Roalf, R. E. Gur, P. J. Moberg
Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

Background: Patients with schizophrenia are impaired on psychophysical tests of odor identification and threshold sensitivity. Neurobiological studies of the olfactory system have now established that 1)specific structural abnormalities exist in the cortical brain regions subserving olfaction; 2)neurophysiological measures of early cortical sensory processing are disturbed; and 3)abnormalities appear to involve the more peripheral olfactory bulbs, as well as central components of the olfactory system. The most peripheral component of the olfactory system - the olfactory epithelium - has not been examined in vivo, although post-mortem data suggest that there are disturbances in the developmental lineage and distribution of olfactory receptor neurons (ORNs) lining the epithelium. Methods: The ORN response to odor stimulation, or electro-olfactogram

(EOG), was recorded in vivo from patients with schizophrenia and healthy controls. A thin wire electrode was placed directly on the olfactory epithelium lining the medial surface of the middle turbinate. H2S was presented via an olfactometer that controlled stimulus concentration, duration and inter-stimulus interval. The odor induced a measurable stimulus-dependent depolarization-repolarization response from ORNs in the olfactory epithelium. The volumes of the nasal cavities were assessed using acoustic rhinometry, and olfactory bulb volumes were measured with high-resolution MRI. Results: EOG responses in patients were markedly amplified over those seen in controls. This was particularly evident for odors presented to the right nostril, with longer duration and/or longer inter-stimulus interval. The posterior nasal cavity, where ORNs are located, was smaller in patients, while anterior nasal volume was normal. Olfactory bulbs were also smaller in patients. Conclusion: Hyper-excitability of ORNs represents a previously unknown fundamental neurophysiological abnormality in schizophrenia. In conjunction with reduced volumes of both the posterior nasal cavities, which are formed in the first-trimester of embryological development, and the olfactory bulbs, which receive axonal inputs from the ORNs, it likely denotes a set of basic developmental anomalies that underlie olfactory dysfunction in schizophrenia. An understanding of the physiological mechanisms regulating ORN response may therefore shed light on the neuronal pathophysiology of the disorder.

GESTALT PERCEPTION AND GAMMA-BAND OSCILLATIONS IN SCHIZOPHRENIA

P. J. Uhlhaas,* E. Rodriguez, D. E. Linden, C. Haenschel, W. Singer
Neurophysiology, Max-Planck Institute for Brain Research, Frankfurt, Germany

The binding problem is the general question of how any kind of distributed information is integrated in the brain to ultimately result in coherent perception and action. Theoretical and empirical data indicate that synchronized oscillations in the gamma frequency band (30-80 Hz) may serve as a temporal code for the integration of neural and cognitive activity (Singer, 1999). Gestalt perception is a paradigmatic example of binding in sensory systems of the brain. Probability and strength of synchronization, for example, reflect elementary Gestalt criteria for perceptual grouping, such as proximity and collinearity (Singer, 1999). There is evidence to suggest that schizophrenia patients are characterized by deficits in the integration of stimulus-elements into coherent object representations as well as by abnormal gamma-band activity (Phillips & Silverstein, 2003). It is unclear, however, whether deficits in Gestalt perception are the result of abnormal gamma-band activity in schizophrenia patients or whether these two deficits are independent. In order to examine the hypothesis that dysfunctional Gestalt perception is related to aberrant gamma-band activity, we studied perceptual integration with Mooney faces in schizophrenia patients (N=10) and normal controls (N=16). Mooney faces consist of degraded pictures of human faces where all shades of gray are removed, thereby leaving the shadows rendered in black and the highlights in white. Perception of Mooney faces involves the grouping of the fragmentary parts into coherent images and is related to synchronization of neural activity in the gamma-band in normal subjects (Rodriguez et al. 1999). We measured induced and evoked-gamma band power as well as phase-synchronization in response to Mooney faces in the scalp-recorded electroencephalogram (EEG) to examine the synchronization of neural circuits in schizophrenia. Compared to normal controls, schizophrenia patients: 1) were significantly impaired in the detection of faces; 2) showed both significantly reduced gamma-band power and phase synchronization; and 3) were characterized by reduced amplitudes of the P1 and P3 event related potential (ERP) components. The results provide evidence for the hypothesis that dysfunctional Gestalt perception is related to aberrant gamma-band activity in schizophrenia, suggesting that deficits in binding mechanisms may constitute a core impairment which underlies the fragmentation of mind and brain in the disorder.

REDUCED P100 AMPLITUDE IN SCHIZOPHRENICS IS ASSOCIATED WITH ABNORMAL EVOKED AND INDUCED GAMMA-BAND ACTIVITY AND INTERTRIAL PHASE-LOCKING VALUES

J. A. Waltz,* C. Haenschel, R. A. Bittner, F. Haertling, A. Rotarska-Jagiela, K. Maurer, W. Singer, D. E. Linden
Psychiatry Dept, Univ of Maryland School of Medicine, Baltimore, MD, USA

Background: Recent models of cognition in schizophrenia (SZ) have emphasized the role that impairments in perceptual and cognitive binding processes might play in schizophrenic psychopathology. These processes have been linked to the occurrence of oscillatory neural activity and coherence in the high-frequency (20-80 Hz) gamma-range, as well as modulations in the amplitudes of event-related potentials (ERPs). Evidence suggests that systematic relationships may exists between these difference types of electrophysiological signals, and that schizophrenic subjects show abnormalities in each of them. We tested the hypothesis that reductions in the amplitudes of ERPs in SZ correspond to abnormalities in oscillatory neuronal activity. Method: Ten patients diagnosed with early-onset SZ according to DSM IV criteria and ten controls participated in a visual working memory experiment. Current psychopathology was assessed with a structured clinical interview (SCID-I), and the cognitive profile was documented. The control group was matched for age, gender, handedness, and parental education. Subjects had to encode up to three abstract shapes that were presented sequentially for 600 ms each. After a delay of 12 seconds they had to compare the memorized shapes to a test shape, which was a match for one of the samples in fifty percent of the trials. Scalp EEG was acquired from 64 channels at a 500 Hz sampling rate. The encoding period was analysed for averaged ERPs, as well as for evoked and induced oscillatory gamma activity (using the Morlet wavelet transform). We used measures of intertrial phase-locking to probe the relationship between narrow-band ERPs and oscillatory activity. Results: Patients showed reduced amplitude of P100 and reduced evoked high frequency (beta and gamma-band) activity. However, for the same time period, they showed enhanced induced activity in the same frequency bands. We show that reductions in evoked high frequency EEG activity and P100 amplitude in SZ correspond to reduced intertrial phase-locking values in the gamma range. Conclusion: The reduction of P1 amplitude and evoked gamma activity observed in SZs might be the result of decreased intertrial consistency and phase-locking of neural responses. Supported by the Max Planck Society and the Koerber Foundation.

CHARACTERIZATION OF DORSAL LATERAL PREFRONTAL CORTEX DYSFUNCTION DURING A WORKING MEMORY TASK IN SCHIZOPHRENIA WITH MAGNETOENCEPHALOGRAPHY

M. P. Weisend,* F. M. Hanlon, M. X. Huang, R. J. Thoma, R. R. Lee, G. A. Miller, J. M. Canive
Radiology, New Mexico VA Health Care System, Albuquerque, NM, USA

Cognitive dysfunction, including deficits in memory, is thought to be a core feature of schizophrenia. Working memory is a temporary, rehearsal-dependent, short-term store that has been linked to prefrontal cortex function through lesion and neuroimaging studies. Hemodynamic neuroimaging techniques have shown abnormal dorsal lateral prefrontal cortex (DLPFC) activation during working memory performance in patients with schizophrenia. To date, the study of DLPFC activity with electrophysiological techniques, electroencephalography and magnetoencephalography (MEG), have been less successful. The present study developed a technique that shows reliable activation of DLFPC in control subjects and abnormal activation in patients with schizophrenia. Control subjects and patients with schizophrenia were asked to perform a low-load, delayed-match-to-sample working memory task while 122-channel MEG data were collected. Source localization was carried out on the recorded MEG signals using MSST, a spatially unbiased dipole localization algorithm. Time courses were calculated for each source. Localized sources were overlaid on each subject's structural magnetic resonance image. Performance on the working memory task was not statistically different for patients with schizophrenia (93% correct) and control subjects (97% correct). Right DLPFC was activated in all 3 control subjects. All control subjects showed activation of the DLPFC beginning in the encoding phase of the working memory task. In contrast, only 2 of 4 patients with schizophrenia showed PFC activation. One patient showed right ventral lateral PFC activation, and the other patient showed left DLPFC activation. The PFC activations in these two patients did not occur during the encoding phase of the trial. Activation of the PFC in patients with schizophrenia was observed only during the matching phase of the trial. The present approach provides a reliable method to assess prefrontal cortical function in a working memory task with MEG and shows that, even when patients with schizophrenia are performing well on a working memory task, the activity of their prefrontal cortex differs from that of control subjects. This research was supported by a NARSAD Young Investigator Award to MPW and NIH 5-R01-MH65304-01 to JMC.

GENDER DIFFERENCES IN THE RELATIONSHIP OF SCHIZOTYPAL SYMPTOMS TO STRESSFUL IMPAIRMENT OF P50 SUPPRESSION

P. M. White,* G. Pellegriti, L. Stewart, V. Perez
Psychology, University of Oregon, Eugene, OR, USA

A series of studies have replicated impaired P50 suppression in schizophrenia patients and their biological relatives relative to normal controls, putatively indexing a loss of normal inhibition (e.g. Freedman et al., 1987). Animal models of sensory gating have demonstrated that response suppression is disrupted by noradrenergic influences; subsequent research suggests that stressors also might influence P50 suppression in humans, e.g., White and Yee (1997). Anxiety also has been associated with impaired P50 suppression in recent-onset schizophrenia patients (Yee, Nuechterlein, Morris & White, 1998). Taken together, these results suggest that physical and psychological stress may disrupt P50 suppression. This study was designed to assess the relationship of schizotypal symptoms to P50 suppression under baseline and stressor conditions, and to investigate possible gender differences in this relationship. P50 suppression, heart rate and EDA were collected for schizotypal subjects (n =13) compared to normal controls (n =14). Schizotypal symptoms were assessed with the SPQ. Comparison of the two tasks using repeated-measures ANOVAs revealed a Gender x Task X Group interaction, F (1,23)=21.38, p <.001; although females did not show group differences or interactions, P50 suppression was elevated in schizotypal males during stress but not baseline compared to control males. In males but not females, the SPQ total correlated positively with stressor but not baseline P50 suppression (r = .895, p <.001). This correlation occurred for all three SPQ factors, with the strongest correlation in subscales for odd speech (r = .864, p <.001), odd behavior (r = .720, p <.01), and suspiciousness(r = .758, p <.01). These results suggest that schizotypal subjects display impaired inhibition under stress, relative to controls, but only in males. In contrast, control females show impaired P50 suppression during stress relative to control males. These findings offer corroborative support for biological parallels between schizotypy and schizophrenia, and suggest differing physiological response patterns during psychological stress for schizotypal males versus females, with greater stress vulnerability in schizotypal males.

PROBING FOR ABNORMAL GAMMA ACTIVITY IN SCHIZOPHRENIA WITH VISUAL BACKWARD MASKING

J. K. Wynn,* G. A. Light, P. Nori, K. A. Tillery, B. Breitmeyer, K. H. Nuechterlein, M. F. Green
Department of Psychology, University of California, Los Angeles, Los Angeles, CA, USA

Schizophrenia patients experience deficits in many aspects of cognition and perception. Abnormalities in gamma activity may underlie some of these deficits, including rapid processing of visual stimuli. This study examined event-related gamma range activity during a visual backward masking task in schizophrenia patients and normal controls. Event-related gamma activity was recorded in 15 normal controls and 32 schizophrenia patients. Participants had event-related gamma activity recorded while viewing 60 unmasked visual targets and 240 trials of visual backward masking. Event-related gamma activity was recorded using 32 cap-mounted electrodes placed in a modified 10-20 international system configuration. Event-related gamma activity was defined as the peak amount of evoked gamma activity in a window of 30-40 Hz, expressed in z-score units. Group differences in the effects of accuracy (correct vs. incorrect), stimulus onset asynchrony (SOA), and regional activity (left vs. right hemisphere, anterior vs. posterior regions) were analyzed. There was no main effect of SOA or correct vs. incorrect in gamma activity to masked targets, therefore data were collapsed across these factors. Schizophrenia patients had significantly reduced gamma activity compared to controls during the backward masking task. Normal controls showed significantly greater gamma activity in the right hemisphere whereas schizophrenia patients did not show this pattern of lateralization. For the unmasked targets, there was no group effect and no significant interactions. These results extend previous findings of abnormal gamma range activity in schizophrenia

patients during visual backward masking. Patients showed overall less gamma activity and they failed to show lateralization of activity to the right hemisphere during masking but showed comparable levels of gamma activity to unmasked trials. These results are consistent with previous findings of a right hemisphere deficit in schizophrenia patients while processing visual stimuli. However, the results were seen only during the masking task which specifically generates neural activity in the gamma range. Schizophrenia patients' poorer performance during a masking task may be partly influenced by this abnormal level and distribution of gamma activity. This research was supported by NIMH grants MH43292 and MH65707.

THE INFLUENCE OF MENSTRUAL CYCLE FLUCTUATIONS IN SEX HORMONES ON HEMISPHERIC ASYMMETRY IN WOMEN WITH SCHIZOPHRENIA

R. A. de Castella,* R. B. Silberstein, P. B. Fitzgerald, K. Filia, J. Kulkarni

School of Psychology, Psychiatry & Psychological Medicine, Monash University, Prahran, VIC, Australia

BACKGROUND: In recent years there has been an explosion of interest and research in the area of schizophrenia gender differences, which are now well accepted but only partially understood. In particular, much work has been conducted in trying to understand the role of estrogen in their etiology and its implications for treatment and outcome. Estrogen is a gonadal steroid, but has neuromodulating effects in a number of regions in the brain. The menstrual cycle provides an excellent opportunity to study the influences of cyclic fluctuations in estrogen on brain function in relation to schizophrenia and other psychiatric illness. Low estrogen phases of the menstrual cycle have been correlated with exacerbation of pre-existing illness and increased risk for first onset of schizophrenia. Measures of resting electroencephalography, as well as more sophisticated electrophysiological tools, have been used to study schizophrenia since their development, and a number of abnormalities have been consistently identified. AIM: The aim of this study was to explore the effect of the menstrual cycle on hemispheric asymmetry. METHOD: A total of 12 women with a current DSM-IV diagnosis of schizophrenia were included. Assessments were conducted at mid-cycle and at pre-menstruation. Blood was was collected to measure serum estrogen, progesterone, LH, & FSH levels. Psychopathology was assessed using the PANSS and the MADRS scales. Resting EEG was recorded at 8 sites according to the 10-20 system and measures of resting EEG hemispheric asymmetry were calculated to determine whether theories of decreased left frontal activation during times of negative emotional affect could be applied to menstrual phase changes in mental state in women with schizophrenia. RESULTS: Estrogen levels were higher, but not significantly, at mid cycle. There was no significant difference in the core symptoms of schizophrenia or in affective symptoms across cycle phases. The subjects had greater left (F3) than right (F4) frontal alpha1 and alpha2 power (i.e. relative right sided activation and left sided hypo-activation) at both menstruation and at mid cycle, and the degree of this asymmetry was greater, but not significantly, at menstruation than at mid cycle, supporting previous findings of relative left frontal hypo-activation at times of negative affect.

17. Eye Movement Physiology

EVALUATION OF COGNITION IN SMOOTH PURSUIT EYE MOVEMENT PHENOTYPES IN SCHIZOPHRENIA

S. S. Awasthi,* D. Cole, B. Thomas, M. Collum, C. Tamminga, G. Thaker
Psychiatry, UT Southwestern, Dallas, TX, USA

Abnormal smooth pursuit eye movements (SPEMs) are one of the most reproducible endophenotypes associated with schizophrenia-most notably an abnormal predictive pursuit occurring in ~50% of schizophrenics, in 20% of unaffected relatives of schizophrenics and <10% of normals. Studies of patients with abnormal SPEMs have suggested a link with cognitive deficits. Deficits in working memory and executive cognition are also characteristic of schizophrenia. Schizophrenia patients have poor eye tracking because of poor predictive pursuit. The construct of predictive pursuit is similar to that of working memory. Therefore, schizophrenia patients with poor predictive pursuit will be expected to perform more poorly in a working memory task (n-back) than normals and also have abnormal activation patterns in the prefrontal cortex. Some schizophrenia volunteers already show abnormal activation patterns in prefrontal cortex (PFC) during performance of the n-back working memory task during fMRI BOLD acquisition and during novelty detection. We propose that persons with schizophrenia and abnormal SPEMs will have greater working memory deficits and altered task-activated cerebral activation patterns in PFC compared with those schizophrenics with normal SPEMs. Schizophrenia volunteers are being recruited with either very good (top 20%) or very poor (bottom 20%) eye tracking performance in the predictive pursuit component of the SPEM. There are three groups: 15 subjects with schizophrenia who are good eye trackers, 15 subjects with schizophrenia who are poor eye trackers, and 15 normal controls. Initial data on SPEM and working memory show a moderate correlation between predictive pursuit gain and working memory ($r=0.58$, $p<0.04$) in our pilot study of 15 patients with schizophrenia. Additional data will be reported showing working memory performance and associated cerebral activation patterns in schizophrenics with good and poor SPEM.

"SCHIZOPHRENIA RELATIVES AND MOOD DISORDER PATIENTS EXHIBIT MILDER ENDOPHENOTYPE IMPAIRMENTS THAN SCHIZOPHRENIA PATIENTS": SHOULD WE INTERPRET "INTERMEDIATE" DEFICITS THIS WAY?

M. E. Calkins
Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

Considerable research is directed at evaluating candidate endophenotypes (EP), believed reflective of genetic risk for mental disorders. Studies of heritability and diagnostic specificity of EP have largely concluded that schizophrenia relatives (REL) and mood disorder patients (MP) have impairments that are "milder," "subtler," or "less severe" than those in schizophrenia (SZ). Such conclusions are based on a group difference profile in which the means of REL and MP fall intermediate between those of SZ and controls. Alternative interpretations of this profile are rarely discussed (e.g., a small number of REL with severe deficits intermixed with REL with superior performance), but could affect interpretation of genetic effects. The goal of this investigation was to inform interpretation of "mild" oculomotor EP deficits in REL and MP. Participants (n=374: SZ n=92, REL n=125; psychotic MP n=36; non-psychiatric control n=121) were administered smooth pursuit, antisaccade and fixation tasks. Within groups, odds were calculated for each whole z-score (based on control mean/sd) ranging from -3 to 3. Odds ratios (OR) [index group odds/SZ odds] provide odds of index group obtaining a z-score compared to odds among SZ. Two distinct patterns emerged. In the first, the odds of average (z=0) to deviant (z=-2) pursuit initiation were comparable in REL and SZ (OR range=0.62-1.17) but the odds of high average (z=1) performance were higher in REL than SZ (OR=14.0). Thus, in this index of pursuit, a number of REL are as severely impaired as SZ, but the impairment appears "diluted" by exceptional performance in other REL. This was also seen in MP on the fixation task. The second pattern is consistent with the interpretation of "milder" deficits. In antisaccade and fixation, the odds of REL exhibiting deviance were significantly lower than odds in SZ (OR range=0.12-0.45), while odds of low average (z=-1), average and high average scores were significantly higher (OR range=1.6-4.4). Antisaccade in MP and pursuit maintenance in REL showed a similar pattern. The results challenge the assumption that intermediate scores reflect "milder" impairments in REL and MP; this interpretation appears accurate for some, but not all, eye movement EP's. Since group differences are well replicated for many candidate EP's, investigations of performance heterogeneity within groups will inform understanding of the genetic and pathophysiological significance of candidate endophenotypes.

BEHAVIORAL PLASTICITY OF ANTISACCADE PERFORMANCE IN YOUNG ADULTS FOLLOWING DAILY PRACTICE

K. A. Dyckman,* J. E. McDowell
Psychology, University of Georgia, Athens, GA, USA

The antisaccade task is of interest to schizophrenia researchers because patients with schizophrenia and their biological relatives perform poorly on this task, which is ostensibly mediated by prefrontal cortex. However, the effect of practice on the antisaccade task is infrequently investigated. The primary goal of this research is to evaluate the effects of different forms of training on the antisaccade task. In the present study, normal subjects' performances on antisaccade tasks were evaluated before and after training on 1 of 3 different eye movement tasks (antisaccade, prosaccade, and fixation). Thirty subjects were tested at 3 time points over a two-week period, and the subjects practiced their assigned task every day between test sessions. Subjects who trained on antisaccades significantly decreased their error rates, while maintaining their reaction time, suggesting accuracy did not improve at the expense of speed. Subjects who practiced the prosaccade task made more errors on the antisaccade task on subsequent test sessions, while those who practiced the fixation task showed no change across test sessions. These results suggest that deliberate practice of eye movement tasks can alter antisaccade performance in normal subjects, and that the direction of the effect is dependent upon the type of practice in which the subject engages. The changes observed in behavioral performance may reflect measurable changes in brain functioning as well. The ability to effect changes in behavior and brain function via practice of a task involving prefrontal cortex could have interesting consequences for

the study of schizophrenia. This study was supported by grants from the UGA Research Foundation and the NIMH.

SACCADIC PERFORMANCE IN QUESTIONNAIRE-IDENTIFIED SCHIZOTYPES OVER TIME

D. C. Gooding,* H. B. Shea, C. W. Matts
Psychology, UW-Madison, Madison, WI, USA

Abnormal performance on an antisaccade task is a putative marker of liability for schizophrenia. In order for a deficit to serve as a disease liability marker it must have temporal stability. Several studies indicate that antisaccade task performance shows moderately high test-retest stability in the normal population. Gooding, Mohapatra, & Shea (2004) reported that antisaccade task deficits are temporally stable in schizophrenia patients. Thus far, there have been no test-retest studies of either schizotypal personality disorder patients or psychometrically-identified individuals. This is important because some of these individuals are expected to develop schizophrenia and/or schizophrenia-spectrum disorders at a later date. In the present study, 121 young adults (mean age = 19 years) hypothesized to be at varying levels of risk for psychosis on the basis of their psychometric profiles, were administered saccadic (antisaccade and refixation) tasks at two separate assessments (mean test-retest interval = 59 months). At both the intake and follow-up assessments individuals posited to be at heightened risk for the later development of schizophrenia spectrum disorders (i.e., those individuals with elevated Social Anhedonia Scale scores) produced significantly more antisaccade task errors than the controls. The antisaccade task performance of the control group displayed temporal stability (Pearson r = 0.70). The antisaccade task performance of the Social Anhedonia group (which included some individuals who by Time 2 met diagnostic criteria for schizophrenia-spectrum disorders such as schizotypal personality disorder) also showed significant temporal stability (Pearson r=0.85). The results of this investigation indicate that antisaccade task performance is temporally stable, even in psychometrically-identified schizotypes over long test-retest intervals. These findings add to the body of literature suggesting that antisaccade task deficits may serve as an endophenotypic marker of a schizophrenia diathesis.

EYE MOVEMENTS REFLECT ABERRANT PROCESSING OF SOCIAL CONTEXT IN SCHIZOPHRENIA

M. J. Green,* J. H. Waldron, M. Coltheart
Macquarie Centre for Cognitive Science, Macquarie University, Sydney, NSW, Australia

Background: Deficits in the processing of contextual information have been related to multiple cognitive dysfunctions in schizophrenia and may constitute a core deficit of the disorder. However, the relevance of poor context processing for the understanding of social cognition in schizophrenia has been relatively overlooked. This study tested the hypothesis that schizophrenia patients may fail to use social contextual information effectively when making mental state attributions on the basis of information contained in facial expressions. Methods: We used visual scanpath recordings as an overt index of directed attention to contextual information contained in pictures of social scenes, and examined the pattern of short-duration saccadic eye movements (saccades < 50 ms) thought to reflect an integrative perceptual grouping process. 20 healthy and 20 schizophrenia participants viewed a series of picture pairs from the Social Context Appreciation Task (SCAT) depicting target facial expressions of characters presented in isolation (Series 1) or embedded in a realistic social context (Series 2). Stimuli were colour photographs (800 x 600 pixels) presented in a pseudo random order for 10 seconds each. Participants were asked to judge the mental state of each character while eye movements were recorded using the SR Eye-Link I binocular eye tracker, monitoring gaze position at a sampling rate of 250 Hz with .01 degree accuracy. Results: Schizophrenia patients showed abnormal attention to contextual information when judging the meaning of ambiguous and fearful expressions. Specifically, schizophrenia patients spent more time viewing faces (versus context) when the face depicted an ambiguous expression, but spent more time viewing contextual information when the face expressed fear. Schizophrenia patients also demonstrated a lack of the normal increase in short-duration fixations when viewing complex social scenes versus faces alone. Conclusion: Results did not support a simple deficit account of social context processing in schizophrenia. Eye-movements to social scenes suggests that ambiguous facial expressions capture the attention of schizophrenia patients, while those displaying overt threat elicit excessive context processing. The reduced number of short-duration fixations in schizophrenia reflects a lack of rapid scanning of visual stimuli that may facilitate effective social context processing in real world environments.

LONGITUDINAL STUDIES OF ANTISACCADES IN FIRST-EPISODE SCHIZOPHRENIA

M. S. Harris,* J. L. Reilly, M. S. Keshavan, J. A. Sweeney
Center for Cognitive Medicine, University of Illinois at Chicago, Chicago, IL, USA

Prefrontal cortical dysfunction has been reported in neuropsychological and functional brain imaging studies of schizophrenia. Some data suggest that treatment, especially with second generation antipsychotic medications, may partially ameliorate some of these deficits. We investigated antisaccade task performance in 39 treatment-naive, first episode schizophrenia patients who were re-evaluated before and 6, 26 and 52 weeks after treatment initiation. Forty-one matched healthy subjects were examined at the same time points. Prior to treatment, schizophrenia patients showed prolonged latencies of antisaccades and higher rates of response suppression failure. Treatment with antipsychotic medication led to a gradual normalization of response latencies throughout the study. While the rate of antisaccade errors of patients improved with antipsychotic medication, they remained significantly elevated throughout the study. Prior to treatment, increased antisaccade error rates were associated with faster visually-guided saccade latencies. This suggests that speeded sensorimotor transformations during the acute phase of illness may compound more enduring deficits in the voluntary control of spatial attention, and perhaps contribute to heightened distractibility during the acute phase of illness. Both typical and atypical antipsychotic medications (in this study, haloperidol and risperidone) reduced the time required to initiate correct antisaccades, documenting a partial amelioration of prefrontal cortical dysfunction underlying the reduced ability to suppress context inappropriate behavior. Supported by NIH MH62134, MH45156, MH01433 and NIH/NCRR/GCRC M01 RR00056.

EYE TRACKING DYSFUNCTION HAS THE SAME QUANTITATIVE CHARACTERISTICS IN SCHIZOPHRENIA PATIENTS AND THEIR FIRST-DEGREE RELATIVES

C. B. Harte,* O. Krastoshevsky, P. S. Holzman, N. R. Mendell, D. L. Levy
Psychology Research Laboratory, McLean Hospital, Belmont, MA, USA

The purpose of the present study was to characterize the quantitative features of eye tracking dysfunction (ETD) in schizophrenia patients and their clinically unaffected first-degree biological relatives, and to determine whether ETD is equally severe in these two groups or whether there is a graded severity continuum. We compared the performance of chronically ill schizophrenia patients (*N*=111), siblings (*N*=85) and parents (*N*=63) of these patients, and normal controls (*N*=104) on several quantitative and qualitative eye tracking measures. Siblings and parents with normal eye tracking did not differ significantly from patients with normal eye tracking or normal controls with normal eye tracking on any quantitative measure (e.g. gain, compensatory saccades, intrusive saccades), indicating that when pursuit is normal, it is normal in the same way in all subject groups. Similarly, siblings and parents with ETD did not differ significantly from patients with ETD on any quantitative measure, again indicating that abnormal pursuit had the same quantitative characteristics in patients and their relatives. Each of the subgroups with abnormal eye tracking differed significantly from their normal eye tracking counterparts. Our results indicate that ETD was characterized chiefly by decreased gain and increased compensatory saccades, specifically catch-up saccades. The finding that ETD segregates in schizophrenia families as an all-or-none trait suggests that it is monogenic in these families. This work was supported in part by grants MH49487, MH31340, MH31154, MH01021, a grant from the Roy Hunt Foundation, and a student fellowship award from the Stanley Medical Research Institute.

REFINING THE SMOOTH PURSUIT EYE MOVEMENT ENDOPHENOTYPES BASED ON NEUROPHYSIOLOGICAL REDUCTIONS

L. Hong,* B. D. Mitchell, M. T. Avila, H. Adami, G. K. Thaker
Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Catonsville, MD, USA

Abnormal smooth pursuit eye movements are some of the most reproducible biological changes associated with the liability for schizophrenia. Global measures of the pursuit deficit such as maintenance pursuit gain have been proposed to be potential endophenotypes that mark the liability for schizophrenia. However, neurophysiological studies have shown that smooth pursuit is primarily maintained by a predictive mechanism. We hypothesized that a measure of the core predictive mechanism is likely to improve the genetic signal of the pursuit eye movement phenotypes. To test this hypothesis we used a sibling pair design and simultaneously measured predictive pursuit and the traditional maintenance pursuit components in sibling pairs of schizophrenic patients. In 70 sibling pairs from 39 sibships, the sibling intraclass correlation coefficient of the peak predictive pursuit component (r = 0.45-0.48) was substantially higher than that of traditional maintenance pursuit component (r = 0.02-0.20). Variance component analysis revealed a high genetic loading for the peak predictive pursuit measure (heritability h^2 =0.90, standard error=0.22, p=0.00005); but relatively low heritability in maintenance pursuit measure (h^2=0.27, standard error=0.21, p=0.079). The result suggests that predictive pursuit as a biologically reduced endophenotype in the smooth pursuit paradigm may be under stronger genetic influences.

THE RELATIONSHIP OF SACCADIC VELOCITY TO LATENCY IN FIRST-EPISODE SCHIZOPHRENIA

S. B. Hutton,* E. M. Joyce, T. R. Barnes, C. Kennard
Psychology, University of Sussex, Brighton, United Kingdom

Reflexive or prosaccades are generally considered to be normal in patients with schizophrenia. However, a recent study found that prosaccade velocity decreased with increasing latency in patients with schizophrenia, a relationship that was not observed in a smaller group of matched controls. Saccade velocity is a function of activity in neurons in the superior colliculus and it was suggested that this "prosaccade abnormality" may reflect a perceptual dysfunction in patients with schizophrenia whereby the effect of the transient visual signal at the saccadic goal decays abnormally quickly, or the continuing presence of the target fails to sustain adequate neural activity in the saccadic system. Given the current status of other oculomotor abnormalities such as impaired smooth pursuit and increased antisaccade errors as potential markers of genetic vulnerability to schizophrenia, it is important to replicate this finding, and determine whether this prosaccade abnormality can also be observed in a group of first-episode patients relatively free from the potentially confounding effects of disease duration and chronic antipsychotic treatment. To this end we examined the relationship between prosaccade latency and velocity in a large group of first-episode patients with a confirmed DSM-IV diagnosis of schizophrenia, and a large group of age-matched healthy controls. All participants performed 24 prosaccades to a sudden-onset target appearing at /- 7.5 or 15 degrees. We found significant correlations between prosaccade velocity and latency in both groups. The correlation was stronger in the control group compared to the patient group, but not significantly. The patients demonstrated increased antisaccade errors and reduced smooth pursuit velocity gain compared to the controls. These findings suggest that, as in non-human primates, saccade velocity is a function of latency, and this relationship is not abnormal in patients with first-episode schizophrenia.

IMPAIRMENT IN VOLITIONAL BEHAVIOR SUPPORTED BY INTERNAL REPRESENTATIONS IN SCHIZOPHRENIA AFTER TREATMENT WITH THE ATYPICAL ANTIPSYCHOTIC RISPERIDONE

C. Nemeth,* J. Reilly, M. Keshavan, J. Sweeney
Psychiatry, University of Illinois at Chicago, Chicago, IL, USA

Purpose: Impairment in executing volitional behavior is a primary negative symptom in schizophrenia. Evaluating the ability to generate accurate saccades without sensory guidance in a predictive task is one way to assess pre-treatment function, as well as the effects of treatment with atypical antipsychotics on neurocognition in schizophrenia. Design: In predictive saccade tasks, individuals make saccades between two target positions at a fixed time interval. Subjects

learn to produce saccades before target appearance by using an internal representation of the spatio-temporal characteristics of the environment. The accuracy and latencies of saccades in a predictive saccade paradigm were assessed in 29 antipsychotic naive schizophrenic patients and 23 healthy controls, who were matched in age, IQ, and parental SES. Patients were tested before and after 6 weeks of treatment; healthy individuals were evaluated over a similar time period. Results: Pretreatment performance was unimpaired in patients. However, after treatment with risperidone, the accuracy-but not timing-of predictive saccades in schizophrenic individuals declined significantly. When sensory guided saccades (latency greater than 150 ms) and predictive saccades (latency less than 80 ms) on this task were analyzed separately, the schizophrenic patients showed a significant decrease in accuracy after antipsychotic administration during predictive-as opposed to sensory guided-saccadic movements. The healthy individuals displayed no difference in accuracy over the same time interval. Conclusion: A predictive saccade task necessitates the creation of an internal representation of the spatio-temporal characteristics of the environment. In addition to the dorsolateral prefrontal cortex, subcortical areas such as the straitum and the posterior hippocampus are employed in this task. The inaccuracy of predictive saccades in the antipsychotic treated patients may be related to alterations in dopamine binding in the striatum, which could have adverse effects on frontostriatal systems supporting accurate volitional movements. Research Support: MHO1433, MH45156, MH62134, NARSAD, RR00056.

THE CONSORTIUM ON THE GENETICS OF SCHIZOPHRENIA (COGS): RELIABILITY AND VALIDITY OF THE ANTISACCADE ENDOPHENOTYPE IN A LARGE MULTISITE STUDY

A. Radant,* M. E. Calkins, A. Olincy, D. J. Dobie, S. P. Meichle, D. W. Tsuang
Psychiatry and Biobehavioral Sciences, University of Washington, Seattle, WA, USA

Introduction: Ten months ago, researchers at the 7 COGS sites began collecting data on 6 different endophenotypes relevant to schizophrenia genetics, including an antisaccade task. Although the antisaccade task is used extensively in schizophrenia research, it is crucial to document the feasibility and reliability of this paradigm in the context of a large-scale multi-site collaboration if it is to be useful in dissecting schizophrenia genetics. Methods: All sites had expertise in neurophysiological research and 4 sites had prior expertise in oculomotor research. Training during the 5 month set-up period consisted of extensive in-person training sessions, biweekly phone conferences, and review of a detailed manual. Three pseudorandom antisaccade tasks (with parameters identical to those that have been successfully used to examine schizophrenia-control differences) were administered sequentially to 44 carefully diagnosed probands with schizophrenia, 102 relatives of the probands, and 89 controls. After visual inspection to exclude data with unacceptable quality, the major saccade in response to each target was identified with a computerized pattern recognition algorithm. Results: The COGS QA process, including on-site inspections and careful review of data quality, detected and corrected several minor methodological differences across sites. Two hundred thirty five subjects had adequate data quality for all 3 runs of the antisaccade task. Proportion of correct antisaccades was significantly higher in controls (0.84 /- 0.12) than probands (0.61 /- 0.28); probands were worse than controls at all sites (differences ranged from 0.09 to 0.45). Analyses of data from relatives are underway. Intraclass correlations among the 3 tasks varied from 0.86 to 0.95 across the 7 sites. There was a learning effect with performance improving from run 1 to run 2; data from the last 2 runs were nearly identical. Discussion: The high intraclass correlations among the 3 antisaccade tasks at all 7 sites are strong evidence that we are collecting reliable data. Presence of the expected schizophrenia-related deficits across sites indicates that COGS is collecting valid data. There were no major differences in data outcomes across sites, indicating that training and quality assurance efforts were successful. We look forward to using this high quality endophenotypic data to parse the genetics of schizophrenia. Supported by NIH RO1 MH 065558-02.

ABNORMAL STRIATAL ACTIVATION DURING INHIBITION OF SACCADIC EYE MOVEMENTS IN UNAFFECTED SIBLINGS OF PATIENTS WITH SCHIZOPHRENIA

M. Raemaekers,* M. Vink, R. S. Kahn, M. P. van den Heuvel, N. F. Ramsey
Psychiatry, Rudolf Magnus Institute of Neuroscience, Utrecht, Utrecht, Netherlands

Schizophrenic patients have difficulty inhibiting automatic saccadic eye movements. Studies addressing this abnormality in healthy relatives of patients came up with mixed results. This raises some doubt on whether this deficit can be regarded as an endophenotype for schizophrenia. Alternatively, maps of regional brain activation during saccadic inhibition could be a better endophenotypical marker. In a previous study, the saccadic inhibition deficit in patients was associated with abnormal striatal activation. The present study investigates whether a deficit in striatal functioning is also present in healthy siblings of patients with schizophrenia. 16 healthy control subjects and 16 healthy siblings of patients without any signs of psychotic illness participated in the experiment. For image acquisition a 3D PRESTO technique was used on a Philips 1.5 T scanner. The subjects were scanned during production of prosaccades and antisaccades in an Event Related fMRI design. Eye movements were recorded during scanning. Siblings demonstrated reduced activation bilaterally in the body of the caudate nucleus during inhibition of saccades compared to the control group ($Z > 3.6$; $p < 0.05$ bonferroni corrected for the total number of voxels in the striatum; MNI x, y, and z coordinates for the maxima are -13,-2,18 for the right caudate, and 16,-2,18 for the left caudate). The percentage of inhibition errors on the antisaccade task did not differ between siblings and healthy controls (mean controls=23%; mean siblings=27%; $t(30)=.57$; $p=.58$) Functional brain abnormalities can be detected in healthy siblings of patients in the absence of a behavioural deficit. The complexity and number of brain regions involved in the neural circuit for saccadic inhibition may provide backup mechanisms, which could mask the striatal deficit at the behavioral level in at least some of the healthy siblings. The penetrance of the brain-activation-based phenotype could therefore be enhanced compared to the behavioral phenotype. In addition, abnormalities in many parts of the oculomotor network can lead to impairments in saccadic inhibition. Phenocopies arise when individuals show a deficit in saccadic inhibition while being unaffected at the striatal level. Increased penetrance, and reduced number of phenocopies could make this striatal deficit a useful enphenotype for genomic linkage analysis.

USING STRIATAL ACTIVITY AS AN ENDOPHENOTYPE MARKER IN A LINKAGE STUDY

N. Ramsey,* M. Raemaekers, M. Vink, M. P. van den Heuvel, R. S. Kahn
Psychiatry, Rudolf Magnus Institute of Neuroscience, Utrecht, Utrecht, Netherlands

The ability to inhibit unwanted saccades during the antisaccade task appears to be impaired in patients with schizophrenia and their first degree relatives and could be an endophenotype for schizophrenia. Recent evidence suggests that regional brain activation maps during saccadic inhibition may be a more suitable endophenotype than the actual behavioural measure. We have shown that patients exhibit diminished brain activation in the striatum during inhibition of saccades. Moreover, we found that their healthy siblings demonstrate the same abnormality in the absence of a clear behavioural deficit (see poster Raemaekers). This suggests that the brain activation map is a more suitable phenotype for a molecular linkage analysis. Here we report preliminary data of our study which aimed at detecting the gene locus associated with this abnormal brain activation in a single large multiplex pedigree. On the day of this writing, 20 members of a total of 28 of the pedigree had participated in the experiment. 4 subjects were diagnosed with schizophrenia, and 1 with bipolar disorder. For the age and gender matched healthy control group, subjects with signs of psychiatric or neurological disorder were excluded. For image acquisition a 3D PRESTO technique was used on a Philips 1.5 T scanner. All subjects were scanned during performance of prosaccades and antisaccades in an Event Related fMRI design. Eye movements were recorded during scanning. Pedigree members demonstrated reduced activation bilaterally in the body of the caudate nucleus during inhibition of saccades compared to the control group ($Z > 3.6$; bonferroni corrected for the total number of voxels in the striatum; MNI x, y, and z coordinates for the maxima are -13,-1,19 for the right caudate, and 13,-7,19 for the left caudate). Furthermore, there was a trend towards an increased number of inhibition errors during antisaccades in pedigree members ($t(38)=1.44;p=0.08$) These preliminary data suggest that abnormal striatal activation may also underlie the saccadic inhibition deficit in this pedigree. Although the abnormal striatal activation scores within the pedigree show evidence for a dichotomous distribution, 8 additional members will be scanned in the near future to obtain sufficient information to establish the actual mode of inherence. A molecular linkage analysis will be performed to reveal the gene locus associated with this deficit, in case of a clear monogenetic dominant inheritance.

ABNORMAL PREFRONTAL REGULATION OF ATTENTIONAL SYSTEMS IN THE ACUTE PHASE OF FIRST-EPISODE SCHIZOPHRENIA

J. A. Sweeney,* J. L. Reilly, M. S. Harris, M. S. Keshavan
Psychiatry, University of Illinois at Chicago, Chicago, IL, USA

Disturbances in attentional systems are widely recognized in schizophrenia. Oculomotor paradigms permit examination of the cortical regulation of spatial orienting, attention-guided shifts in gaze, and motor programming, all of which are impaired in schizophrenia. Performance on visual fixation and visually-guided saccade tasks was examined in 43 never-medicated schizophrenia patients who were re-evaluated 6, 26, and 52 weeks after starting antipsychotic treatment with risperidone or haloperidol. 37 matched healthy individuals were examined at similar time points. The ability to sustain peripheral and central fixation for 15 sec was unimpaired in patients before and after treatment. In contrast, patients showed faster latencies of visually-guided saccades relative to healthy individuals prior to beginning treatment. An association between this speeding of response latencies and antisaccade error rates before treatment suggests a common mechanism of reduced prefrontal regulation of cortical and subcortical attentional systems in the acute phase of illness. After treatment, saccade latencies slowed to normal levels in patients treated with risperidone but not those treated with haloperidol, despite comparable clinical outcomes. However, a modest but statistically significant reduction in the spatial accuracy of saccades was seen after risperidone treatment. Dysregulation in the prefrontal control of visual sensorimotor systems in the acute phase of schizophrenia may result in reduced attentional engagement reflected in speeded and involuntary responses to visual inputs. This abnormality may contribute to the heightened distractibility observed in some acutely psychotic patients. The observation that the abnormality in visual orienting systems was improved by risperidone but not haloperidol suggests that the atypical antipsychotic risperidone may be more effective in normalizing the prefrontal regulation of some aspects of visual attention systems.

THE ROLE OF ATTENTION IN SMOOTH PURSUIT EYE TRACKING

D. Tegally,* S. B. Hutton
University of Sussex, Brighton, United Kingdom

Patients with schizophrenia reliably demonstrate impaired smooth pursuit eye tracking, characterised by a reduction in velocity gain and an increase in compensatory catch-up saccades. There is currently no consensus concerning the underlying mechanisms. One early hypothesis was that pursuit dysfunction is secondary to attentional deficits, but although attentional dysfunction is well documented in schizophrenia, this explanation has not been systematically explored. Whilst attentional processes have traditionally been closely linked to the production of saccadic eye movements, their role in the control of smooth pursuit eye movements remains unclear. The few studies addressing this issue have produced conflicting results. Some recent research appears to support the notion that smooth pursuit is a relatively automatic behaviour that is performed most efficiently in the absence of controlled attention. However, earlier research found that performing attentionally demanding tasks whilst attempting to track a smoothly moving target led to varying degrees of impairment. In two experiments we used dual task paradigms to vary the attentional resources available for pursuit eye tracking in healthy participants. In both experiments we found that attentionally demanding secondary tasks impaired smooth pursuit performance, resulting in decreased velocity and increased position error, and a consequent increase in catch-up saccades. These findings suggest that attention is important for the maintenance of accurate smooth pursuit, and that reducing attentional resources in healthy participants can lead to a pattern of pursuit dysfunction very similar to that observed in patients with schizophrenia. The exact role played by attention in the maintenance of pursuit remains unclear, but one possibility suggested by these findings is that it facilitates motion processing.

18. Therapeutics: Treatment Trials

DIFFERENTIAL RATES OF CLINICAL TRIAL DISCONTINUATION AS A MEASURE OF TREATMENT EFFECTIVENESS AMONG ANTIPSYCHOTIC MEDICATIONS

D. H. Adams,* B. J. Kinon, H. Liu-Seifert
Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA

Objective: Antipsychotic treatment discontinuation may be used to measure overall treatment effectiveness. Few studies systematically assess early treatment discontinuation differences among antipsychotics. We investigate olanzapine discontinuation compared to other atypical antipsychotics. Methods: A post hoc, pooled analysis of 4 randomized, double-blind clinical trials of 24-28 week duration included 822 olanzapine-treated and 805 risperidone-, quetiapine-, or ziprasidone-treated patients. Discontinuation rate difference was assessed using Fishers exact test comparing olanzapine to the other atypicals combined. Kaplan-Meier estimators for probability of staying in treatment were obtained for both groups and treatment difference investigated by the log-rank test. Results: Olanzapine-treated patients were significantly more likely to complete treatment (53.9% vs. 39.3%, p<.001) and stayed in treatment longer (19.1 vs. 16.1 weeks, p<.0001) than other atypical-treated patients. Treatment difference was primarily driven by differential discontinuation rates due to poor response/symptom worsening (olanzapine 14.23% vs. other 24.60%, p<.0001). There was no difference in discontinuation due to medication intolerability or other reasons. Conclusions: The predominant reason for difference in early discontinuation between olanzapine and other antipsychotics was significantly higher dropouts due to poor response/symptom worsening with the other antipsychotics. Early treatment discontinuation may be an important gauge of relative treatment effectiveness among antipsychotics.

SUPERIOR COGNITIVE EFFICACY OF ATYPICAL ANTIPSYCHOTICS OLANZAPINE, RISPERIDONE, AND QUETIAPINE, AS A GROUP, RELATIVE TO LOW DOSES OF CONVENTIONAL ANTIPSYCHOTICS

E. Antonova,* V. Kumari, R. Halari, E. Zachariah, R. Mehrotra, A. Kumar, T. Sharma
Division of Psychological Medicine, Institute of Psychiatry, London, United Kingdom

Three atypical antipsychotics most commonly used in clinical practice are olanzapine, risperidone and quetiapine. Although divergent in broader pharmacological profile, three drugs share a common property: serotonin-dopamine antagonism, which is thought to explain their superior cognitive efficacy compared with typical antipsychotics. The present study aimed to evaluate the cognitive efficacy of these atypical antipsychotics as a group relative to low doses of typical antipsychotics (Mean = 255.88, SD = 220.71 mg/day in chlorpromazine equivalent) in a within-subject design. Thirty patients (Male/Female = 20/10) with chronic schizophrenia (DSM-IV) taking typical antipsychotics were switched to one of the three atypical antipsychotics in a randomised controlled single-blind (blinded investigators) design and followed for 6 weeks. Starting doses for each atypical antipsychotic were according to the Summary of Product characteristics. Optimal dosage for each patient was achieved within 14 days after the switch. Patients were assessed on a comprehensive neuropsychological battery, including the tests of executive and motor functions, working memory, verbal and spatial immediate memory, logical memory, verbal fluency, sustained and selective attention. Twenty-five healthy participants (Male/Female = 14/9) were assessed at the same interval as patients to control for test-retest practice effect. The effect of atypical relative to conventional antipsychotics on neuropsychological test performance was assessed with a mixed-model analysis of variance (ANOVA) with time (baseline vs. 6 week scores) as a within-subject factor and an atypical antipsychotic (olanzapine, risperidone, or quetiapine) as a between-subject factor. For neuropsychological tests showing significant improvement (p<.001 Bonferroni corrected), a mixed-model ANOVA with time (baseline vs. 6 weeks) as a within-subject factor and a group (patients vs. controls) as a between-subject factor was used to ascertain whether the observed improvement superseded normal practice effects. Twenty-two patients who completed the trial were found to improve significantly on verbal working and immediate memory, regardless of the atypical antipsychotic they were taking. This improvement could not be explained by practice effect. To conclude, atypical antipsychotics as a group appear to improve verbal working and immediate memory relative to low doses of conventional antipsychotics beyond normal test-retest gains.

AMOXAPINE AS AN ATYPICAL ANTIPSYCHOTIC: A COMPARATIVE STUDY VS. RISPERIDONE

R. Apiquian,* A. Fresan, R. E. Ulloa, H. Nicolini, S. Kapur
Psychiatry, National Institute of Neurology and Neurosurgery, Mexico, Mexico City, Mexico

Amoxapine is marketed as an antidepressant. However, its receptor occupancy, in vitro and in vivo, and its effects in pre-clinical models are very similar to atypical antipsychotics.Objective: To Examined the antipsychotic and side-effect profile of amoxapine vs. risperidone in a double-blind study for six weeks in patients with with schizophrenia. Methods: A total of 48 schizophrenic patients were recruited,and 39 patients completed the 6-week follow-up. The doses of Amoxapine and Risperidone starting with a fixed-starting dose (150 mg/d and 3mg/d respectively) with standardized titration up to 250 mg/d for amoxapine and 5mg/d for risperidone,if required. Positive, negative, affective symptoms and side-effects were monitored using standardized weekly assessments. Results: The mean amoxapine dose at the end of the study was 228mg/day(SD.34.6), while for risperidone the mean dose was 4.5mg/day(SD.0.7. Both treatment groups showed significant improvement in PANSS positive, negative and total syndrome scores-the improvement was significant from baseline at the end of the study, without significant differences between groups. No differences were found between groups in terms of akathisia weight or abnormal involuntary movements. Nevertheless, a significant increase in extrapyramidal symptoms was observed in the risperidone group compared to the amoxapine group at the end of the study (t=-2.4, df 37, p=0.02).Prolactin elevation was observed at the end of the study (t=-2.4, df 37, p=0.01), without significant differences in both groups. Conclusion: These clinical data lend support to the pre-clinical suggestions that amoxapine may be an atypical antipsychotic. Given its lack of weight gain and that it is considerably less expensive than current options,amoxapine could be a valuable alternative for some patients.

ETHYL-EICOSAPENTAENOIC ACID (E-EPA) SUPPLEMENTATION IN EARLY PSYCHOSIS. A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL (RCT) COMPARING 2G E-EPA VERSUS PLACEBO ADD-ON THERAPY IN 80 DRUG-NAIVE OR EARLY TREATED FIRST-EPISODE PSYCHOSIS (FEP) PATIENTS

G. E. Berger,* T. M. Proffitt, M. A. McConchie, S. J. Wood, H. P. Yuen, P. D. McGorry
Department of Psychiatry, ORYGEN Research Centre, Parkville, VIC, Australia

80 FEP patients were either treated with 2g E-EPA or placebo added on to a flexible low dose of an atypical antipsychotic (AP) for a period of 12 weeks. Remission, psychopathology, antipsychotic dose, and cognitive (memory, spatial working memory, verbal memory, attention) and structural and metabolic MRI were further outcome measures. We used complete-case analysis (ANCOVA), Last-observation-carried-forward (LOCF) and Multiple imputation (Schafer 1997). Participants were acutely ill (PANSS total around 80, GAF 40) were 20.5years, were males and had either schizophrenia or schizophreniform disorder, the remaining other psychotic disorders completed the trial. By week 12 both treatment groups showed high level of remission (~40%). At end of study period, no difference between psychopathology could be found. However, there was a treatment-groupx-diagnosis interaction for non-affective psychosis (Cox-regression P<0.023) with favorable time-to-first-remission in non-affective psychosis (P<0.065) for the EPA group. In females negative symptoms improved 3.01 units more (P<0.003-0.006) at week 3 and had a better overall functioning at the end of the trial (P<0.034) using complete-case analysis. There was a treatment-groupxDUP interaction for positive symptoms (P<0.04) at week 3, negative symptoms (P<0.007) at week 9, and global clinical illness severity (P<0.012) and negative symptoms (P<0.05) at week 12. EPA group needed less medication (between week 3 and 6 EPA group used a total of 4041mg chlorpromazine equivalent vs. 5064mg in placebo group, P<0. 03) as well as less PRN medication (P<0.05). EPA group had lower rates of movement abnormalities (SAS) at week 3 and 6 (cox-regression models P<0.001-0.003). Unexpected was the finding that EPA group performed 2.7 units (P<0.03) worse on CDSS at week 9 and 12, however the baseline CDSS score was already two units lower in the EPA group at baseline. EPA group improved four times more in spatial working memory (CANTAB), however only half as much in spatial span (CANTAB) compared to placebo. EPA increased glutathione levels by 30% and glutamine/ glutamate levels (H-MRS) in the temporal lobe (see paper by Wood et al). In conclusion, non-affective psychosis patients, particular females, treatment responders and patients with a DUP of >3months may benefit from add on EPA treatment. EPA may be a cognitive enhancer (SWM) and support the glutamine-glutamate-glutathione cycle in the living human brain of FEP patients.

DIMENSIONS OF SCHIZOPHRENIA AND THEIR TIME COURSE OF RESPONSE TO A NOVEL ANTIPSYCHOTIC (OLANZAPINE): A CLINICAL STUDY

B. Birur,* N. Janakiramaiah, T. Jagadisha, B. N. Gangadhar
Psychiatry, NIMHANS, Bangalore, Karnataka, India

Background: Atypical antipsychotics are being increasingly preferred because unlike with typical antipsychotics, negative symptoms particularly respond to atypicals, as well as causing less EPS. As atypicals are used commonly, it is useful to have an empirically established time frame of reference to enable the clinician to rationally monitor patient progress. Objective: The authors examined the short term differential time course of response of negative symptoms and positive symptoms to treatment with the atypical antipsychotic olanzapine in never treated schizophrenia patients. Method: Fifty seven never treated schizophrenia patients (DSM IV) were treated with olanzapine 10mg/day, which was increased to 20mg/day within the end of first week and was maintained till the end of 4-week period. Before starting treatment (baseline assessment) patients were rated on Positive and Negative Syndrome Scale (PANSS) and Simpson Angus Scale (SAS), and their weight was recorded. Assessment on PANSS, SAS and weight were repeated at weekly intervals for four weeks. Results: Forty-three patients completed four weeks of assessment. There was significant reduction of scores on each of the dimensions: positive syndrome and negative syndrome. With four weeks of treatment reduction occurred significantly in positive and negative symptoms with positive/negative ratio close to 1.1 at baseline, and with four weeks of treatment with olanzapine the ratio progressively dropped close to 0.9 and this drop was significant. Percentage improvement in positive syndrome score was significantly more than negative syndrome scores at all assessments. Over four weeks of treatment with olanzapine there was a significant weight gain of 2kg and statistically significant extrapyramidal symptoms. Conclusions: Within a four-week treatment period olanzapine, an atypical antipsychotic failed to show better therapeutic effect on negative than positive syndrome scores of schizophrenia patients. The positive to negative syndrome score ratio infact reduced over four week period suggesting that olanzapine in the early part of treatment lowered positive syndrome scores more effectively than negative. It also produced EPS and significant weight gain. These clinical effects raise doubt if the term atypical is the best adjective for olanzapine.

REMISSION IN SCHIZOPHRENIA AND PATIENT RATINGS OF HEALTH OUTCOMES

C. A. Bossie,* R. A. Lasser, Y. Zhu, G. M. Gharabawi, J. M. Kane
Janssen Medical Affairs, LLC, Titusville, NJ, USA

Data suggest patient-reported well-being is a different domain vs investigator ratings of psychopathology; we therefore analyzed the relationship between patient quality-of-life ratings and attaining remission. In a large, 50-week, open-label trial, stable patients with schizophrenia/schizoaffective disorder received long-acting, injectable risperidone (LAR) Q2 weeks. Remission criteria were applied (PANSS, absent–mild ratings on 8 core symptoms for ≥6 mo). We measured PANSS, CGI-S, and patient-rated health status (SF-36) and Drug Attitude Inventory (DAI) at regular intervals. SF-36 mental-health subscales were: mental-health index, vitality, social functioning, role emotional. At study entry, 65% (394/578) of "stable" patients were unremitted (Andreasen, inpress). After LAR, 21% of these achieved remission for ≥6 months. Remitted patients claimed substantial improvements in self–rated mental health status; 76.8% met the mean US normative value (USNV) for ≥1 on the 4 SF-36 mental health subscales at endpoint (EP), vs 48.8% at baseline (BL). The mean USNV on ≥2 subscales was met by 56.1% EP, vs 25.6% BL. Remitted patients' mean DAI improved at EP (P<0.001). SF-36 USNV (BL vs EP) changed substantially less among those who remained unremitted (n=302). Of these, 60.3% met the USNV for ≥1 subscale at EP, vs 57.3% BL; 37.8% met the USNV for ≥2 subscales at EP, vs 33.8% BL. Mean DAI did not change significantly at EP in

those not meeting 6-month remission (P=0.118). Among those who met remission (severity-level criteria) at BL, but not EP (n=28), those meeting ≥1 mean SF-36 USNV decreased: 35.7% EP; 75.0% BL. Mean △DAI was not significant (P=0.134). By logistic regression analysis, a CGI-S of not ill (0;95%CI, 0.00, 0.18) was associated with a 97.1% probability of meeting the remission criteria (symptom severity) at EP; a CGI-S of very mild (1;95% CI, 0.89,1.11), with 86.8% probability. Using PANSS-defined remission criteria, many patients considered stable were "remitted" at study entry; 21% achieved remission with LAR. Remission was associated with significant improvements in multiple symptom domains and patient-rated drug attitude and health status. Our results verify the remission criteria and suggest a possible association between clinician-rated remission and patient ratings of mental health. The criteria merit further study, as they may represent meaningful clinical outcome and a step toward functional recovery.

BIOEQUIVALENCE OF AN ORALLY DISINTEGRATING TABLET COMPARED TO THE ORAL TABLET FORMULATION OF THE ANTIPSYCHOTIC ARIPIPRAZOLE

D. Boulton,* D. Dressler, G. Kollia, M. Vachharajani, S. Mallikaarjun, W. Carson, D. Kornhauser
Bristol-Myers Squibb, Lawrenceville, NJ, USA

To confirm the bioequivalence of aripiprazole oral tablet and when administered as an orally disintegrating tablet (ODT), two open-label, randomized, three-period, two-treatment, crossover studies were conducted in healthy subjects to assess the bioequivalence of the ODT compared to the oral tablet, administered at doses of 5 mg (n=38) and 30 mg (n=30). Serial blood samples were collected from subjects for up to 384 hours during the studies. Bioequivalence was to be concluded if the 90% confidence intervals for the ratio of adjusted geometric means of the ODT to oral tablet were within 80% to 125% for aripiprazole C_{max} and AUC_{inf}. Both the C_{max} and AUC_{inf} for aripiprazole met criteria for bioequivalence at both doses. Point estimates and 90% confidence intervals for the ratios of the aripiprazole ODT to oral tablet adjusted geometric means were 1.02 (0.96, 1.08) for C_{max} and 1.00 (0.96, 1.04) for AUC_{inf} at the 5 mg doses. Point estimates and 90% confidence intervals for the ratios of the aripiprazole ODT to oral tablet adjusted geometric means were 1.03 (0.95, 1.12) for C_{max}, and 1.01 (0.94, 1.08) for AUC_{inf} at the 30 mg doses. Median T_{max} and mean $T_{1/2}$ were comparable between the formulations at each dose. No serious adverse events occurred with either formulation at either dose. Bioequivalence was established between the orally disintegrating tablet of aripiprazole and the oral tablet with respect to aripiprazole C_{max} and AUC_{inf} in healthy subjects. The aripiprazole orally disintegrating tablet offers a convenient alternative formulation for patients who have difficulty swallowing tablets.

A RETROSPECTIVE CASE SERIES OF ARIPIPRAZOLE AUGMENTATION OR SUBSTITUTION IN SIX CLOZAPINE-TREATED PATIENTS

I. Bratti,* J. Boyd, S. A. Resnick, J. M. Pierre, D. A. Wirshing, W. C. Wirshing
Department of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Aripiprazole is the newest compound added to our list of available somatic therapies for psychosis. It has a unique pharmacologic profile, and therefore may have utility in patients refractory to, or unable to tolerate, clozapine. Data on this retrospective case series of six patients with schizophrenia or schizoaffective disorder was culled from the Veterans Affairs computerized medical record, and from consultation with the attending physician. We attempted to switch six patients from clozapine to aripiprazole, although four of the six were ultimately maintained on a combination of both medications. The rationale for initiating aripiprazole was both for residual symptom improvement and to decrease clozapine side effects. We found that three of the patients did well after aripiprazole initiation; two of the three were maintained on combination therapy with clozapine. Of the three patients who did not do well, one appeared to become acutely manic with full discontinuation of clozapine, necessitating its reinstitution. The other two patients remained densely psychotic despite aripiprazole therapy and were re-hospitalized within three months of their last discharge, with aripiprazole subsequently being discontinued. Four of the six patients lost weight following the initiation of aripiprazole; two patients gained weight. Three patients demonstrated significant reductions in their fasting glucose levels. Of the four patients with sufficient data, two showed a decrease in their lipid panel values, and two showed no significant change. Aripiprazole conferred mixed results in these clozapine-refractory patients. While about half improved significantly with the addition or substitution of aripiprazole, one became acutely manic and two others showed limited or no clinical improvement. On the whole, the addition of aripiprazole improved metabolic profiles in all but one patient, though there was variability in regards to which measures improved. This study was supported by a grant from Bristol-Myers Squibb.

SAFETY AND TOLERABILITY OF ARIPIPRAZOLE TREATMENT FOR PSYCHOSIS OF ALZHEIMER'S DEMENTIA: A POOLED DATA ANALYSIS

C. Breder,* E. Stock, H. Goyvaerts, W. Carson, T. Iwamoto, D. Kostic, R. Wilber
Bristol-Myers Squibb, Wallingford, CT, USA

The aim of this analysis was to characterize the safety and tolerability of aripiprazole in elderly patients with psychosis associated with Alzheimer's dementia (AD). Safety data for this analysis were pooled from two 10-week, double-blind, placebo-controlled trials of aripiprazole treatment in 458 patients with psychosis of AD. The dosing regimen of aripiprazole consisted of titration in the 2–15 mg/day range. The discontinuation rate due to adverse events was 8% with placebo and 12% with aripiprazole. There was no clear pattern of adverse events leading to discontinuation with either treatment. The most commonly reported adverse event in both groups was accidental injury (placebo, 18%; aripiprazole, 15%). Somnolence was the only adverse event in the aripiprazole group that occurred with an incidence rate more than 5% higher than in the placebo group (placebo, 3%; aripiprazole, 11%). Most cases of somnolence reported with aripiprazole were mild to moderate in intensity, and only two patients discontinued therapy because of this adverse event. EPS-related adverse events were reported in 4% of patients treated with placebo and 5% of those treated with aripiprazole. Analysis of pooled data from two trials involving patients with psychosis of AD indicates that aripiprazole is safe and well tolerated in this patient population, with low rates of EPS and of discontinuation due to adverse events.

GLUTAMATERGIC AGENTS FOR THE TREATMENT OF COGNITIVE IMPAIRMENTS IN PATIENTS WITH SCHIZOPHRENIA

R. W. Buchanan,* J. M. Gold, R. Bilder, M. Green, D. C. Javitt, S. R. Marder, N. R. Schooler, U. Heresco-Levy, R. P. McMahon, W. T. Carpenter
Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD, USA

Patients with schizophrenia are characterized by a broad range of cognitive impairments. These impairments include: attention/information processing; problem solving; processing speed; social cognition; visual and verbal learning and memory; and working memory. Despite appropriate treatment with either conventional or second generation antipsychotics, patients continue to exhibit pronounced cognitive impairments. This has led to the investigation of adjunctive co-therapy for the treatment of these impairments. Glutamatergic agents are one class of agents that has been proposed for this purpose. Previous small-N studies with agents that act at the glycine-site of the NMDA receptor have produced mixed results. The current multicenter, 16-week, placebo-controlled, double-dummy, parallel group, RCT was designed to examine the efficacy of glycine and d-cycloserine for the treatment of cognitive impairments. 171 patients with either DSM-III-R/DSM-IV schizophrenia or schizoaffective disorder entered the study. A comprehensive neuropsychological battery was administered at baseline and at the end of treatment. For analyses we grouped all tests within each cognitive domain to create individual domain summary scores and combined all domain scores to create a global summary score. We estimated glycine versus placebo and d-cycloserine versus placebo effects on both the global and individual domain scores, using a mixed model for repeated measures, where the cognitive measure is the repeated factor within the individual. Results: The primary analysis for cognitive improvement showed a modest worsening for d-cycloserine vs. placebo {p = 0.014} which disappeared when two outliers on one cognitive domain were removed {p = 0.95}. Glycine was similar to placebo with no meaningful change in either group {p = 0.33}. Conclusion: Glycine and d-cycloserine efficacy and effectiveness hypotheses are not supported. Supported by NIMH R01 MH59807.

READINESS FOR HOSPITAL DISCHARGE: RELATIONSHIP WITH MEASURES OF SYMPTOM IMPROVEMENT IN SUBJECTS WITH SCHIZOPHRENIA

P. F. Buckley,* M. Rupnow, A. Greenspan, G. Gharabawi, C. Bossie, Y. Zhu, C. Kosik-Gonzalez, C. Ruetsch, D. Revicki, R. Anand
Department of Psychiatry, Medical College of Georgia, Augusta, GA, USA

Background: Recent clinical research has focused on readiness for hospital discharge as an important end point in trials for patients with mental illness. The Readiness for Discharge Questionnaire (RDQ) is a new tool specifically designed for use in clinical studies of hospitalized patients with schizophrenia to assess readiness for discharge from the inpatient setting. This analysis examined how the RDQ findings related to findings on clinician- and patient-reported scales in a double-blind study of inpatients with a recent exacerbation of schizophrenia. Methods: 382 patients entered the study and were rated with the PANSS, CGI, HAM-D, medication satisfaction questionnaire, and the RDQ (a 6-item questionnaire that assessed readiness for discharge from the inpatient setting). Data were stratified by readiness for discharge status (Yes or No) by the RDQ at day 14 end point (LOCF). Between-group differences were tested by ANOVA or ANCOVA. Results: Patients who were ready for discharge at end point had significantly lower mean PANSS total scores at baseline than those who were not ready for discharge (93.2±18.0 and 97.6±18.7, respectively; p=0.02). Baseline HAM-D and CGI-S scores were comparable in the 2 groups. Patients who were ready for discharge had significantly greater improvements than those who were not ready for discharge, as measured by the mean (SE) change scores on the PANSS total (−31.7±1.2 and −15.7±1.2, respectively; p<0.001), HAM-D total (−6.0±0.3 and −3.9±0.3, respectively; p≤0.001), and CGI-S (−2.1±0.1 and −0.9±0.1, respectively; p<0.001). Patient-reported medication satisfaction questionnaire scores were significantly higher at end point in patients ready for discharge compared with those not ready for discharge (5.5±0.1 and 4.2±0.1, respectively; p<0.001). Conclusion: These data suggest that readiness for hospital discharge, as determined by the RDQ, is associated with improvements in several independent measures including psychotic symptoms, depressive symptoms, overall clinical status, as well as greater patient satisfaction with their medication. These data support the usefulness and validity of the RDQ as a meaningful research tool. Supported by Janssen Medical Affairs, L.L.C.

CLARIFYING THE CLINICAL INTERPRETATION OF PANSS SCORES: AN ANALYSIS OF OVER 3,000 PATIENTS

B. J. Campbell,* Y. Zhu, R. A. Lasser, C. Smith, R. J. Baldessarini
Janssen Medical Affairs, LLC, Titusville, NJ, USA

INTRODUCTION: The Positive and Negative Syndrome Scale (PANSS) is a well-validated, 30-item clinical rating scale (score range: 30–210) commonly employed in experimental therapeutics for psychotic disorders. Although valuable for research, PANSS ratings are not readily understandable as clinical status. Accordingly, we evaluated relationships of PANSS ratings to those with the Clinical Global Impression of Severity (CGI-S) scale, a validated 7-point scale (range: 1 = "not ill", to 7 = "extremely ill") to enhance clinical interpretation of PANSS ratings. METHODS: We analyzed relationships of paired CGI-S and PANSS ratings (15,298 assessments) from 3,118 patients diagnosed with DSM-IV schizophrenia or schizoaffective disorder in 7 treatment trials by linear regression modeling, and used proportional-odds analysis to build a probability model for CGI–S ratings predicted by PANSS–total scores. RESULTS: A regression model [CGI = 0.899 + (0.040)(PANSS)] yielded r2 = 0.580. We constructed a proportional-odds model: Logit(gi[CGI]) = yi + [k(PANSS total)] with a common slope (k= –0.104), and y–intercept (yi) values for CGI scores of 1–6, of: 1.713, 4.282, 6.599, 9.427, 11.78, and 14.87. The model indicates, e.g., that a PANSS-total score of 100 corresponded to CGI-S scores with respective likelihoods of: 0.0% (CGI=1), 0.2% (CGI=2), 2.0% (CGI=3), 25.2% (CGI=4), 52.4% (CGI=5), 19.0% (CGI=6), and 1.1% (CGI=7), or most likely to CGI=5 ("markedly ill"). Similarly, a PANSS score of 70 indicates "moderate" severity, and 50 indicates "mild" morbidity. A patient has an 80% chance of being rated "not-ill to mildly ill" (CGI-S ≤3) at PANSS = 50, 34% at 70, and only 2% at 100. CONCLUSIONS: The reported model supports estimation of the most likely global clinical rating of illness-severity corresponding to specific PANSS scores and demonstrates the feasibility of simple translations of PANSS scores into readily clinically appreciated outcomes.

TESTING TWO EFFICACY HYPOTHESES FOR THE TREATMENT OF NEGATIVE SYMPTOMS

W. T. Carpenter,* R. W. Buchanan, D. C. Javitt, S. R. Marder, N. R. Schooler, U. Heresco-Levy, B. Kirkpatrick, R. P. McMahon
Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD, USA

Background: Enduring forms of negative symptoms are an unmet therapeutic need in schizophrenia. Based on the hypoglutamatergic hypothesis and preliminary RCT data from Javitt, Goff, and colleagues, we evaluated the efficacy of glycine and d-cycloserine. This 5-site, multicenter study is the largest study to date of these agents. Method: The design is a RCT with co-administration of experimental drug or placebo with previously prescribed antipsychotic for 16 weeks in patients who have low to moderate psychosis, EPS, and depression that remain stable throughout the study. All subjects met criteria for persistent negative symptoms and are stratified according to SDS deficit/non-deficit categorization. 171 patients were randomly assigned to placebo or glycine or d-cycloserine. Analysis is based on a mixed model analysis of variance for repeated measures with negative symptom change as the primary dependent measure. Results: The primary analysis for negative symptom effectiveness revealed slight improvement in each group with d-cycloserine vs placebo {p=0.90} and glycine vs placebo {p=0.63 } with no difference in the proportion of >20% responders. There was not a deficit/non-deficit schizophrenia difference. Baseline and change during treatment values for glycine did not relate to response. At week 16, 9 responders on glycine actually had lower blood glycine levels and less change from baseline than 30 non-responders (t=1.57, df=34.3, p=0.12). A significant treatment x site interaction resulted from one site (total n=17) with modest improvement on active drugs and little placebo response while another site (n=24) had worsening on active drugs combined with a large placebo response. Conclusions: Efficacy and effectiveness hypotheses for glycine and d-cycloserine were not supported for negative symptoms. This study had power=0.80 to detect an effect size of 0.25 s.d. at alpha=0.05. A small effect, or a small treatment responsive sub-group can not be excluded. Supported by NIMH RO1 MH59807.

LONG- AND SHORT-TERM EFFECTS OF ARIPIPRAZOLE TREATMENT ON THE PANSS EXCITEMENT/HOSTILITY CLUSTER OF SCHIZOPHRENIA SYMPTOMS

W. H. Carson,* R. Marcus, M. Radhakrishnan, S. Hardy, T. Iwamoto, D. Kostic
Otsuka America Pharmaceutical Co, Princeton, NJ, USA

This abstract presents an analysis of the effects of aripiprazole on the excitement and hostility symptoms associated with schizophrenia. Changes in the excitement and hostility cluster, derived using factor analysis of PANSS scores from long- and short-term studies, were subjected to analysis. Short-term data were pooled from five short-term, multicenter trials of patients with schizophrenia or schizoaffective disorder, randomized to either aripiprazole (n=885) or placebo (n=405). A 52-week study comparing aripiprazole (n=853) with haloperidol (n=430) in patients with schizophrenia was used in the long-term data analysis. Short-term study results showed a significant difference in the excitement and hostility factor score between the aripiprazole and placebo groups, with a mean increase (i.e., worsening) of 1.29 points with placebo compared with a mean decrease of 0.94 points with aripiprazole (P<0.001). Analysis of two fixed-dose studies which included haloperidol arms also showed that both aripiprazole and haloperidol treatments significantly improved excitement and hostility scores compared with placebo (aripiprazole, –1.17; haloperidol, –1.11; placebo, 1.48; P<0.001). Results from the long-term study showed that at week 8, the excitement and hostility score had decreased from baseline by 2.56 points with aripiprazole and 2.43 points with haloperidol treatment. This effect was maintained over the 52-week study period. Reduction of the excitement and hostility symptoms associated with schizophrenia was shown to be more effective with aripiprazole treatment than placebo and comparable to treatment with haloperidol.

COGNITIVE PERFORMANCE IN PATIENTS WITH SCHIZOPHRENIA AFTER RIVASTIGMINE TREATMENT

S. Chouinard,* J. Poulin, E. Stip, R. Godbout, P. Lalonde, J. P. Melun, G. Zahirney, L. Ait Bentaleb, H. Cohen
Centre de Recherche Fernand-Seguin, Hopital Louis-H-Lafontaine, Montreal, QC, Canada

Objective: Previous studies have shown that the cholinergic system is implied in cognitive functioning. It also have been suggested that it might be involved in schizophrenia symptoms. Cholinergic agonists, including acetylcholinesterase inhibitors like rivastigmine, have been shown to slow down the cognitive decline in demented patients. The aim of this study was to evaluate the effects of rivastigmine a cholinesterase inhibitor on cognitive functions in patients with schizophrenia. Methods: Twenty patients with schizophrenia (age=30-8years; M=15, F=5) stabilized with atypical antipsychotics and cognitively impaired participated to a 24-week crossover study. Patients were randomly assigned to condition 1 (rivastigmine for the first 12 weeks and no cholinergic treatment for the next 12 weeks) or condition 2 (no cholinergic treatment for the first 12 weeks and rivastigmine for the next 12 weeks). Patients had neurocognitive evaluations performed with Cambridge Neuropsychological Test Automated Battery (CANTAB) at three times (baseline, after 12 and 24 weeks). Drug titration was 3mg/day reaching 6mg by the first month and progressively increased to 9mg/day, depending of tolerability. Tasks used were: Stockings of Cambridge (SOC), Rapid Visual Processing (RVP), Spatial Working Memory (SWM), Paired Associates Learning (PAL), and Reaction Time (RT) to evaluate executive functions, sustained attention and visual detection, working memory, explicit memory and procedural memory respectively. Results: Latin Square analyses on all neurocognitive variables showed no significant difference after rivastigmine treatment. The results failed to show improvement in attention, memory, or executive functions. Conclusion: Results suggest that acethylcholinesterase inhibitors as rivastigmine have no specific effect on cognitive functioning in patients with schizophrenia stabilized with antipsychotics treatment. No improvement or deterioration was observed after rivastigmine treatment. Our future research will examine the relationships between cognitive performance, subjective complaints and sleep variables after rivastigmine treatment.

ZIPRASIDONE VS HALOPERIDOL FOR THE TREATMENT OF AGITATION

L. Citrome,* S. Brook, A. Loebel, F. S. Mandel
Clinical Research and Evaluation Facility, Nathan S Kline Institute for Psychiatric Research, Orangeburg, NY, USA

The purpose of this study is to compare the efficacy of sequential IM/oral ziprasidone vs IM/oral haloperidol in the treatment of agi-

tation in patients with an acute psychotic disorder. Our methods included a post hoc analyses of pooled data from 2 randomized studies comparing mean reductions in BPRS agitation, activation/aggression, anxiety/depression, positive, and negative factor scores over the first 3 and 7 days among patients with an acute psychotic disorder. In the first study (a 7-day study of subjects with an acute non-organic psychosis), 90 patients received <3 days IM ziprasidone, then oral ziprasidone (80-200 mg/d, mean 90.5 +/- 44.9 mg/d) and 42 patients received IM haloperidol, then oral haloperidol (10-80 mg/d, mean 14.0 +/- 10.1 mg/d). In the second study (a 6-week study of subjects with an acute exacerbation of schizophrenia or schizoaffective disorder), 417 patients received IM ziprasidone, then oral ziprasidone (80-160 mg/d, mean 116 +/- 30.4 mg/d) and 133 patients received IM haloperidol, then oral haloperidol (5-20 mg/d, mean 11.5 +/- 3.6 mg/d). Effect was assessed by Hierarchical Linear Model analysis - repeated assessments of a BPRS factor over time served as the dependent variable. The two independent variables were 'treatment group' (between subject factor) and 'time' (within subject factor). Interaction between treatment group and time was included in the model. Our results demonstrated that in the first three days of treatment ziprasidone was superior to haloperidol on the agitation (p=0.0013), activation/aggression (p=0.0276), and anxiety/depression factors (p=0.0256), but no differences were seen on the positive (p=0.3129) or negative factors (p=0.1235). The differences observed might be attributable to a slight initial worsening of symptoms for the subjects receiving haloperidol in one of the two studies from which the data was drawn. After three days efficacy measures for each of the two treatments converged and further improvement was likely due to a time effect. Thus, post hoc analyses indicate possible efficacy advantages of ziprasidone over haloperidol for the treatment of agitation. Given the tolerability advantages of ziprasidone over haloperidol, overall effectiveness would be expected to be greater for ziprasidone. Appropriately designed clinical efficacy trials will need to be done to confirm these preliminary findings.

THE INVESTIGATOR'S ASSESSMENT QUESTIONNAIRE (IAQ): A NEW CLINICAL MEASURE FOR OVERALL TREATMENT EFFECTIVENESS

P. Corey-Lisle,* J. Han, S. Ray, H. Li, L. Hanssens, G. L'Italien
Bristol-Myers Squibb, Wallingford, NJ, USA

Success of long-term therapy in schizophrenia is contingent upon treatment effectiveness. Effectiveness is concerned with several domains (efficacy, safety, and tolerability) in routine care of patients in usual settings[1]. We compared a new instrument measuring overall treatment effectiveness, the Investigator's Assessment Questionnaire (IAQ), to standard clinical assessments. The IAQ was used as a secondary measure in two identically designed, randomized, open-label studies of atypical antipsychotic treatment in patients with schizophrenia or schizoaffective disorder (Total N = 1926). The IAQ is a validated[2] 10-item, clinician administered questionnaire evaluating the efficacy, safety, and tolerability of antipsychotic therapy. Each IAQ item is scored on a 5-point Likert scale, items are summed for a total score with lower scores indicative of greater overall effectiveness. The mean total IAQ scores were correlated to time-to-discontinuation (TTD), Clinical Global Impression-Improvement (CGI-I), and preference of medication (POM), using the pooled clinical trial data. Criterion-related validity is suggested by the favorable correlation between mean total IAQ scores and CGI-I ($r = 0.75$, $p < 0.0001$) and POM ($r = 0.69$, $p < 0.0001$); construct validity is demonstrated by the moderate correlation between the IAQ and TTD ($r = 0.40$, $p < 0.0001$). Clinical relevance is demonstrated by the finding that a 1-unit increase in mean total IAQ score would correspond to a 23% increase in hazard for time-to-discontinuation. These results provide continued validation of the IAQ as a measure of overall effectiveness. Given the large number of antipsychotic treatments available, it is important for practitioners to have simple-to-administer, validated clinical instruments to evaluate comparative overall effectiveness between agents. 1. Jaffe AB, Levine J, 2003. Efficacy and effectiveness of first- and second-generation antipsychotics in schizophrenia. *J Clin Psychiatry* 64(Suppl 17):3-6. 2. Tandon R, DeVellis RF, Han J, Li H, Frangou S, Dursun S for the IAQ Validation Study Group. Validation of the Investigator's Assessment Questionnaire, a new clinical tool for assessing response to antipsychotics in patients with schizophrenia and schizoaffective disorder. Manuscript under review.

THE PROBLEM OF LAST OBSERVATION CARRIED FORWARD IN PSYCHIATRIC RESEARCH

S. M. Cotton,* H. Yuen
ORYGEN Research Centre, Department of Psychiatry, University of Melbourne, Parkville, VIC, Australia

Missing data is an unfortunate but foreseeable element of longitudinal psychiatric research. Data may be missing due to numerous factors that may be either exogenous and/or endogenous to the patient. One of the most prevalent techniques for dealing with missing data is last observation carried forward (LOCF). Although LOCF is straightforward and easy to implement, recent research has indicated that this technique has serious flaws. The aim of this paper will be to explain the problems that can occur when using LOCF for research on first episode psychosis. Of particular interest is the effect that LOCF can have on study parameters such as mean change scores, standard error of the mean change scores, and type I error rates. Data will be sourced from a number of studies on patients with first episode psychosis. It will be demonstrated that LOCF can lead to deleterious outcomes including overestimating and underestimating treatment effects, inflating type I error, and distorting covariance matrices. Caution is warranted with the use of LOCF in research on first episode psychosis.

DRUG-SPECIFIC CORRELATES OF RELAPSE RISK IN SCHIZOPHRENIA: A RETROSPECTIVE ANALYSIS OF RANDOMIZED, DOUBLE-BLIND COMPARATOR STUDY OF OLANZAPINE VERSUS RISPERIDONE

W. Deberdt,* H. Liu-Seifert, J. Csernansky, P. Buckley, J. Peuskens, S. Kollack-Walker, D. VanBrunt
Eli Lilly and Company, Indianapolis, IN, USA

Purpose: To compare correlates of relapse during olanzapine (OLZ) and risperidone (RIS) treatment. Methods: In a 28-week study, we examined correlates or relapse in responders (≥20% improvement on PANSS at 8 weeks) to 10-20 mg OLZ (n=105) or 4-12 mg RIS (n=94) through logistic regression. Results: Among responders, more patients relapsed (≥20% worsening on PANSS and CGI-S ≥3) with RIS (28.7%) than with OLZ (12.4%). Significant correlate-by-treatment interactions were found with severity and improvement of

symptoms (PANSS Total and Positive), akathisia, and having useful work at Week 8, as well as dose decrease. Within-group analyses found significant associations with relapse for dose decrease (Odds Ratio [OR]=5.4, Confidence Interval [CI]=1.3-22.1, p=.02) and less useful work at Week 8 (OR=2.5, CI=1.25-5.0, p=.02) in the OLZ group. Unexpectedly, but consistent with an earlier analysis, more robust positive symptom improvement at Week 8 was associated with relapse in the RIS group (OR=1.1, CI=1.02-1.2, p=.02). No significant association was found with disease duration, negative symptoms, parkinsonism, or weight gain in either group. Conclusions: Relapse correlates appear to be drug-specific. Further research is warranted to confirm this finding and determine its generalizability.

ASSESSING THE NEUROPROTECTIVE EFFICACY OF LOW DOSE LITHIUM IN INDIVIDUALS AT ULTRA HIGH RISK OF DEVELOPING PSYCHOSIS

M. L. Dell'Olio,* G. E. Berger, L. J. Phillips, J. Regan, A. Thampi, S. Wood, L. D. Tennakoon, D. C. Kelly, A. R. Yung, P. D. McGorry
Dept. of Psychiatry, University of Melbourne, Parkville, VIC, Australia

Background: Recent evidence suggests that neurodevelopmental changes may occur during the transition to a full-blown psychotic illness. Previous post-mortem analysis of the temporal cortex of patients with schizophrenia and bipolar disorder, demonstrated a 25% reduction of bcl-2 protein, indicating apoptotic regulatory mechanisms may be affected. Neuroprotective agents such as lithium may counteract such postulated regressive processes and support neurotrophic development. Clinical studies have also demonstrated an increase in overall N-acetyl-aspartate (NAA) concentrations in the frontal, temporal, parietal and occipital lobes in bipolar individuals following four weeks of lithium treatment. Aim: This trial is investigating whether low-dose lithium treatment prevents the progression to a first episode of psychosis or reduces the severity of symptomatology. We are further investigating the influence of low dose lithium on NAA concentrations, and structural grey and white matter volume changes in ultra high risk patients. Method: The PACE Clinic (Melbourne, Australia) is currently conducting an open-label, pilot scale trial using low-dose lithium (450mg) in a cohort of individuals identified as having an ultra high risk for developing a psychotic illness. Results: Biological and psychopathology assessments are continuing, and interim analyses (including imaging data) will be presented.

ADJUVANT THERAPEUTIC EFFECTS OF GALANTAMINE ON NEGATIVE SYMPTOMS AND APATHY IN INPATIENTS WITH CHRONIC SCHIZOPHRENIA: AN OPEN LABEL PROSPECTIVE STUDY

S. I. Deutsch,* M. W. Nelson, R. B. Rosse, R. L. Benham
VISN 5 Mental Health Service Line, Department of Veterans Affairs, Washington, DC, USA

A regionally selective deficiency of the expression of the alpha7 nicotinic acetylcholine receptor (nAChR) has been reported in schizophrenia. This selective impairment of neurotransmission explains some of the disturbances in pathophysiology (e.g., impaired sensory inhibition and impaired voluntary smooth pursuit eye movement performance) and psychopathology (e.g., inability to sustain attention and loosening of associations). Further, impaired sensory inhibition occurs in unaffected first-degree biological relatives, is inherited in an autosomal dominant manner, and serves as an endophenotype for genetic studies. Galantamine is a positive allosteric effector of nAChRs, in addition to inhibiting acetylcholinesterase activity. Galantamine's adjuvant therapeutic properties were studied in inpatients with chronic schizophrenia using an open-label design. Galantamine was added to stable regimens of antipsychotic medications and titrated to the maintenance dose of 24 mg/day over a 3 week period; thereafter, this dose was maintained for two-months. 11 patients have been enrolled and 7 have received study medication. Formal ratings were obtained on baseline, at the end of titration, and after one and two months on the maintenance dose (24 mg/day). Adjuvant galantamine has been well-tolerated and no subjects were withdrawn due to intolerable side effects nor was worsening of either extrapyramidal side effects or mood observed. To date, 7 male patients with a mean duration of illness of greater than 27 years completed this open-label trial; 5 of them smoked ≥1 packs of cigarettes per day. Graphical displays of the data show galantamine-associated improvements on the modified SANS Summary Scores, BPRS negative symptom scores, BPRS positive symptom scores, and Marin Apathy Evaluation Scale scores. Further, the display of data suggests that, for several of these measures, improvement was noted as early as week 3 and sustained for the duration of the trial. Importantly, 2 of the patients have requested to remain on galantamine after their completion of the protocol. The data suggest a possible adjuvant therapeutic effect of galantamine, including the treatment of negative symptoms and apathy, in patients with chronic schizophrenia and residual symptoms.

HIGH-DOSE ZIPRASIDONE: EFFICACY AND TOLERABILITY IN CLINICAL PRACTICE

D. A. Deutschman,* D. Deutschman
Southwest General Health Center, Case Western Reserve University, Middleburg Heights, OH, USA

Ziprasidone's clinical development program evaluated safety and tolerability at dosages ≤200 mg/d. Limited data on higher dosages are available. We review ongoing clinical experience at dosages ≤480 mg/d. Variously diagnosed patients given ziprasidone 240 mg/d met the following criteria: (1) treatment-resistant history, (2) robust but incomplete response at 160 mg/d, (3) minimal side effects. Similar criteria were applied to patients advanced stepwise to 320, 400, and 480 mg/d. An electronic medical record, Behavior 2003, allowed analysis of dosages, demographics, diagnoses, efficacy, and adverse events (AEs). A total of 51 patients received ≥240 mg/d for ≤18 months, 37 for ≥14 days and a minimum of 3 visits; ages ranged from 19-84 years, with 5 patients being ≥60 years old. Of these, 21 (ages 19-62 years) were advanced to 320 mg/d, 3 (ages 20-36 years) then to 400 mg/d, and 2 (age 36-48 years) then to 480 mg/d. Most patients improved in primary illness severity (Likert scale, clinician rated). Improvements in negative, depressive, and anxiety symptoms were particularly noteworthy. Treatment was well tolerated; no patients discontinued due to AEs. No clinically significant ECG changes were observed. In conclusion, our research indicates that treatment-resistant patients who partially respond to ziprasidone at 160 mg/d may benefit from dosages as high as 480 mg/d, with good toleration.

PLASMA LEVELS OF OLANZAPINE: FINDINGS FROM AN OPEN-LABEL STUDY OF ADOLESCENTS AND YOUNG ADULTS WITH SCHIZOPHRENIA

R. Dittmann,* H. Clement, W. Knebel, F. Roesch, U. Hagenah, J. Junghanss, A. Maestele, C. Mehler, C. Meyer, M. Pitzer, H. Remschmidt, D. Schlamp, M. Schulte-Markwort, O. Weiffenbach
Medical Department, Lilly Deutschland GmbH, Bad Homburg, Germany

Objectives: To present results both on olanzapine plasma concentrations and efficacy and safety from an open-label study in the treatment of adolescent patients with schizophrenia. Background: The majority of psychotropic compounds do not have regulatory approval for use in adolescents. As efficacy and safety data on these drugs, including olanzapine, are scarce for this age group, this holds for pharmacokinetic data as well. Methods: This is an open-label multicenter trial of olanzapine (5-20mg/day, QD) in patients (12-21 y.) with DSM-IV diagnosis of schizophrenia. Blood samples were drawn throughout the study, up to 9 samples/patient. For a comparison with adult plasma concentrations (from a registration study) we considered patients that were on a given dose for at least 6 days and had their weight recorded. We used BPRS0-6 (response criterion at Wk 6: ?30% reduction) to assess the efficacy of olanzapine; safety was assessed based on adverse events (AEs), weight, laboratory analyses, and Simpson-Angus scores. Results: 100 pts. entered the study, 96 were treated with olanzapine, 80 reached week 6, and 34 of 60 responders completed the 6-months. Mean length of treatment (mean max dose =16.7mg/day) was 97.2 days. 489 olanzapine plasma concentrations were collected from 93 pts.; for the comparison with adults, 301 plasma concentrations from 82 pts. were included. For weight-normalized olanzapine doses the trend of the data suggests that adolescents on average had plasma concentrations that were higher (Cpss=194xDose + 4.4) than concentrations in adults (Cpss=139xDose + 3.5), but values still fell within the expected range for pts. treated on a once-daily schedule. The response rate was 62.5% (N=60/96), the BPRS0-6 total score was decreased by 17.0 ($p<0.01$). 3 pts. had serious AEs; 4 pts. discontinued for non-serious AEs. The most common AEs were weight gain (N=29; 30.2%) and increased prolactin (N=24; 25.0%). Mean change in Simpson-Angus score was -0.2. Conclusions: Data from this ICH-compliant trial revealed the following: Adolescents show consistency in the progressive increase in olanzapine plasma concentrations corresponding to the increase in dose; these findings suggest that adolescents generally have plasma concentrations within the same range as those for adults. Olanzapine was effective in this population, few patients discontinued due to an adverse event.

QUALITY OF LIFE IMPROVEMENT AMONG PATIENTS WITH SCHIZOPHRENIA WHO ACHIEVED REMISSION CRITERIA DURING TREATMENT WITH ANTIPSYCHOTIC AGENTS

E. Dunayevich,* G. Sethuraman, M. Enerson, C. Taylor
Eli Lilly and Company, Indianapolis, IN, USA

Purpose: Patients with schizophrenia who attain symptomatic remission over the course of antipsychotic treatment are likely to experience greater improvements in quality of life (QOL) than those who do not. However, how to best define remission for patients with schizophrenia has not been well established. We analyzed QOL data among patients who met or did not meet symptomatic criteria of two proposed definitions of remission during treatment with antipsychotic agents. Methods: Scores on the Heindrichs-Carpenter quality of life scale (QLS) total score were pooled from 6 double-blind olanzapine comparator clinical trials. Mean QLS change from baseline at 8, 16, and 24-week endpoints were grouped according to whether patients met one (nonexclusive), both, or neither symptomatic criteria for remission (ie, met all remission criteria except the duration requirement). The definitions of remission used for these analyses were Kane's (scores of ≤3 on PANSS items delusions, conceptual disorganization, hallucinatory behavior, blunted affect, passive/apathetic social withdrawal, lack of spontaneity, mannerisms and posturing, and unusual thought content) and Lieberman's (50% reduction in BPRS Total score from baseline, scores of ≤3 on BPRS items unusual thought content, suspiciousness, hallucinations, conceptual disorganization, mannerisms and posturing, and CGI-severity score ≤3). Results: At each visit, patients who met both or either one of the symptomatic criteria for remission attained significantly greater mean improvement in QLS scores than those who met neither ($P<0.001$). At Week 24, mean QLS change from baseline was 20.6 ± 21.3 (n=396) for patients who met both definitions of remission, 19.6 ± 20.9 (n=456) for those who met Lieberman's, 15.4 ± 20.6 (n=719) for those who met Kane's, and 3.8 ± 15.8 (n=610) for those who met neither. Conclusions: Quality of life appears to be most improved for patients who showed the greatest symptomatic improvement during treatment, as demonstrated by meeting symptomatic criteria for both definitions of remission. Patients who met one remission definition also fared better than those who met neither. These data indicate that increasingly more stringent definitions of remission may be associated with greater improvement in QLS scores.

ZIPRASIDONE IN TREATMENT-RESISTANT SCHIZOPHRENIA: LONG-TERM EFFICACY AND TOLERABILITY

J. Dunn,* J. Kane, S. Khanna, E. Giller, S. Rajadhyaksha, A. Loebel
Pfizer Inc, New York City, NY, USA

This study was conducted to evaluate the efficacy and tolerability of long-term ziprasidone therapy, flexibly dosed at 40-160 mg/d, in subjects with treatment-resistant schizophrenia. All subjects in this 52-week, open-label study were adults who had received oral ziprasidone or chlorpromazine in a core 12-week, double-blind, comparison of these agents following lack of response to 6 weeks of haloperidol. Study visits occurred at baseline of the extension study and at Weeks 1, 3, 6, 9, 12, 16, 24, and 52 (or early termination). Safety/tolerability, assessed in all subjects who received >1 post-baseline dose of ziprasidone (N=129), was based on adverse events, laboratory values, ECGs, and movement disorder rating scales (SARS, BAS, and AIMS). Efficacy was based on summary scores on the PANSS, the CGI-S, and the CGI-I scales for subjects with a baseline and >1 post-baseline assessments. Efficacy parameters in observed subjects showed steadily increasing improvement at all time points. For subjects completing 24 weeks of ziprasidone therapy, mean CGI-S score decreased from 4.29 at baseline to 3.26 at endpoint, and mean PANSS Total from 80.73 to 57.10. At endpoint (last visit or Week 52), mean improvements in all subjects with >1 post-baseline efficacy evaluation (n=82) were −0.70 for CGI-S and −15.60 for PANSS Total. Ziprasidone was well tolerated, with no clinically important changes in laboratory values or ECG

parameters, and no change in median body weight. Discontinuations were due to subject default (25.6%), lack of efficacy (10.9%), adverse events (7.0% [treatment-related, 3.9%]), and other (3.9%). The rate of movement disorder symptoms was consistent with that observed in the core study. Mean decreases in SARS and BAS scores occurred from baseline to Week 24, 52, or discontinuation, except for the Barnes Akathisia Objective Score at Week 52, which showed no change from baseline; AIMS scores showed slight increases from baseline to study endpoint. In conclusion, this 1-year-long study in treatment-resistant schizophrenic subjects found that ziprasidone was associated with continued symptom improvement in a difficult-to-treat population and that it demonstrated good tolerability.

CLINICAL BRIDGING STUDIES EMPLOYING BOTH PATIENTS WITH SCHIZOPHRENIA AND HEALTHY NORMAL VOLUNTEERS CAN SPEED ANTIPSYCHOTIC DRUG DEVELOPMENT

L. Ereshefsky,* S. Jhee, M. Rosenthal
California Clinical Trials, Glendale, CA, USA

Pharmacokinetic and safety evaluations in Phase I for novel antipsychotics are usually performed in healthy normal volunteers (HNV). However, maximum tolerated dose (adverse events) and pharmacokinetic (PK) and pharmacodynamic (PD) parameters can be different in patients with schizophrenia in contrast to HNVs. We summarize our experience with a variety of classes of antipsychotic compounds, in which we have studied both HNVs and patients in the same PK/PD protocol. The implications for expediting an experimental medicine approach and speed drug development are significant in this era of cost efficient research programs. Compound and Class and Sponsor of studies completed include: Apripiprazole, D2 autoreceptor agonis, Otsuka/BMS Iloperidone, D2/D3 antagonist, Novartis Ziprasidone, D2/5HT2 antagonist, Pfizer DU 127090, D2/5HT2 antagonist, Solvay PNU 170413, D3 antagonist, Pharmacia Fanaserine, D4 antagonist, RPR Sertindole, DA, 5HT, alpha 1 antagonist, Lundbeck/Abbott MDL 100,907, 5HT2a antagonist, HMR Talnetant, tachykinin antagonist, GSK Our completion rate, on average for these clinical trials was more than 91% with over 490 subjects enrolled in these studies. Specific data will be presented for many of the drugs listed above, though four important observations are supported by the data: 1. Alpha adrenergic, dopaminergic, and muscarinic effects predict lower MTD in HNVs than in patients, oftentimes by more than a 3 fold factor. 2. Drug metabolism in patients with schizohrenia is quantitatively different than HNVs. These differences include a history of substance of abuse, less good health maintenance, and increased smoking exposure. 3. Patients, in contrast to HNV's interpret side effects differently, with the former group 'expecting' to experience drug effects while the HNV's do not have prior treatment experience with CNS compounds. 4. Patients might have differing sensitivities to key PD targets (therapeutic and adverse effects) including drug mediated metabolic syndrome, cognitive changes, and orthostatic hypotension. We propose that the first multiple dose study in Phase I be conducted as a bridging study in HNV's and schizophrenia. This approach accelerates drug development by estimating therapeutic doses prior to proof of concept studies, evaluate therapeutic/surrogate markers, and to insure that adverse event data is obtained in the target population.

EFFECTS OF DISCONTINUATION OF ATYPICAL ANTIPSYCHOTICS ON NEUROCOGNITION IN FIRST ONSET PSYCHOSIS

G. Faber,* H. G. Smid, R. J. van den Bosch
Psychiatry, De Grote Rivieren Mental Health Institution, Dordrecht, Netherlands

Neurocognition is an important factor in the outcome of psychosis. The effects of antipsychotics are therefore relevant for treatment. In contrast to older antipsychotics, atypical antipsychotics have been shown to have a positive effect on neurocognition. In most of these studies however atypical antipsychotics were compared to older antipsychotics in chronic patients. The purpose of the present study was to investigate the net effects of atypical antipsychotics on neurocognition in first onset psychosis. Design: in this randomised, open label trial patients with a first onset psychosis recieved atypical antipsychotics (mainly risperidone and olanzapine). 54 patients were included; of 42 patients complete data are available. One group discontinued their medication after 6 months of stable remission, the other group continued their medication and served as the control group. One month before and two months after discontinuation of the antipsychotics in the first group (and at the same point of time in the control group) patients recieved a comprehensive neurocognitive battery covering several domains of neurocognition. Results: first analysis of the data show a differential effect of the atypical antipsychotics on different domains of neurocognition. Further analysis will determine the relevance of these findings. Conclusion: discontinuation of atypical antipsychotics has a differential effect on neurocognitive functioning in first onset psychosis.

OUTCOME REVEALED BY PREFERENCE IN SCHIZOPHRENIA (OPS): A PROOF OF CONCEPT STUDY FOR THE DEVELOPMENT OF A NEW CLASS OF OUTCOME MEASUREMENTS

B. Falissard,* N. Bazin, V. Olivier, M. Hardy-Bayle
Departement de Sante Publique, Hospital Paul Brousse, Villejuif, France

There is growing interest in developing outcome measurements in psychiatry, especially in serious chronic illnesses like schizophrenia. Cognitive status, clinical symptoms, functional status, satisfaction and quality of life all claim to capture aspects of the very broad and loose concept of outcome. But all have limitations. Here a new approach is presented, based on a methodology of revealed preference obtained from the ranking, by subjects, of short written "slices of life" of schizophrenic patients. The 15 texts used comprise about 20 lines each on the day-to-day life of 15 schizophrenic patients. These patients were selected for the wide range in outcomes. The observed situations thus described were then ranked in terms of acceptability by a second group of 10 schizophrenic patients and by a group of 12 relatives of schizophrenic patients. From these rankings, 6 situations were selected so as to obtain a positioning at equal intervals on an axis ranging from a very unacceptable situation to a very acceptable situation.

These six situations compose the final instrument. In administration, the patients are first asked if the "slices of life" that are described are acceptable or not (on a 4-point response scale). Then in the second step the patients are asked if the "slices of life" described are more or less acceptable than the patient's own life. Two scores are derived: the summation of the answers collected in the second step is proposed as an estimate of the absolute level of the patient's quality of life; this sum minus the summation of the answers collected at the first step is proposed as an estimate of the relative level of the patient's quality of life. Preliminary validation results are presented on a new sample of 31 schizophrenic patients. The internal consistency appears good and the initial ranking of the 6 situations in terms of acceptability is confirmed.

TOWARDS PROOF OF ETHICAL RESEARCH IN SCHIZOPHRENIA: DEVELOPING THE MODIFIED EVALUATION TO SIGN CONSENT

B. A. Fischer,* W. T. Carpenter, K. J. Prentice
Psychiatry, Maryland Psychiatric Research Center of The University of Maryland, Baltimore, MD, USA

This work represents the development of a tool which could be used to assess ability to consent to research. Compassionate and respectful research demands that participants be allowed to freely choose whether to take part in studies. Over the course of research into schizophrenia, some critics have expressed concern that patients may be exploited in research. However, psychiatric researchers have data that research involving patients with schizophrenia can be done with informed consent. The ability to provide informed consent has traditionally been tested in 4 domains also used by U.S. law to assess competency: Understanding of the basic facts; appreciation of the applicability and personalization of the risks and benefits; reasoning, or the ability to manipulate information in service of making a decision; and ability to express a choice. Prior popular assessments of capacity to consent have been the Evaluation to Sign Consent (ESC)[1], developed in 1988, and the MacArthur Competency Assessment Tool (MacCAT)[2], developed in 1995. Both tools have strengths and weaknesses. The ESC is a quick, six-item scale designed to assess understanding of risks, random assignment, responsibilities, and right to withdraw. The MacCAT is interview-based with a number of free-recall questions. Although it contains elements addressing all four domains, it is heavily weighted towards understanding. It is also sometimes time consuming and difficult to score. Neither tool directly addresses the concept of therapeutic misconception; that the patient may not comprehend the difference between research and clinical care. Our new tool, the modified ESC (mESC), is time-efficient, uses standardized questions with scoring anchors, directly addresses therapeutic misconception, and is more balanced across domains (8 understanding, 7 appreciation, 6 reasoning, and 3 questions on therapeutic misconception). The mESC will be useful for screening patients before study participation, to assess effectiveness of educational interventions, and track degradation of elements of consent over time. [1]DeRenzo, EG, Conley, RR, Love, R: Assessment of capacity to give consent to research participation: State of the art and beyond. *Journal of Health Care Law & Policy*. 1998; 1:66-87. [2]Appelbaum, PS, Grisso, T: The MacArthur Treatment Competence Study: I. Mental illness and competence to consent to treatment. *Law & Human Behavior*. 1995; 19(2): 105-126.

PHARMACOLOGICAL LONG-TERM TREATMENT STRATEGIES IN FIRST EPISODE SCHIZOPHRENIA: PRELIMINARY RESULTS OF AN ONGOING RANDOMISED CLINICAL TRIAL WITHIN THE GERMAN RESEARCH NETWORK ON SCHIZOPHRENIA

W. Gaebel,* M. Riesbeck, M. von Wilmsdorff, J. Zielasek
Department of Psychiatry and Psychotherapy, Heinrich-Heine-University, Duesseldorf, Germany

In first-episode schizophrenia, the advantages of new atypical neuroleptics compared to low-dose haloperidol, and the duration of neuroleptic maintenance treatment have still to be elucidated. Accordingly, a multi-center study on the optimization of acute and long-term treatment in first-episode schizophrenia is currently being carried out as part of the German Research Network on Schizophrenia. We here report on the design, methods and preliminary results of the two-year randomized, double-blind study comparing risperidone and low-dose haloperidol accompanied by psychological interventions. In the second treatment year, relapse rates under continued neuroleptic treatment are compared with those under stepwise drug withdrawal substituted by prodrome-based early intervention (intermittent treatment). As of July 2004, 159 first episode schizophrenia patients have been included in the long-term study. One-year relapse rates were very low (about 3%). On average, symptoms as well as drug-induced side-effects decreased steadily under maintenance treatment. Although compliance on average was high, about 65% of the patients dropped out during the first study year. More pronounced psychopathology, (neurological) side-effects, lower compliance at study entry, and absence of psychological treatment seemed to enhance the risk for drop-out. In conclusion, either treatment (typical and atypical neuroleptics) in first episode schizophrenia is effective to decrease schizophrenic symptoms, but these patients are at high risk for treatment drop-out. This emphasizes the need for a special support program. Grant support: Germany Federal Ministry of Education and Research, Bonn, Germany (grant 01 GI 9932/7) References: Gaebel W, Moeller HJ, Buchkremer G, Ohmann C, Riesbeck M, Woelwer W, von Wilmsdorff M, Bottlender R, Klingberg S Pharmacological long-term treatment strategies in first episode schizophrenia - study design and preliminary results of an ongoing RCT within the German Research Network on Schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2004;254:129-140. Woelwer W, Buchkremer G, Haefner H, Klosterkoetter J, Maier W, Moeller HJ, Gaebel W. German research network on schizophrenia - bridging the gap between research and care. *Eur Arch Psychiatry Clin Neurosci* 2003;253:321-329.

EQUIEFFICACY OF QUETIAPINE VERSUS RISPERIDONE IN THE TREATMENT OF DEPRESSION IN PATIENTS IN THEIR FIRST EPISODE OF A SCHIZOPHRENIFORM PSYCHOTIC ILLNESS: INTERIM RESULTS OF AN 8 WEEK RANDOMISED SINGLE BLIND TRIAL

R. Gafoor,* R. Kerwin, P. Power, T. Craig, P. McGuire
Institute of Psychiatry, London, United Kingdom

Background: Depression and anxiety are common features of schizophrenia. Some antipsychotic drugs affect both the dopaminergic and serotonergic systems, making them potentially useful medications for the treatment of depression and anxiety as well as psychosis.

The present study examined the efficacy of two antipsychotics in treating depressive and anxiety symptoms in patients presenting with a first episode of schizophreniform psychosis. Aims: To examine the efficacy of risperidone and quetiapine in the treatment of depressive and anxiety symptoms in first episode schizophreniform psychosis. Hypothesis: We tested the hypothesis that both quetiapine and risperidone would be effective in treating depressive and anxiety symptoms in first episode schizophreniform psychosis. Methods: 60 patients were randomized to either risperidone or quetiapine and followed up for 8 weeks. Raters were blinded to randomized medication. Treatment involved low doses of risperidone (3.3 mg; SD 1.8 mg) and quetiapine (mean dose 420 mg; SD 174 mg). The prescribers followed dosing guidelines, but the dosing was driven by the patient's clinical needs. Patients were assessed at baseline, 1 and 2 months after initiation of treatment using the Calgary Depression Scale (CDS) for Schizophrenia and the Calgary Anxiety Scale (CAS). Results: Depression Treatment was associated with a decrease in depressive symptoms over time (mean CDS score at baseline = 5.1 (SD= 6.5), at 4 weeks = 3.9 (SD=4.9) and at 8 weeks = 2.9 (SD=4.2) that showed a trend towards statistical significance. There was no difference in the effect of quetiapine and risperidone On CDS score. Anxiety At baseline, the mean anxiety score was 1.8 (SD= 2.6). At 1 and 2 months the scores were 1.1 (SD=2.0) and 1.3 (SD=2.2) respectively. These changes were statistically significant over the eight week period (p=0.05) but there was no statistical difference between the effect of the 2 drugs. Conclusions Antipsychotic treatment in patients with a first episode of a schizophreniform psychosis was associated with an amelioration of both their anxiety and depressive symptoms. There was a trend towards statistical significance, and the effect may become more evident with larger groups and longer follow up, as may differences between the relative efficacy of the two drugs. The present study is ongoing, and these issues will be addressed with further subject recruitment and follow up.

QUETIAPINE VERSUS HALOPERIDOL DECANOATE FOR LONG-TERM TREATMENT OF SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER

I. Glick,* S. R. Marder
Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA

The objective of this analysis was to compare the long-term efficacy and tolerability of oral quetiapine with that of intramuscular haloperidol. Patients with schizophrenia or schizoaffective disorder requiring long-term antipsychotic treatment were randomly assigned to open-label oral quetiapine or haloperidol decanoate for 48 weeks. Clinicians were instructed to target dosing at 500 mg/d of quetiapine or 200 mg of haloperidol decanoate every 4 weeks. The Positive and Negative Syndrome Scale was used to assess efficacy; the Simpson-Angus and Barnes Akathisia Scales were used to assess safety and tolerability. For statistical analyses, a general linear mixed-model repeated-measures analysis of covariance was used, with change scores for dependent variables computed with the baseline score as covariate. Thirty-five patients were enrolled. Six patients refused to participate after being informed of their treatment assignment; 4 of the 6 refusals were for assignment to haloperidol decanoate. Mean dose at week 48 was 493 mg/d for quetiapine and 170 mg/28 d for haloperidol decanoate. In a survival analysis, we found no between-group differences in estimates of the number of patients remaining exacerbation-free over time. Both drugs were efficacious, but quetiapine was significantly superior to haloperidol decanoate in controlling negative symptoms ($P<0.05$). The incidence of extrapyramidal symptoms was low in both groups, but patients receiving quetiapine showed significantly greater improvement in rigidity and akathisia ($P<0.05$). Anticholinergics were not routinely used. Oral quetiapine was as efficacious as intramuscular haloperidol in preventing symptom exacerbation over 48 weeks in patients with schizophrenia or schizoaffective disorder, with fewer extrapyramidal symptoms, especially rigidity and akathisia. Quetiapine was more efficacious than haloperidol decanoate in treating negative symptoms.

A RETROSPECTIVE ANALYSIS OF CUMULATIVE TIME SPENT IN REMISSION DURING TREATMENT WITH OLANZAPINE AND RISPERIDONE USING TWO DEFINITIONS OF REMISSION

S. Gopalan,* M. Enerson, C. C. Taylor, E. Dunayevich
Eli Lilly and Company, Indianapolis, IN, USA

Purpose: A lack of consensus on how to define remission in schizophrenia has limited comparisons among antipsychotic agents. We used two proposed definitions of remission to retrospectively evaluate time spent meeting remission criteria during treatment with olanzapine (OLZ) and risperidone (RIS). Methods: Data were collected from a 28-week, double-blind, randomized clinical trial comparing 10-20 mg/day OLZ (N=172) with 4-12 mg/day RIS (N=167) among patients with schizophrenia. The definitions of remission were Kane's (scores of ≤3 on PANSS items delusions, conceptual disorganization, hallucinatory behavior, blunted affect, passive/apathetic social withdrawal, lack of spontaneity, mannerisms and posturing, and unusual thought content) and Lieberman's (50% reduction in BPRS Total score from baseline, scores of ≤3 on BPRS items unusual thought content, suspiciousness, hallucinations, conceptual disorganization, mannerisms and posturing, and CGI-severity score ≤3). The percentage cumulative time spent meeting remission criteria (hereafter referred to as "in remission") was calculated as: 1) total number of days meeting criteria divided by 28 weeks for the intention-to-treat (ITT) sample, and 2) total number of days meeting criteria between Week 8 and Week 28 (or discontinuation) divided by 20 weeks for Week 8 remitters. Results: In the ITT analysis, OLZ-treated patients spent a significantly greater mean percentage of study time in remission using Lieberman (OLZ=18%, RIS=11%; p=0.01) and Kane's criteria (OLZ=40%, RIS=31%; p=0.03). There were numerical but no significant between-group differences in the percentage of patients who met remission criteria at Week 8 using either Kane's (OLZ=57% [74/129], RIS=49% [61/125]) or Lieberman's definition (OLZ=22% [28/129], RIS=19% [24/125]). For Week 8 remitters, significantly more cumulative time was spent in remission during OLZ treatment than during RIS treatment using either Kane's (OLZ=88%, RIS=65%; p<0.0001) or Lieberman's definition (OLZ=84%, RIS=62%; p=0.007). Conclusions: In this dataset, Lieberman's remission definition was more stringent than Kane's. For patients who achieved remission using either definition, OLZ treatment was associated with greater cumulative time spent at this level of improvement than RIS treatment. Prospective application of these remission definitions to clinical trials of longer duration and examination of the relationship between remission and functional outcomes are needed.

RIVASTIGMINE IMPROVES MEMORY OF SCHIZOPHRENIA PATIENTS: A BEHAVIORAL AND ERP STUDY

F. Guillem,* S. Chouinard, J. Poulin, R. Godbout, P. Lalonde, L. A. Bentaleb, E. Stip
Psychiatry, F-Seguin Research Center, Montreal, QC, Canada

Recent studies have documented the beneficial effects of cholinergic enhancers, e.g., rivastigmine (RIV), on memory impairment in dementia and Parkinson disease. On the other hand, despite the progress in the pharmacological treatment of schizophrenia, cognitive functioning of the patients remains impaired. This study was thus aimed at investigating the effect of RIV on memory function in schizophrenia patients. Eighteen patients treated with atypical antipsychotics were assigned to two treatments, i.e., with or without add-on RIV, in a randomized, crossover design. They were assessed first at baseline (T1) and on two subsequent occasions (T2 and T3) at 2 month interval, where one half of the subjects were taken RIV and the other half not. They participated in a continuous recognition memory task during which event-related potentials (ERPs) were recorded. Behavioral (scores and RT) and ERP data were analyzed a posteriori using mixed ANOVA models first at T1 to detect potential group differences and for the trial (T1-T2) to determine the influence of RIV treatment i.e., Session x Group interactions. The results showed no group difference at T1 except a trend for one group to be less efficient than the other on RT measures. When controlling for this difference the results on the trial data showed a trend for a benefit of RIV on the RT memory (old/new) effect. ERP analysis revealed that RIV affects the amplitudes of two components elicited within 150-300ms over posterior (reduced N2b) and frontal sites (enhanced P2a). It also enhanced the magnitude of the memory (old/new) effect on two later components over posterior (N400) and frontal sites (FN400). The classical latest positive component (P600) was not affected. These results suggest that RIV improves selective attention by enhancing interference inhibition processes (P2a) and lowering the reactivity to incoming stimulus (N2b). RIV also improves the integration of information the with knowledge (N400) and with its context (FN400). On the other hand, RIV does not affect the mnemonic binding (P600), however this component is usually not found impaired in schizophrenia. Generally, this study showed that the beneficial effects of RIV on memory is not unitary but rather come from its action at different time-points within information processing cascade. This may also reflect a differential action on different (nucleus basalis, diagonal band, septohippocampal) parts of the cholinergic system.

THE EFFECT OF TREATMENT WITH OLANZAPINE OR RISPERIDONE ON SOME COGNITIVE FUNCTIONS: RESULTS OF A ONE YEAR RANDOMIZED TRIAL IN OUTPATIENTS WITH SCHIZOPHRENIA WITH PROMINENT NEGATIVE SYMPTOMS

M. Gurpegui,* E. Alvarez, M. Bousono, A. Ciudad, J. Gomez, J. Olivares
Dept. of Psychiatry and Institute of Neurosciences, University of Granada, Granada, Spain

The cognitive performance of patients with schizophrenia is very relevant in terms of both pathophysiology and functional outcome, and there is some evidence that atypical antipsychotics are superior to typicals on their effect on some cognitive dimensions. The aim of this analysis was to compare olanzapine (OLZ) and risperidone (RIS) on their effect on attention, reaction time, and executive function. This was a multi-center, randomized, open-label, parallel, dose-flexible, 1 year study of outpatients with schizophrenia with prominent negative symptoms (defined by a SANS Global score ≥10). Patients were assigned to treatment with an initial dose of 10 mg/day OLZ (N=120) or 3 mg/day RIS (N=115). Cognitive performance was assessed at baseline and other intervals, with some tasks of the COGLAB neuropsychological battery (reaction time, a modified version of the Wisconsin Card Sorting Test (WCST), and Asarnow Task —which measures vigilance and span of apprehension). The results were compared by an ANCOVA, where the dependent variable was the change in score (from baseline to last observation carried forward); the factors were OLZ or RIS and center; and the covariate was baseline score; changes within groups were analyzed with paired Wilcoxon tests. The patients' mean (±SD) age was 36.5 (±10.7) years (range 18-65) and age at diagnosis was 23.9 (±6.9). 72% were males, 89% had primary education or lower and 60% were current smokers. The mean dose was 12.2 (±5.8) mg/day for OLZ and 4.9 (±2) mg/day for RIS. Regarding the Asarnow task, both treatment groups presented a statistically significant improvement on condition 2, and only the OLZ group on condition 3. There was a treatment effect (favoring OLZ $p=0.026$; effect size of 0.23), a center effect ($p<0.001$), and a baseline effect ($p<0.001$). On the WCST, only the OLZ group showed statistically significant improvement in both perseverative ($p=0.032$) and random errors ($p=0.0019$), but the ANCOVA demonstrated a statistically significant effect for only the baseline score ($p<0.001$). No improvement was observed on the reaction time. Ambulatory patients with schizophrenia with prominent negative symptoms treated with OLZ or RIS showed a modest improvement (in some cases statistically significantly higher with OLZ) on some neuropsychological functions (attention and executive function), but not in reaction time.

COMPARISON OF CLINICAL EFFICACY OF QUETIAPINE VERSUS HALOPERIDOL IN MINIMALLY-TREATED EARLY SCHIZOPHRENIA

R. Hammond,* J. Lauriello, J. Bustillo, L. Rowland, C. Fryer
Psychiatry, University of New Mexico, Albuquerque, NM, USA

Quetiapine has been demonstrated as efficacious in schizophrenia, however, there is limited information concerning its efficacy early in the illness. This paper reports the clinical responses of patients who completed the first 3 months of a longitudinal study of efficacy of quetiapine versus haloperidol in minimally-treated psychotic subjects. The study includes subjects with DSM-IV diagnoses of schizophrenia, schizophreniform disorder, and schizoaffective disorder-depressed type. Patients were randomized in a double blind fashion to either quetiapine or haloperidol. Dose ranges allowed were 100-600mg for quetiapine and 2-12mg for haloperidol. Outcome measures include symptom ratings (PANSS,CGI) and EPS ratings (AIMS,SAS,Barnes). Of 33 subjects randomized into the study, there were 17 subjects remaining in the study at 3 months who were still on their originally assigned drug. There were no statistically significant differences between the 2 groups (quetiapine, n=7; haloperidol, n=10) on any of the clinical rating scales at initial screening. Overall, at 3 months, both groups showed clinical improvement. On the CGI at 3 months both groups showed statistically significant

improvement (quetiapine, P<0.004; haloperidol, P<0.001). The improvement was greater for haloperidol than quetiapine (P<0.02). On the PANSS Positive subscale at three months both groups showed significant improvement (quetiapine, P<0.05; haloperidol, P<0.001). The improvement tended to be greater for haloperidol than quetiapine, (P<0.06). Both groups improved on the PANSS total, (quetiapine, P<0.07; haloperidol, P<0.001). This was not a statistically different result between the 2 groups (P<0.21). Measured side effects were minimal for both groups throughout the study. There were no statistically different results on the side effect scales between the 2 groups at any point during the 3 months but the haloperidol group used more medication for side effects. This study supports the efficacy of both quetiapine and haloperidol in minimally-treated early schizophrenia. Haloperidol tended to perform somewhat better than quetiapine by the 3 month point in this study. This may be related to the comparatively slower initial titration of quetiapine and to relative differences in average dose between the two groups at 3 months (quetiapine=329mg; haloperidol=4mg). This study was supported by a grant from the MIND Institute and AstraZeneca.

ANTIPSYCHOTIC TREATMENT DISCONTINUATION IN THE OUTPATIENT TREATMENT FOR SCHIZOPHRENIA: 24-MONTH RESULTS FROM THE PAN-EUROPEAN SOHO (SCHIZOPHRENIA OUTPATIENT HEALTH OUTCOMES) STUDY

J. Haro,* D. Novick, M. Belger, S. Tzivelekis, D. Murray, J. M. Texeira, J. Alonso, M. G. Bousono, I. Gasquet, H. Kristensen, P. B. Jones, T. Croudace, M. Knapp, J. P. Lepine, V. Mavreas, D. Naber, P. Pancheri, C. J. Slooff
Sant Joan De Deu-SSM, Barcelona, Spain

OBJECTIVE: To report the frequency, correlates and reasons of antipsychotic treatment discontinuation in outpatients with schizophrenia and how they vary among medications. METHODS: SOHO is a 3-year, prospective, outpatient, observational study of health outcomes associated with antipsychotic treatment. Patients were enrolled in SOHO only if they had an antipsychotic medication initiation or change. Patients were evaluated at baseline, 3, 6, 12, 18 and 24 months thereafter. Treatment was at the discretion of the participating psychiatrist and the patient. No treatment instructions or limitations were included in the protocol. Patients were followed regardless of medication changes. Medication discontinuation was defined as stopping the medication prescribed at baseline. The study design included stratified sampling leading to approximately 50% of patients initiating olanzapine. RESULTS: 10,218 patients were eligible for analyses at baseline. The current analysis is limited to the 6,915 patients that were prescribed only one antipsychotic at baseline and were assessed at two years. Approximately 30% of the patients discontinued the medication initiated at baseline before two years, with figures being highest for amisulpride (46%), quetiapine (49%) and typical antipsychotics (44%). Clozapine (24%) and olanzapine (23%) were associated to the lowest medication discontinuation. The most frequent reason for discontinuation of treatment was lack of effectiveness (44%) followed by patient's request (27%), lack of compliance (22%) and intolerability (22%). Higher symptom severity, later age of onset, younger age and not being never-treated patients were associated to frequency of medication change. CONCLUSIONS: Rate of medication discontinuation varied among medications. 44% of those patients who discontinued treatment did so due to lack of effectiveness. Two important limitations are that due to the sampling strategy, we have much more power to detect differences between the olanzapine and other cohorts than between the other cohorts, and that participating psychiatrist may have tended to enrol compliant patients in the SOHO study.

DO ALL PATIENTS WITH SCHIZOPHRENIA NEED ANTIPSYCHOTIC MEDICATIONS CONTINUOUSLY?: A 20-YEAR MULTI-FOLLOWUP STUDY

M. Harrow,* T. H. Jobe, L. S. Grossman, E. M. Martin, R. N. Faull
Psychiatry, University of Illinois College of Medicine, Chicago, IL, USA

Purpose: The current prospective, longitudinal, multi-followup 20-year research was designed to study a) whether patients with schizophrenia who are not on antipsychotic medications function as well as patients who are on antipsychotic medications, and b) if schizophrenia patients not on medications are functioning adequately and experiencing intervals of recovery, what factors are involved in this? Can it be accounted for by differences in early levels of functioning and premorbid developmental characteristics? Method: 215 patients from the Chicago Follow-Up Study, including 55 patients with schizophrenia, were assessed at acute hospitalization and then followed up 6 times over 20 years. Using standardized research instruments, patients were studied for positive symptoms, negative symptoms, depressive syndromes, cognitive impairment, and treatment. This included assessments of first- and second-generation antipsychotic medications and other treatments at each follow-up. Results: 1. At each of the 6 follow-ups over 20 years, 35-45% of schizophrenia patients were not on antipsychotics, with some having left treatment and others having been removed from antipsychotic medications. 2. Schizophrenia patients not on antipsychotics showed better global functioning and were more likely to experience episodes of recovery (p<.01). 3. The better functioning of the schizophrenia patients not on antipsychotics at the 15- and 20-year follow-ups was not primarily a function of their medication status, but of inherent long-term characteristics of these patients (p<.05). 4. Schizophrenia patients switched from first-generation antipsychotics to second-generation antipsychotics did not show less psychosis, but did show reductions of depressive syndromes (p<.05). Conclusions: The current longitudinal multi-followup results identify a subtype of patients with schizophrenia who do not immediately relapse while off antipsychotics and experience intervals of recovery. These schizophrenia patients, who left the mental health caretaking system after hospitalization, are less likely to come to the attention of treatment or research groups. Our longitudinal, multi-followup data indicate that their more favorable outcome is partly a consequence of inherent long-term characteristics of these patients, including less vulnerability, greater resilience, better premorbid developmental achievements (p<.01) and better prognostic factors (p<.01) present before they became ill.

A COMPARISON OF THE DETERMINANTS OF SUBJECTIVE AND OBJECTIVE MEASUREMENTS OF QUALITY OF LIFE IN SCHIZOPHRENIA

K. P. Hayhurst,* J. A. Massie, S. Browne, S. W. Lewis
School of Psychiatry & Behavioural Sciences, University of Manchester, Manchester, United Kingdom

As an outcome measure, quality of life is increasingly used in clinical trials involving patients with schizophrenia. Conceptually, how-

ever, quality of life is a broad term, consisting of a sense of well-being, life satisfaction and access to resources and opportunities. A subjective measure of quality of life, the Lancashire Quality of Life Scale was compared with an objective measure, the Heinrichs Quality of Life Scale, in 80 subjects (26 F/ 54 M) entering a randomised controlled trial comparing atypical antipsychotics with conventional agents and clozapine. A significant correlation was found between the two scales ($r = 0.387$, $p = 0.001$). Determinants of subjective and objective quality of life were explored using multiple regression analyses and were found to differ. Significant determinants of subjective quality of life were depression, measured on the Calgary scale, insight (Birchwood Scale), and the patients evaluation of their own health, which together explained 51% of the variance ($p < 0.01$). Depression was responsible for 37% of this variance. In contrast, the significant determinants of objective QLS were PANSS negative score, gender, number of previous hospitalisations, insight (g12 PANSS item), the patients evaluation of their own health and their accommodation status. These determinants together explained 46% of the variance with PANSS negative score accounting for most (34%) of this ($p < 0.05$). The choice of subjective or objective quality of life measures is likely to reflect different dimensions of outcome, reflecting the underlying psychopathology of schizophrenia as opposed to measuring a discrete construct. A value judgement must therefore be made as to which of these measures best encapsulates what is meant by quality of life in schizophrenic illnesses.

ADHERENCE/AGITATION IMPROVEMENT WITH ORALLY-DISINTEGRATING OLANZAPINE IN SCHIZOPHRENICS

A. Hill,* J. P. Houston, B. J. Kinon, H. Liu-Seifert, K. Tohen, D. Hay
Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA

Background: Rapid reduction of agitation and improved attitude toward compliance were assessed in 85 acutely-ill, noncompliant schizophrenic patients treated with orally disintegrating olanzapine tablets. Methods: Longitudinal effects of orally disintegrating olanzapine on agitation were assessed using Positive and Negative Symptom Scale-Excited Component (PANSS-EC). This post-hoc analysis of 6-week olanzapine treatment examined patient attitude toward compliance for correlation with clinical psychopathology ratings. Association between previously derived PANSS factors and Rating of Medication Influences (ROMI) compliance and noncompliance subscores was investigated using a multiple regression analysis. Results: Agitation, measured by PANSS-EC, was significantly reduced at 1 week and beyond ($p<.001$). Most ROMI improvement occurred within 1 week of treatment. A significant correlation between PANSS-EC and ROMI compliance occurred at all time points during active treatment ($p<.05$). Regarding relative influence of different PANSS domains on patient attitude toward compliance, 1-week ROMI compliance correlated most strongly with PANSS-hostility/impulsivity (negatively correlated); ROMI noncompliance with PANSS-positive. Conclusions: Orally disintegrating olanzapine tablets rapidly reduced agitation (PANSS-EC) in noncompliant patients with schizophrenia. Effective resolution of acute agitation was associated with greater patient acceptance of medication treatment that may help to establish a more enduring therapeutic alliance. Improvement in comorbid hostility and psychosis contributed to improved treatment attitude.

A RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND TRIAL OF AUGMENTATION OF CLOZAPINE WITH RISPERIDONE

W. Honer,* G. W. MacEwan, R. Williams, P. Falkai, P. J. McKenna, E. Pomarol-Clotet, E. Y. Chen, S. P. Leung, J. Wong, E. Stip
Centre for Complex Disorders, UBC, Vancouver, BC, Canada

Incomplete or partial improvement of symptoms following treatment with clozapine is not infrequent in chronic schizophrenia. Commonly, patients are prescribed an additional antipsychotic medication, although there is little evidence from controlled studies of the efficacy of this practice. We performed a placebo controlled study of risperidone augmentation of partial response to clozapine in schizophrenia. Subjects were required to be treated with clozapine at a stable dose of 400 mg or more for at least 12 weeks prior to screening. Concurrent psychotropic medications were discontinued at least 2 weeks prior to study entry. At baseline (on clozapine), the total PANSS score was 97.1 (n=69), and following one week of placebo augmentation run-in the total PANSS score was 99.6. Subjects were randomized to continuation of clozapine+placebo, or to clozapine+risperidone 3.0 mg for 8 weeks. Clozapine doses were unchanged. The study completion rate was 94% (n=65). Using a last observation carried forward approach, the total PANSS score at the end of the double blind phase was 87.7- there were no statistically significant differences between the placebo- and the risperidone augmentation groups. According to a 20% decline in total PANSS score approach to categorize subjects as responders, the rates of response were 26% (n=9/35) in the placebo augmentation group, and 18% (6/34) in the risperidone augmentation group. Addition of the requirement of a CGI score of 3 or less to define treatment response resulted in a rate of 11% (4/35) in the placebo augmentation group, and 3% (1/34) in the risperidone augmentation group. Addition of risperidone to clozapine does not appear to offer significant advantages in reducing the symptoms of schizophrenia in patients with poor or incomplete response to clozapine alone. Supported by the Stanley Medical Research Institute.

PREDOMINANCE OF PSYCHIATRIC-BASED REASONS FOR ANTIPSYCHOTIC TREATMENT DISCONTINUATION

L. Hong,* B. J. Kinon
Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA

Introduction: Antipsychotic treatment discontinuation in controlled, clinical trials was examined to provide insight into overall treatment effectiveness. Methods: A post-hoc, pooled analysis of 4 randomized, double-blind clinical trials of 24-28 week duration included 822 olanzapine-treated and 805 risperidone-, quetiapine-, or ziprasidone-treated patients. Results: A majority of patients (53%; 866/1627) discontinued early from antipsychotic treatment with poor response/symptom worsening the most frequent reason for discontinuation (36%; 315/866). Patients who discontinued early appeared to have slower initial improvement compared to patients completing the study. Discontinuation due to poor response was overwhelmingly linked to patient preference as compared to physician preference alone (80% vs. 20%). Patient perception of poor response occurred sooner than physician perception alone. Additionally, 17% of discontinuations were due to worsening of the underlying psychiatric condition and 12% were due to medication intolerability. Patients

discontinuing due to adverse events showed a response rate comparable to patients completing the study. Conclusions: Poor treatment response, underlying psychiatric symptom worsening, medication intolerability, and patients perception of failure to improve contributed to treatment discontinuation, which can threaten patient well-being through illness exacerbation. A better understanding of causes for discontinuation may help improve patient engagement in long-term therapy and realization of treatment goals.

ORAL OLANZAPINE TRANSITION DOSE FOLLOWING INTRAMUSCULAR OLANZAPINE TREATMENT

J. P. Houston,* C. J. Kaiser, J. Ahl
Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA

Background: Intramuscular (IM) antipsychotics are first line treatment for acute agitation in patients with schizophrenia. After stabilization, patients are transitioned to oral medication. Methods: This was a post-hoc analysis of transitional oral antipsychotic dose per IM group in a double-blind, randomized study. Over 24 hours, agitated inpatients received 1, 2, or 3 injections of IM olanzapine (OLZ) 10 mg (n=92, 26, 3, respectively), haloperidol (HAL) 7.5 mg (n=82, 32, 1, respectively), or placebo (PBO, n=24, 21, 2, respectively) followed by 4 days of oral treatment with 5-20 mg/d OLZ for IM OLZ and PBO groups and 5-20 mg/d HAL for IM HAL group. Agitation was assessed by the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC). Results: Median/means of mean oral doses in patients receiving 1, 2, and 3 injections, respectively, were 10.0/12.0 mg, 13.8/13.8 mg, and 20.0/18.3 mg OLZ for OLZ IM group; 10.0/9.9 mg, 11.3/11.8 mg, and 10.0/10.0 mg HAL for HAL IM group; and 10.0/10.6 mg, 11.3/12.5 mg, and 8.8/8.8 mg OLZ for PBO IM group. Reduction in agitation continued during transition to oral antipsychotic for HAL and PBO groups and for OLZ patients who received 1 IM dose. Reduction in agitation was maintained during transition for patients who received multiple OLZ IM doses. Conclusions: Reduction in agitation was maintained following transition from IM to oral therapy. Transitional oral doses increased with the number of OLZ injections.

SWITCHING ANTIPSYCHOTICS IN INPATIENT SCHIZOPHRENIA CARE: PREDICTORS AND OUTCOME

B. Janssen,* S. Weinmann, W. Gaebel
Psychiatry, Heinrich Heine University, Duesseldorf, Germany

Within a pharmacoepidemiologic study as part of the German Research Network in Schizophre-nia characteristics of patients with schizophrenia switched from first (FGA) to second generation antipsychotics (SGA) or to antipsychotic polypharmacy in comparison to those maintained on FGA were investigated. The primary aim was to assess factors associated with antipsychotic switching and to compare disease course with regard to mental state and social functioning. Adult inpatients with an ICD-10 diagnosis of schizophrenia or schizoaffective disorder were as-sessed in 7 psychiatric hospitals. For those patients (n=847) with an antipsychotic prescription at discharge, t-tests, covariance and logistic regression analyses were used to evaluate the relationship between demographic and clinical characteristics, and antipsychotic switching. Patients switched from FGA to SGA had fewer previous psychiatric admissions, a shorter illness duration, less substance disorders, a higher probability of competitive working, but more pro-nounced symptoms than those maintained on FGA. Mental state and social functioning after case-mix adjustment was more favourable in the group switched to SGA monotherapy, but not in those administered FGA and SGA concurrently at discharge. Logistic regression controlling for demographic and clinical variables revealed that a short disease duration, fewer previous psychi-atric hospitalisations, voluntary admission and pronounced thought disorder were significantly correlated with FGA/SGA switching. Hospital differences were also observed. In conclusion, re-maining on FGAs or switching to SGAs in schizophrenia care depends strongly on institutional practices in addition to the previous disease course and health care utilisation. Grant support: Germany Federal Ministry of Education and Research, Bonn, Germany (grant 01 GI 9932/7) References: Weinmann S, Janssen B, Gaebel W: Switching Antipsychotics in Inpatient Schizophrenia Care: Predictors and Outcome, *J Clin Psychiatry* 2004;65:1099-1105 Woelwer W, Buchkremer G, Haefner H, Klosterkoetter J, Maier W., Moeller HJ, Gaebel W: German research network on schizophrenia. Bridging the gap between research and care *Eur Arch Psychiatry Clin Neurosci* 2003;253: 321-329.

A COMPARATIVE STUDY OF ATYPICALIZED ANTIPSYCHOTIC TREATMENT OF PSYCHOSIS IN ADOLESCENTS

J. Jensen,* J. Wozniak, T. J. White, B. Baker, A. Guimares, S. C. Schulz
Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA

Few studies have compared antipsychotic efficacy for adolescents with psychosis. Therefore, clinicians have little data to inform them about which medication to choose in patients under 18 years of age. The purpose of this study was to compare the efficacy and safety of risperidone, olanzapine, and olanzapine in adolescents with psychotic disorders. Patients were given the KIDDIE-SADS to assess their episodes of psychopathology according to DSM-III-R and DSM-IV criteria. All patients who met criteria for schizophrenia, schizoaffective disorder, and psychosis, NOS were included. The PANSS scale was administered at the beginning of the trial and at every other visit for twelve weeks (i.e. six PANSS total). In addition to symptom ratings, each subject underwent a neuropsychological test battery at baseline and endpoint of the study. In this unblinded study, dosing was adjusted by a psychiatrist on alternate weeks. This strategy was employed to maximize tolerability of antipsychotic medication dose. On alternate weeks, dosing was adjusted by a psychiatrist. This pilot study seeks 30 subjects. Six patients have completed the study and two patients are currently enrolled. Symptom reduction has been seen for the patients, but the number of subjects is too small for a comparison of different compounds. This poster will present the available data. Clinicians caring for adolescents with psychotic disorders have indicated an interest in a head-to-head comparison of the atypical agents. The results of this study will provide a valuable comparison of the safety and efficacy of these new agents. Six patients have completed the study and two patients are currently enrolled.

OLANZAPINE IN THE TREATMENT OF SCHIZOPHRENIA IN ADOLESCENTS: AN ONGOING DOUBLE-BLIND PLACEBO-CONTROLLED STUDY

S. Joan,* W. R. Earley, L. Kryzhanovskaya, C. Miner, R. W. Dittmann
Eli Lilly and Company, Indianapolis, IN, USA

Objective: To present the design and the current status of an ongoing study of olanzapine 2.5 to 20 mg/day in the treatment of adolescents with schizophrenia. Background: More that 20% of all female patients and more than 35 % of all male patients with schizophrenia experience onset of schizophrenia during adolescence. Methods: This is a multi-center, randomized, double-blind, placebo-controlled parallel trial in adolescent patients (13 to 17 years) who meet diagnostic criteria of schizophrenia (295.10, 295.20, 295.30, 295.60, 295.90) according to the DSM-IV-TR 2000, confirmed by the Kiddie-SADS-PL. The study consists of a 2-14-day screening/washout period, a 6-week, double-blind, acute treatment period (randomization: 2 olanzapine : 1 placebo) and a 26-week, open-label, olanzapine treatment period. We are using the Anchored Version of the Brief Psychiatric Rating Scale for Children (BPRS-C) total score to assess the efficacy of olanzapine. Safety will be assessed based on the incidence of adverse events, changes in vital signs and laboratory values. EPS will be assessed by the Simpson-Angus Scale, the Barnes Akathisia Rating Scale, and the Abnormal Involuntary Movement Scale (AIMS). Results: As of 15/JUL/2004 105 patients had entered this ongoing study, and 98 patients had been randomized. 52 patients had completed the double-blind period and 25 patients had completed the open-label period.

RANDOMISED CONTROLLED TRIAL OF EFFECT ON QUALITY OF LIFE OF PRESCRIPTION OF SECOND GENERATION (ATYPICAL) VERSUS FIRST GENERATION ANTIPSYCHOTIC DRUGS IN SCHIZOPHRENIA

P. B. Jones,* L. Davies, T. R. Barnes, R. M. Murray, G. Dunn, K. P. Hayhurst, A. Markwick, H. Lloyd, S. W. Lewis
Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom

Objectives: To compare the class of conventional, first generation antipsychotic drugs (FGA) with the atypical, second generation drugs (SGA) other than Clozapine, in people with schizophrenia needing a change in treatment because of poor response or side effects. We hypothesized that SGA drugs would be associated with improvement in health-related quality of life. Design: A five-centre, RCT with three, blinded follow-up assessments over one year. The trial was conducted in general adult mental health settings in 14 NHS Trusts in Greater Manchester, Nottingham, Cambridge and London. Participants: 227 participants age 18-65 with schizophrenia and related disorders. Intervention: Random allocation to prescription from the class of SGA drugs, other than Clozapine, available at the time of the trial (Amisulpride, Olanzapine, Quetiapine, Risperidone) or to an FGA drug; choice of drug from within the randomised class was made by the managing clinician. Main Outcome Measures: The primary outcome was the Quality of Life Scale (QLS). Secondary outcomes included symptoms (PANSS), side effects and participant satisfaction. Results: The primary hypothesis of a five point improvement in QLS over the year following commencement of SGA compared with FGA drugs was excluded by an intention to treat analysis. Participants in the FGA arm showed a trend towards greater improvements in QLS and symptoms scores, suggesting failure to find the predicted advantage for SGA drugs was unlikely to be due to low statistical power (75%). Participants reported no clear preference for either class of drug. Conclusion: In people with schizophrenia whose medication is being changed because of intolerance or broadly-defined ineffectiveness, there is no disadvantage over one year in terms of quality of life, symptoms or associated costs of care in commencing conventional FGA drugs rather than atypical SGA drugs. This result is not accounted for by inadequate power or by patterns of drug discontinuation.

BELIEFS ABOUT MEDICATION AND ITS RELATIONSHIP TO MEDICATION COMPLIANCE

H. Jonsdottir,* S. A. Friis, A. Birkenaes, J. Engh, P. A. Ringen, A. Vaskinn, S. Opjordsmoen, K. Sundet, O. A. Andreassen
Division of Psychiatry, Research Department, Ullevaal University Hospital, Oslo, Norway

Poor compliance of medication is the most important risk factor for rehospitalization in schizophrenia and it is reported that up to 50% of patients do not follow up their treatment in the first year after discharge from hospital. Insight and beliefs about medication have among other been proposed as important risk factors associated with poor compliance. The aim of this study is to evaluate compliance and find out more about the reasons for poor compliance. This study will focus on insight and beliefs about medication as risk factors for future non-compliance. It will also seek to quantify patients beliefs about the necessity of their prescribed medication and their concerns about taking it. As a part of a large ongoing study of patients with schizophrenia and bipolar disorder all patients recruited in the study and having completed a SCID I interview, the necessary questionnaires and given a blood sample have been included. Patients beliefs about their medicines were assessed using the Beliefs about Medicines Questionnaire (BMQ, developed by Robert Horne) which comprises two scales assessing the patients beliefs about the necessity of their medication (scale 0-25) and their concerns about the potential adverse consequences of taking it (scale 0-30). Insight was measured using an 8 item insight scale developed by Birchwoods team. The BMQ scale of necessity of taking medication correlated highly with insight (r=0,62, p=0,000). Compliance was measured using a questionnaire and by doing serum analyses of medicines. The patients are evaluated every 6 months over two years. At present (September 2004) 126 subjects have been included in the study. By January 2005 we expect to have the first follow up data for the whole group and to be able to compare the serum analyses with the compliance questionnaire. Mean compliance at baseline, using the questionnaire, was 90% for the whole group. The mean score on the BMQ necessity scale was 18,0 (SD 4,4) and on the BMQ concern scale 17,4 (SD 4,4) . Beliefs in the necessity of taking the prescribed medication had a significant correlation with compliance rates (r= 0,28, p=0,002). Concerns about taking the prescribed medication was not significantly correlated with compliance. These preliminary data show a cross-sectional relationship between medication compliance and believing in the necessity of medication. Whether beliefs about medication can predict future compliance rates remains to be seen.

SAFETY AND EFFICACY OF SERTINDOLE AND RISPERIDONE IN TREATMENT RESISTANT PATIENTS WITH SCHIZOPHRENIA

J. M. Kane,* S. Potkin, P. Buckley, D. G. Daniel
Psychiatry, The Zucker Hillside Hospital, Glen Oaks, NY, USA

Sertindole is a new generation, non-sedating antipsychotic discovered by H. Lundbeck A/S. Sertindoles nonclinical profile is atypical as sertindole is selective for the mesolimbic dopamine neurons and possesses a high affinity for serotonin 5-HT2 receptors. Sertindole is well tolerated and effective in the treatment of schizophrenia, including negative symptoms, with placebo-level extrapyramidal symptoms (EPS). The objective of this study was to compare the efficacy, safety and tolerability of 12 to 24mg of sertindole administered once daily to 6 to 12mg of risperidone administered twice daily to treatment resistant patients with schizophrenia. The study was a multicentre, randomised, double-blind, active-comparator, flexible dose trial in two parallel groups, with a screening period (4-6 weeks of haloperidol 10-30 mg/day treatment), a placebo run-in period (4 days), a titration period, and a flexible dose period (12 weeks). The study was designed to include a total of 400 patients in a 2:1, sertindole:risperidone ratio, but due to the suspension of sertindole from the market, the study was prematurely terminated, resulting in reduced power (sertindole n = 216; risperidone n = 105). The study population was moderately severe to severely ill patients with schizophrenia (DSM-IV, baseline mean total PANSS score: ?60), aged 18 to 55 years, who had failed one adequate antipsychotic treatment in the last 6 months, and who had experienced a <25% reduction in their PANSS total score at day -4. Both treatment groups showed improvement in PANSS total score from baseline to endpoint, with risperidone treated patients showing a trend to improve numerically more than sertindole treated patients, however, with the gap between the two treatment groups narrowing towards the end of the treatment period (OC data). The incidence of treatment emergent adverse events (TEAE) occurring with ?10% frequency was similar for the two groups, apart from dyspepsia and abnormal ejaculation for sertindole, and pain, infection, injury accidental, and akathisia for risperidone. The proportion of patients who reported EPS-related TEAEs in the risperidone-treated group was statistically significantly greater than that of sertindole-treated patients (risperidone: 36.2%; sertindole: 20.8%). In conclusion, both treatments showed improvements in PANSS total score, and thus seemed to be effective for treatment resistant schizophrenia.

BASELINE CHARACTERISTICS AND TREATMENT OUTCOMES FOR OUTPATIENTS WITH SCHIZOPHRENIA SWITCHED TO SECOND GENERATION ANTIPSYCHOTIC THERAPY: AN INTERIM ANALYSIS FROM A CANADIAN OBSERVATIONAL STUDY

J. Karagianis,* J. Srinivasan, P. Tahlan, L. Chapman, G. Gray, R. Juarez, R. Dickson
Eli Lilly Canada Inc., Toronto, ON, Canada

This study aims to describe the demographic, clinical, and functional status of outpatients switched to second generation antipsychotics, and evaluate their treatment. This is an interim analysis of the Health Outcomes of a Canadian Community Cohort (HOCCC) study, examining the outcomes associated with second generation antipsychotic treatment for schizophrenia or related psychotic disorders (DSM-IV). Outpatients switching to a second generation antipsychotic were allocated (in approximately equal proportions) to either olanzapine or non-olanzapine treatment groups, and assessed every 3 months up to 12 months or until the antipsychotic prescription they originally switched to changed. Data for only 248 of the first 300 patients to complete the study were captured within the prescribed visit intervals. A further 8 patients had discrepant 'last dose of study drug' and 12 month summary visit dates, and were not considered 'treatment completers'. Patients were, on average, aged 41.6±11.1 years (mean±SD), mildly ill (mean±SD BPRS total score 30±17), Caucasian (85%, n=210), with a diagnosis of schizophrenia (56%, n=140). Males accounted for 52% (n=130) of all patients. Many of these were patients with long duration illnesses: 26% (n=65) had been receiving treatment for 10-20 years, with a further 24% (n=60) having a prior duration of therapy in excess of 20 years. Despite 60% of patients being unemployed and unable to work due to their psychiatric condition, the majority of patients (66%) maintained an independent residence. Olanzapine was prescribed to 53 % (n=132) of patients. Of the non-olanzapine treatment group, risperidone (22%, n=55) and quetiapine (23%, n=58) accounted for almost all of prescriptions, with only 3 patients (1%) prescribed clozapine. The most common reason for switching to olanzapine was inadequate control of psychotic symptoms (41.7%). Whilst this was also true for 21.6% of patients switching to other antipsychotics, weight gain was also a common reason given for medication change (19.0%). Patients prescribed olanzapine were significantly more likely to maintain their original antipsychotic for a period of 12 months than those prescribed other second generation antipsychotics, (64.9% [n=85] for olanzapine, 40.0% [n=22] for quetiapine, 45.1% [n=23] for risperidone, and 0% for clozapine, p=0.001). Olanzapine therapy was associated with treatment maintenance at one year in this population of outpatients. This was supported by Eli Lilly.

A 12 WEEK, DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL OF DONEPEZIL ADJUNCTIVE TO HALOPERIDOL FOR THE COGNITIVE IMPAIRMENTS IN PATIENTS WITH CHRONIC SCHIZOPHRENIA

Y. Kim,* J. C. Shim, Y. S. Suh, B. J. Lee
Department of Psychiatry, Inje University, Busan, South Korea

Objective: This study aimed to provide evidence on the benefical effect of acetylcholinesterase inhibitors for the management of cognitive dysfunctions in schizophrenia. The effects of 12 week donepezil adjunctive treatments on the cognitive impairments were investigated in patients with chronic schizophrenia. Method: Twenty-four subjects stabilized on haloperidol (5-30mg/day) treatment for a minimum period of 3 months were entered into a double-blind, placebo-controlled trial of donepezil adjunctive treatment. Subjects were randomly assigned under double-blind conditions to receive 5 mg/day donepezil (n=12) or placebo (n=12) for 12 weeks. At baseline, 4, 8, 12 week, they were evaluated with the Mini Mental State Examination (MMSE), Brief Psychiatric Rating Scale (BPRS), and standardized neuropsychological assessments. Results: Donepezil treatment resulted in no significant improvement in BPRS. Subjects showed slight improvements in several cognitive measures. A significant improvement was noted in MMSE scores ($p<0.05$). Difference in the mean score of MMSE between the donepezil and placebo group at the endpoint of study approached significance, $p=0.056$. Among several domains of cognitive functions, strong improvements were found in verbal recognition and visual recall memory ($p<0.05$).

In addition, adjunctive donepezil tended to improve in digit span backward (p<0.1). But there were no effects on the executive function tests. No significant changes were noted in adverse events following the addition of donepezil to haloperidol. Conclusion: Donepezil appears to be an effective treatment for the management of impaired cognitions, but not for the control of psychotic symptoms in patients with chronic schizophrenia. To confirm our findings, further investigation is mandated with a larger sample of subjects.

PANSS AND COGNITION CHANGE IN D-CYCLOSERINE COMBINATION TREATMENT OF SCHIZOPHRENIA

S. Kim,* Y. W. Jeon, J. S. Yi
Psychiatry, Korea University, Seoul, South Korea

Objectives: Recently, there are many reports that glutamate receptors have close relationships with a pathophysiology of schizophrenia. The purpose of this study was to assess the effects of D-cycloserine, which is glycine site partial agonist in NMDA receptor on psychopathologic symptoms and cognitive functions. Methods: This study was done for chronic schizophrenic inpatients taking typical antipsychotics for more than 4 months. Exclusion criteria were patients with over 8 points according to Simpson-Angus scale for EPS or those with over 17 points of Hamilton Depression Scale. Patients were randomized to classify into two groups, D-cycloserine group (n=13) and placebo group (n=13). Each group received D-cycloserine 100 mg or placebo separately for 8 weeks. Psychopathology was evaluated with PANSS at baseline, 2nd week, 4th week and 8th week. Cognitive function was evaluated with KWIS at baseline and 8th week. Result: Total 26 patients completed this trial. The average period of morbidity was 10.39 years and the average doses of antipsychotic was 1228.35 mg based on chlorpromazine equivalent. In positive subscale, negative subscale, general psychopathology subscale, total PANSS scale and KWIS, there were no significant differences between D-cycloserine and placebo groups. However, negative subscale scores had decreased from 24.92(baseline) to 23.46(week 8). Conclusion: There were no clear changes in positive symptom, negative symptom, memory, language function, and performance intelligence when D-cycloserine 100 mg was given with antipsychotic medication. However, some patients showed clear improvement in negative symptom, especially blunted affect. Therefore, D-cycloserine combination therapy could be effective for negative symptom. In future, study that can show effectiveness in psychopathology and cognitive function according to drug dosage is needed.

IMPROVEMENT OF COMORBID DEPRESSION WITH OLANZAPINE VERSUS ZIPRASIDONE TREATMENT IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

B. J. Kinon,* I. Lipkovich, S. E. Edwards
Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA

Background: Comorbid depression is a significant symptom domain in schizophrenia, which adversely affects other core symptoms and functional outcomes. The primary objective of this study was to assess the efficacy of olanzapine (OLZ) compared with ziprasidone (ZIP) in improving depressive symptoms in patients with schizophrenia or schizoaffective disorder. Methods: Double-blind, 24-week study in patients with ≥16 on the Montgomery-Asberg Depression Rating Scale (MADRS) who were randomized to: 10-15 or 20 mg/day OLZ (n=202) or 80-120 or 160 mg/day ZIP (n=192). The primary efficacy measure was the Calgary Depression Scale for Schizophrenia (CDSS). Results: At study end OLZ-treated patients showed significant improvement (p=.017) in depressive symptoms on the CDSS, which was not evident at 8 weeks. OLZ-treated patients also experienced greater improvement on the MADRS (p<.001), PANSS total (p=.008), and positive (p=.008), negative (p=.049), and cognitive (p=.003) subscales. Decreased appetite, aggravated psychosis, influenza, and migraine symptoms occurred significantly (p≤.05) more often in the ZIP treatment group; whereas increased appetite, peripheral edema, and weight occurred more often in the OLZ treatment group. Between-group differences in QTc intervals, fasting glucose, cholesterol were not significant, but triglycerides were elevated in patients treated with OLZ (p=.016). Differences in weight changes were significant (OLZ, +3.53 kg, and ZIP, -1.65 kg, p<.001). Conclusion: Patients suffering from significant comorbid depression in schizophrenia or schizoaffective disorder may experience greater symptom improvement with OLZ treatment.

TREATMENT OUTCOME OVER 1-2 YEARS IN FIRST-EPISODE SCHZIOPHRENIA

C. G. Kohler,* W. Bilker, S. J. Siegel, S. J. Kanes, C. Brensinger, R. E. Gur
Neuropsychiatry Section, Dept. of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA

Treatment of first episode schizophrenia patients (FE-SZP) presents as a challenging undertaking. Over the past 15 years, atypical antipsychotics have largely supplanted typical antipsychotics as first line medications. We examined the effects of antipsychotics in a group of FE-SZP, who underwent treatment as clinically indicated, and was followed over a period of 1-2 years. 63 FE-SZP (M:F=39:24) were evaluated and followed between 1986-2004. Subjects were assessed by reliable raters, using the SCID and positive, negative, overall psychiatric and depressive symptom scales. According to treatment for >80% of the follow up period, including >30 days prior to follow up evaluation, patients were grouped into adequate (ATG: n=41) or inadequate treatment (ITG: n=22) groups. ATG was further separated into primary treatment with typicals (TYP) and atypicals (ATY). The three groups were compared using nonparametric analyses, adjusting for symptom severity at intake. ATG and ITG did not differ in distribution of gender, ethnicity, age at onset and status at intake (in- or outpatient). Duration of illness was higher in ITG (p=.02). At intake, ATG rated higher in thought disorder (p=.04). The group subsequently treated with ATY had lower total negative (p=.04) and positive (p=.004) symptoms, lower hallucinations (p=.01), bizarre behavior (p=0.06) and depression (p=.01). At follow up, ATG experienced lower total positive (p=.04) and delusions (p=.08) and higher alogia (p=.06). Comparing ATG, ATY (ave. chlorpromazine equiv./day=30, ave. olanzapine equiv./day=14.3) experienced lower ratings on depression (p=.005), including cognitive (p=.018) and vegetative (p=.046) symptoms, and alogia (p=.06), than TYP (ave. chlorpromazine equiv./day=205, ave. olanzapine equiv./day=1.5). Duration of illness before treatment may be a reflection of treatment noncompliance. Gender, ethnicity and hospitalization status at intake were not associated with treatment outcome.

Patients subsequently treated with atypicals rated lower on some positive, negative and depressive symptoms, perhaps indicating increasing awareness of symptoms and earlier treatment over the recent years. Adequate treatment was associated with lower positive symptoms, in particular delusions and higher alogia, the latter may be the function of typicals. These data support previous findings showing better improvement in mood symptoms, rather than positive and negative symptoms, with atypical antipsychotics.

MAINTENANCE OF RESPONSE IN CHRONIC SCHIZOPHRENIA: EFFECTS OF ARIPIPRAZOLE AND HALOPERIDOL ON AFFECTIVE SYMPTOMS

D. Kostic,* R. N. Marcus, E. G. Stock, W. H. Carson, S. Tourkodimitris, D. G. Archibald
Bristol-Myers Squibb, Lawrenceville, NJ, USA

The long-term effects of aripiprazole and haloperidol on the affective symptoms of schizophrenia were evaluated in a randomized, multicenter, 52-week study. Maintenance of response in 1283 patients with acute exacerbation of chronic schizophrenia was compared between aripiprazole- and haloperidol-treated patients. Affective symptoms of schizophrenia were evaluated using the PANSS depression/anxiety symptom cluster derived by factor analysis, the PANSS depression item (G6), and the Montgomery-Asberg Depression Rating Scale (MADRS) score. There was a greater improvement in the PANSS depression/anxiety cluster score and the PANSS depression item score in the aripiprazole group than in the haloperidol group at Week 8. This effect was maintained throughout the study period. At Week 52 there was a significant difference between treatments; for the depression/anxiety cluster, mean treatment difference was 0.52 (P=0.015), and for the depression item, mean treatment difference was 0.14 (P=0.027). Stratification of patients by baseline scores showed a particularly pronounced difference in the depression/anxiety cluster (mean treatment difference 1.10; P=0.02) in patients from the most severe tertile. Similar results were produced after analysis of MADRS scores. In particular, reductions in MADRS score were significantly greater with aripiprazole than with haloperidol (6.0 vs. 3.5; P=0.029) among patients with pronounced depressive symptoms at baseline (MADRS >16). Long-term therapy with aripiprazole is more effective than haloperidol for the reduction of affective symptoms in patients with schizophrenia, as measured by changes in MADRS and relevant PANSS items scores.

OPTIMIZATION OF LONG-ACTING RISPERIDONE FOR MAINTENANCE THERAPY IN SCHIZOPHRENIA

R. A. Lasser,* S. C. Rodriguez, I. Turkoz, A. R. Mahableshwarkar, G. M. Gharabawi, G. M. Simpson
Janssen Medical Affairs, LLC, Titusville, NJ, USA

Continuous therapy with antipsychotics is essential to achieving remission and optimal outcome in patients with schizophrenia; we examined long-term clinical outcomes and dosing in patients with psychotic disorders who were transitioned from oral antipsychotics to long-acting, injectable risperidone (LAR). Patients with psychotic disorders were randomized, to LAR 25 or 50 mg Q2 weeks in a 52-week, prospective, double-blind, multicenter study. Patients were symptomatically stable, with no relapse for 4 months and stable doses of oral antipsychotics for 4 weeks prebaseline, stratified by average or higher-than-average risperidone equivalents to examine optimal long-term dosing. Measurements included: Efficacy—Positive and Negative Syndrome Scale (PANSS), Clinical Global Impressions of Severity (CGI–S) scale; Safety—Treatment-emergent adverse events (AEs) reporting, Extrapyramidal Symptom Rating Scale (ESRS), Abnormal Involuntary Movement Scale (AIMS). Six-month, blinded, interim data for an ongoing trial of 324 stable patients (62.3%men; mean age, 40.9±11.9 y) with previous treatment (monotherapy or combination therapy) including (n, %): 57, 17.7%, conventional antipsychotics; 312, 96.3%, atypical antipsychotics: aripiprazole, 18, 5.6%; olanzapine, 95, 29.3%; quetiapine, 38, 11.7%; risperidone, 145, 44.8%; ziprasidone, 16, 4.9% are reported there in. Mean±SD total PANSS scores decreased significantly, 66.5±16.4 to 60.2±15.8 (P<0.001). Patients rated by CGI–S as not ill–mildly ill increased significantly, 45.5% to 62.3%. Mean±SD CGI–S scores improved, 3.50±0.9 to 3.2±1.0 (P<0.001). Treatment–emergent AEs (≥10%) were insomnia, 23%; headache, 14%; anxiety, 11%; and schizophrenia not otherwise specified, 11%. ESRS subjective scores (mean±SD) decreased, 2.0±2.9 to 1.7±2.4 (P<0.05). Physician's rating of parkinsonism (mean±SD) decreased, 4.6±6.8 to 3.5±5.3 (P<0.001), and physician's rating of dyskinesia (mean±SD) decreased, 1.5±3.4 to 1.1±2.8 (P<0.05). Physician's ratings of dystonia and akathisia were very low at baseline and through month 6. AIMS scores (mean±SD) for items 1–7 improved significantly, 1.6±3.0 to 1.3±2.6 (P<0.05). Interim data suggest that maintenance therapy with LAR provides further symptomatic improvements, is well tolerated, and decreases movement-disorder severity in stable patients with schizophrenia or schizoaffective disorder. Unblinded 1-year data will be available at the time of presentation.

AMISULPRIDE AS ADD-ON TREATMENT IN RESISTANT SCHIZOPHRENIC PATIENTS

V. Lerner,* J. Bergman, U. Loewenthal, C. Miodownik
Ben Gurion University, Be'er Sheva, Israel

Background: The problem of treatment-resistant psychosis in this subpopulation of patients is an important and difficult one. Several approaches have been considered by clinicians in order to deal with this clinical challenge (1). A recent review regarding treatment-resistant schizophrenia with combinations of different atypical antipsychotics demonstrated that this approach may be successful and safe, but it needs further investigations (2). We hypothesized that the addition of a selective D2/D3 antagonist (amisulpride) to the present treatment of partial or nonresponders may augment its antipsychotic activity and benefit negative symptoms. The aim of the present study was to investigate the efficacy of amisulpride as add-on treatment in management of resistant schizophrenic patients. Methods: In this open retrospective study we examined the clinical records of resistant schizophrenic patients who were treated with a combination of amisulpride and another antipsychotic during the last year. A total of 15 resistant schizophrenic patients (7 men, 8 women, 54.0 SD 16.9 years old) were included in the study. Before adjunction of amisulpride, the patients were treated with atypical neuroleptics. Results: Of 15 subjects, five patients were treated with the combination of amisulpride and clozapine, another 5 patients with the olanzapine, 4 patients with the risperidone, and 1 patient with ziprasidone combinations. The mental state of 12 (80%) patients treated with combination was improved. Three (20%) patients showed no change in their mental state. Only two patients treated with combination of risperidone and amisulpride had mild side effects. Nobody demonstrated worsening of mental symptoms. Conclusions: The results

are preliminary and require confirmation in a randomized controlled trial. The authors suggest that amisulpride may be a promising option as an augmentation strategy in treatment-resistant schizophrenic patients. References 1. Zarate CA, Jr., Daniel DG, Kinon BJ, et al. Algorithms for the treatment of schizophrenia. *Psychopharmacol Bull* 1995;31:461-467 2. Lerner V, Libov I, Kotler M, et al. Combination of "atypical" antipsychotic medication in the management of treatment-resistant schizophrenia and schizoaffective disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2004;28:89-98.

RISPERIDONE LONG-ACTING INJECTABLE SIGNIFICANTLY IMPROVED EFFICACY AND TOLERABILITY IN PATIENTS WITH PSYCHOTIC DISORDERS PREVIOUSLY RECEIVING CONVENTIONAL ORAL NEUROLEPTICS

A. Lex,* V. Milanova, I. Tuma, M. Gheorghe, H. J. Moeller
Medical Affairs, EMEA, Janssen-Cilag, Beerse, Belgium

Objective: Investigation of the maintained efficacy and safety of risperidone long-acting injectable in patients with schizophrenia disorders who were changed directly from conventional oral neuroleptics without an oral risperidone run-in. Methods: Patients considered clinically stable on their previous medication for ≥1 month, but needing a therapy change as judged by their treating physician, received i.m. injections of long-acting risperidone 25 mg (increased to 37.5 mg or 50 mg, if necessary) every 14 days for 6 months. Results: The analysis included 86 male and 33 female patients; mean age 42 years. 82% suffered from schizophrenia (DSM-IV; mostly paranoid subtype) or schizoaffective disorder (11%). Previous treatments were mainly haloperidol, zuclopenthixol and flupentixol. Reasons for a treatment change were insufficient efficacy (49%), non-compliance (43%) and/or side effects (24%). 81% of patients completed the trial. 76% received a starting dose of long-acting risperidone 25 mg, while 13% and 11% received 37.5 mg and 50 mg, resp. CGI-S scores improved significantly from baseline to endpoint; 3% of patients were classified as 'not ill/borderline ill' at baseline compared with 18% at endpoint. The mean total PANSS score was reduced significantly ($p<0.001$) from baseline (79 points) to 1 month (71 points), and at all subsequent visits until endpoint (68 points). Improvement ≥20% from baseline in the PANSS total score was seen in 37% of patients. Significant reductions were also noted in all PANSS subscales and the symptom factors (acc. to Marder et al.) at all visits. GAF improved significantly ($p<0.001$) from baseline to endpoint, and there were also significant improvements in the mean scores for all components of the SF-36 QoL questionnaire except Bodily Pain, Vitality and the Physical Component Summary. Patient satisfaction with treatment improved significantly; at baseline, 2% of patients rated their treatment satisfaction as 'very good' vs 26% at endpoint. The mean total ESRS and Parkinsonism scores were reduced significantly ($p<0.001$) at 1 month and at all subsequent visits. Only 7 patients (6%) discontinued due to adverse events. Conclusion: The treatment change from conventional oral neuroleptics to risperidone long-acting injectable resulted in immediate significant improvements in both clinical symptoms and movement disorders. Significant improvements were also seen in patients' quality of life and in their satisfaction with treatment.

EFFECTS OF ATYPICAL AND CONVENTIONAL ANTIPSYCHOTIC DRUGS ON COGNITIVE PERFORMANCE IN TREATMENT NAIVE FIRST-EPISODE SCHIZOPHRENIA: A 3 YEAR RANDOMIZED TRIAL OF CLOZAPINE VERSUS CHLORPROMAZINE

J. A. Lieberman,* M. Phillips, H. Gu, R. Bilder, P. Zhang, Z. Ji, G. Koch
Psychiatry, UNC School of Medicine, Chapel Hill, NC, USA

To address the treatment effects on cognitive performance with atypical and conventional antipsychotic drugs, we compared clozapine and chlorpromazine with treatment naive patients in a randomized double-blind clinical trial. The trial was conducted in Beijing Hui Long Guan Hospital, one of the largest psychiatric hospitals in China. The sample included 80 per arm first-episode schizophrenia patients screened from October 1995 to December 1998 that had been followed up to 3 years. Patients in the two treatment groups had similar distribution of age, gender, education level, handedness, diagnosis, baseline symptom severity, and duration and age of onset of psychotic symptoms. The clinical neurocognitive battery was conducted at baseline, 3 months of inpatient treatment, 1 year outpatient follow-up and annually afterwards. The battery included tests on semantic fluency, language fluency, motor skill, trail-making, Wisconsin Card Sorting, Wechsler Memory Scale and WAIS-R. Random coefficient linear growth-curve models were used to capture the longitudinal trends for changes in cognitive functioning in two phases, the inpatient acute treatment phase between 0-3 months and the outpatient follow-up phase between 3 months to 3 years. While controlling for age, gender, education, duration of untreated illness, BPRS and SANS total scores, the model found significant decline in overall WAIS-R IQ score after 3 months of inpatient treatment with chlorpromazine. No similar decline was observed in patients treated with clozapine. In the follow-up phase of treatment (3 months to 3 years), both groups had improvement in their IQ, with significant recovery to the chlorpromazine treated patients. A similar pattern of treatment effect was observed in Wechsler Memory Scale, semantic fluency, language fluency, Wisconsin Card Sorting task, but to a less degree to the pegboard, finger tapping, and handedness tasks. The findings were important to our understanding for short and long-term effects of antipsychotic treatments on cognitive functioning in first episode schizophrenia patients.

A RANDOMIZED, DOUBLE-BLIND STUDY OF OLANZAPINE VS HALOPERIDOL IN THE TREATMENT OF PRIMARY NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

J. Lindenmayer,* A. Iskander, T. Abad, B. Parker, M. Lerman, A. Khan
Psychopharmacology Research Program, Manhattan Psychiatric Center, Wards Island, NY, USA

Primary negative symptoms are intrinsic to the pathology of schizophrenia and are associated with significant deficits in motivation, verbal and nonverbal communication, interest in socialization, affect, cognitive and social functioning. Data on negative symptom effects of atypical vs conventional antipsychotics are confounded by concomitant improvements on positive, depressive and extrapyramidal symptoms. The authors present preliminary results examining the effect of olanzapine and haloperidol on persistent primary negative

symptoms in schizophrenics with low levels of concomitant positive, depressive and extrapyramidal symptoms. METHOD 34 subjects with Schizophrenia and severe primary negative symptoms participated with either olanzapine 15 mg or haloperidol 15 mg. Inclusion criteria for persistent primary negative symptoms was PANSS negative score > 20, PANSS positive score < 20 minimal extrapyramidal symptom and depression score at baseline. PANSS, CDSS, HDS, SAS, AIMS and laboratory values were assessed at Week 1,2,4,6,8,10 and 12. A neuropsychological battery administered at baseline and endpoint. RESULTS Of the 34 patients 29 patients completed the 12 week period; of the remaining 5 patients 1 was a screening failure, 4 completed up to Week 2, 5, 8 and 10. For these patients LOCF was used, resulting in 33 patients. 16 were on haloperidol and 17 on olanzapine. No significant differences between the groups were found in age (Mean 38.15), ethnicity, length of hospitalization, prior antipsychotic or antiparkinsonian medication use. Mean baseline PANSS negative score was 27.8 and mean baseline positive score was 14.1. There was a significant decrease in PANSS total score for the olanzapine compared to haloperidol group ($p<.05$ $N = 16$) while there was significant overall effect for improvement on PANSS negative symptoms ($F=14.789$ $p<.05$ $N = 33$) in both groups, there were no differences between groups. There was significantly greater improvement in neurocognitive functions for all neuropsychological domains from baseline to endpoint for the olanzapine group ($p<.05$). CONCLUSIONS: The results suggest olanzapine is efficacious for primary negative symptoms in schizophrenia at a comparable level as haloperidol. However, olanzapine effect on negative symptoms may be predominantly on secondary negative symptoms, mediated by effects on positive, affective and extrapyramidal symptoms. A larger sample size and further analysis are planned.

EARLY INTERVENTIONS IN FIRST EPISODE PSYCHOSIS AND THE CRITICAL PERIOD

D. H. Linszen,* L. D. Haan, T. van Amelsvoort, L. Wouters, M. Lenior, P. Dingemans
Psychiatry, AMC University of Amsterdam, Amsterdam, Netherlands

Early recognition and intervention of florid psychosis in schizophrenia and related disorders in studies in England, America and Australia have shown earlier symptom remission, a high rate of remission, delay of psychotic relapse and prevention of psychosocial deterioration in twelve months intervention studies. After the first year follow-up studies shown an increase in relapse rate and a decrease of psychosoical funtioning tend to increase in first episode samples, ie with a relatively long duration of untreated psychosis. In a Dutch phase specific intervention study a sample of 76 young patients (mean age 20.6 years) with first psychotic episode schizophrenia and related psychotic disorders and a relatively short duration of untreated psychosis (mean duration 5,6 months) was included. The intervention showed a beneficial effect on the occurrence of psychotic relapse during the 15-months intervention (16%) with an excellent drug compliance during the intervention. The results of a five year follow-up study showed that the beneficial effects did not last. As in ohter follow-up studies most of the patients relapsed. Other five year follow-up studies showed the same initial beneficial effect, followed by a return to the relapsing course of schizophrenia. Therefore we started a 5 year randomized intervention study examining the role of continuity of care by the same staff and the effect of parent groups. Risk and protective factors were assessed of 183 randomized patients at the start of the study and at 6 months intervals with the Life Chart Schedule (WHO, 1992). Results after 4 year intervention showed a beneficial non relapsing effect of early and sustained intervention in more than 60% of the first episode patients. Also a treatment reluctant group of less than 40% of young patients emerged, who relapsed once or more or developed continuous psychosis within 2 years. Main poor outcome predictors turned out to be lack of insight, cannabis abuse and non-compliance as assessed during the first 6 months of the intervention. The early course stabilised after 2 years. This study was funded in part by grant (28, 1204) form the "Health Research and Development Council (ZON)".

THE EFFECTIVENESS OF SWITCH TO ARIPIPRAZOLE STRATIFIED BY PRIOR ANTIPSYCHOTIC THERAPY

H. Liston,* W. H. Carson, R. N. Marcus, J. Dogin, M. Pans, T. Iwamoto
Bristol-Myers Squibb, Plainsboro, NJ, USA

This study in a naturalistic setting examined how prior therapy affects aripiprazole's effectiveness in treating psychosis. Outpatients with schizophrenia or schizoaffective disorder for whom an alteration in medication was considered clinically reasonable (N=1119) were switched to aripiprazole. An evaluation was made of the effectiveness of aripiprazole therapy after 8 weeks using the CGI-I scale. Patients and caregivers were asked to assess aripiprazole therapy in comparison to previous medication. Mean CGI-I scores at endpoint indicated that aripiprazole had produced some or much improvement regardless of whether patients were previously receiving atypical antipsychotics, typical antipsychotics, or more than one antipsychotic (CGI-I values of 2.4–3.0). Most patients preferred aripiprazole to previous medication regardless of previous therapy. The proportion of patients who classified aripipiprazole as much better than previous medication was 50%, 48%, 49%, 60%, 53%, and 49% among those switched from olanzapine, risperidone, quetiapine, ziprasidone, typicals, and >1 antipsychotic, respectively. Among caregivers, 34–48% classified aripiprazole therapy as much preferable to their previous therapy. In this naturalistic study, improvements were observed after a switch to aripiprazole regardless of prior treatment. In general, patients and caregivers preferred therapy with aripiprazole to the previous treatment and this preference was not significantly impacted by prior medication history.

MAINTENANCE THERAPY WITH LONG-ACTING RISPERIDONE: FUNCTIONING AND QUALITY OF LIFE IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

J. Locklear,* R. A. Lasser, S. C. Rodriguez, I. Turkoz, A. R. Mahableshwarkar, D. Feifel
Janssen Medical Affairs, LLC, Titusville, NJ, USA

Improvements in patient functioning and quality of life (QoL) are important goals of long-term treatment of psychotic illness; we therefore examined the impact of maintenance therapy with long-acting, injectable risperidone on functioning and QoL in clinically stable patients with schizophrenia or schizoaffective disorder. Data are from an ongoing, 52-week, prospective, randomized, double-blind, multicenter study in 324 patients with schizophrenia or schizoaffective disorder, previously taking oral antipsychotics, randomized to long-acting risperidone 25 or 50 mg Q2 weeks. Patients were sympto-

matically stable, without signs of relapse during the 4 months prebaseline (no psychiatric hospitalization due to worsening symptoms; no clinically significant self-injury, suicidal or homicidal ideation; or violent behavior), and taking stable doses of oral antipsychotic medication for 4 weeks prebaseline. Functioning and QoL were assessed using the Strauss-Carpenter Level of Functioning Scale (LOF), the Personal and Social Performance Scale (PSP), and the Schizophrenia Quality of Life Scale (SQLS). We report results for the interim, 6-month timepoint. Seven of 9 items on the LOF improved: frequency of social contacts (≥1/month) increased, from 73.0% at baseline to 75.2%, and the percentage of at least moderately close relationships improved, from 64.0% to 70.0%. The quality of useful work increased, from 91.9% to 98.6%, and the percentage of patients with slight to no signs and symptoms improved, from 63.4% to 66.4%. At baseline, 83.5% of patients reported requiring little to no help with basic needs; 85.8% reported this level at the 6-month endpoint. The percentage of patients who reported a moderate to very full life increased, from 58.3% to 61.6%, and, while 75.4% of patients had moderate to no impairment in function at baseline, 81.0% reported this level of function at the 6-month endpoint. The PSP score (mean±SD) improved significantly, from 62.1±14.2 at baseline to 63.7±13.7 ($P<0.01$). The SQLS scores indicated that QoL was maintained, with no significant changes. Baseline measures of clinical status confirmed a symptomatically stable patient population. Even so, 6-month, interim data indicated improvements in measures of functioning and maintenance of QoL. Further functional benefits, will be explored when final data become available.

NEGATIVE SYMPTOM SPECTRUM DISORDERS: A FOCUSED LOOK AT ASPERGER'S DISORDER. DOES RISPERIDONE TREATMENT IMPROVE FUNCTIONING?

D. L. Londino,* J. Rausch
Psychiatry, Medical College of Georgia, Augusta, GA, USA

Asperger's disorder is a diagnosis new to the DSM-IV. Although it is included in the autistic spectrum disorders, debate has exibited about the overlap between this disorder and other disorders with social deficiencies, including schizotypal and schizoid personality disorder, and infrequently schizophrenia. Historically, autism was considered childhood schizophrenia, based on clinical presentations of social isolation, lack of attachment and social reciprocity, and restricted affect. We examined the overlap between negative symptoms seen in several psychiatric disorders followed by an open label trial of risperidone use in Asperger's disorder based on the hypothesis that symptoms of "negativity" as defined in this disorder may respond to the newer antipsychotic agents which have shown benefit in improving negative symptoms of schizophrenia. Methods: 12 week, open-label, pilot trial of risperidone in thirteen males (ages 6 to 18) with Asperger's disorder. Assessment scales included the Scale for Assessment of Negative Symptoms (SANS), the Asperger's Syndrome Diagnostic Scale (ASDS-Modified),the Montgomery and Asberg Depression Rating Scale (MADRS), the Brief Psychiatric Rating Scale (BPRS), the Global Assessment Scale (GAS), and the Positive and Negative Symptoms Scale (PANSS). Adverse events were monitored throughout. Results: Mean SANS scores were reduced significantly ($F=9.6$; $p<0.0001$) from baseline to week 12. Statistically significant improvement over baseline was also seen in the ASDS, MADRS, BPRS, GAS, and PANSS. Improvement in disruptive behavior did not significantly account for the noted improvement in social interaction. The mean dose of risperidone (0.75 mg) was overall well tolerated. Conclusions: Current concepts of mental illness include targeting of problematic symptoms which may overlap in different diagnosis. Deficits in social interactions, both in primary psychotic disorders, and as the core deficit in autistic disorders, are increasingly being investigated through neuroimaging techniques, including functional MRI and MR Spectroscopy. Considerations of possible benefits that may be obtained on core social deficits through the use of newer antipsychotics has been investigated to some extent in autistic disorders; however, few studies have examined Asperger's disorder in isolation. Preliminary data suggest that risperidone may benefit social interactions in this subpopulation of autistic individuals.

SWITCHING FROM RISPERIDONE TO QUETIAPINE IN ELDERLY PATIENTS WITH DEMENTIA: A RETROSPECTIVE STUDY

S. Madhusoodanan,* O. Bogunovic
St. John's Episcopal Hospital, Far Rockaway, NY, USA

A chart review was performed to collect data on the techniques used and outcomes obtained when switching from risperidone to quetiapine in elderly nursing home residents with behavioral and psychological symptoms of dementia. Nursing home medical records were reviewed to identify all patients with dementia switched from risperidone to quetiapine between May and December 2003. Demographic, efficacy, and safety data were collected. Response to treatment was retrospectively assessed using the Clinical Global Impression (CGI) scale at the time of the switch and at weeks 4 to 6. Data from 15 men and 52 women (mean age, 82.8 y) were evaluated. Alzheimer's disease was the primary diagnosis in 37 patients and a secondary diagnosis in 19 patients; other psychiatric diagnoses included vascular dementia, schizophrenia or schizoaffective disorder, depression, anxiety, and dementia related to alcohol abuse. The mean daily dose of risperidone at the switch was 1.42 mg (range, 0.25–6.0 mg). Switching was abrupt in all but 2 patients. Mean daily dose of quetiapine after the switch was 87.3 mg (range, 25–200 mg). After the switch, the CGI-Severity of Illness score remained unchanged, but the CGI-Improvement score was positive. Fourteen patients reported somnolence after the switch; 3 patients discontinued quetiapine because of lack of response. Most of the 67 elderly patients in this retrospective study were successfully switched from risperidone to quetiapine with no worsening of clinical status. Although not generally recommended in elderly patients, abrupt switching from risperidone to quetiapine did not appear to cause significant adverse events.

EFFECTS OF INTRODUCTION OF NEUROLEPTICS ON SYMPTOMATOLOGY IN CHRONIC SCHIZOPHRENIA INPATIENTS

B. Mancevski,* G. Rosoklija, M. Kurzon, T. Serafimova, V. Ortakov, I. Trencevska, J. Keilp, A. J. Dwork
Neuroscience, New York State Psychiatric Institute, New York, NY, USA

When chlorpromazine was introduced for the treatment of schizophrenia in the mid-1950, it was adopted on a large scale in the institutions of the New York State Office of Mental Health (OMH). Clinicians from that era describe the initiation of neuroleptic therapy (INL) in "whole wards" of patients simultaneously. Such a practice could allow the determination, in a naturalistic setting, of the

effects of initiating antipsychotic treatment, and the clinical factors influencing these effects, relatively free of bias related to the decision to initiate treatment for a particular patient. In particular, in these institutionalized patients, the duration of untreated psychosis (DUP), now widely believed to influence the outcome of treatment, was determined primarily by the timing of the introduction of the drugs, rather than by clinical or social factors that may influence DUP in the modern clinical setting. We reviewed the records 62 subjects with schizophrenia, in whom neuroleptic treatment was initiated between 1954 and 1959, and who died and were autopsied in OMH institutions between 1982 and 1993. The modified Diagnostic Evaluation After Death (mDEAD) was used to establish DSM-IV diagnoses, to catalog symptoms during each of 6 age epochs, and to establish whether clinical evidence of definite cognitive impairment (DCI) was present for at least the last two years of life. Changes in symptoms with neuroleptic treatment were taken as the number of symptoms in the epoch following INL minus the number of symptoms in the epoch of INL. Mean age at death was 79. DUP ranged from 2 years to 40 years, with a mean of 20 years and 90% at least 9 years. There was no significant change in negative symptoms with INL. INL was associated with a decrease in positive symptoms, but this did not differ significantly from the decrease in positive symptoms across other epochs and was not significantly correlated with DUP. In logistic regressions, improvement in positive symptoms predicted sparing from DCI, while DUP and changes in positive symptoms across other epochs did not. These results suggest: (1) Effects of DUP on outcome may plateau once DUP is in the range of a decade or more. (2) A common mechanism may underlie poor antipsychotic response and eventual development of cognitive impairment in schizophrenia. Support contributed by: MH60877, NARSAD, Lieber Center for Schizophrenia Research.

BROAD EFFECTIVENESS OF ARIPIPRAZOLE

R. Marcus,* E. Stock, M. Nyilas, A. Torbeyns, R. McQuade, T. Iwamoto, D. Kostic
Bristol-Myers Squibb, Wallingford, NJ, USA

This study examined the overall effectiveness of aripiprazole treatment following a switch from prior antipsychotic therapy in a naturalistic setting. Outpatients with schizophrenia or schizoaffective disorder for whom a switch or initiation of antipsychotic medication was required were randomized in a 4:1 ratio to aripiprazole (n=1295) or a safety-control group (primarily risperidone, olanzapine, ziprasidone, or quetiapine; n=304) for 8 weeks in this multicenter, open-label study. Aripiprazole treatment was initiated at a 15 mg/day, with the option to adjust within a dose range of 10–30 mg/day. The key measures of effectiveness included the CGI-Improvement scale (CGI-I) and preference of medication scale (POMS). The mean aripiprazole dose was 19.9 mg/day at study endpoint, with 47% of patients receiving the 15 mg dose. The effectiveness of aripiprazole was demonstrated as early as Week 1. Among patients completing the study, 69% of those in the aripiprazole group responded to treatment (CGI-I score of 1 or 2) with a mean CGI-I score of 2.17. Aripiprazole was rated as much better than prior antipsychotic therapy (score of 1) in over 60% of aripiprazole-treated patients and 54% of caregivers. Nausea and insomnia were the only adverse events reported with aripiprazole treatment with an incidence of 10% or above (14% and 20%, respectively). Aripiprazole demonstrated overall effectiveness with an early onset of action in patients with schizophrenia and schizoaffective disorder in a general psychiatric setting.

EARLY DETECTION AND INTERVENTION IN FIRST EPISODE PSYCHOSIS: EMPIRICAL UPDATE OF THE TIPS AND PRIME PROJECTS

T. H. McGlashan,* P. Vaglum, S. Friis, J. O. Johannessen, E. Simonsen, T. K. Larsen, I. Melle, U. Haahr, S. Opjordsmoen, R. Zipursky, D. Perkins, J. Addington, T. Miller, S. Woods, R. Hoffman, A. Preda, I. Epstein, D. Addington, S. Lindborg, Q. Trzaskoma, M. Tohen, A. Breier
Psychiatry, Yale University, New Haven, CT, USA

Background: Two prevention projects began in 1997. TIPS (Norway/Denmark) aims to attenuate psychosis severity by reducing the duration of untreated psychosis (DUP) in first episode psychosis (FEP). PRIME (North America) aims to delay/prevent psychosis by treating the pre-onset prodromal syndrome. TIPS Update: Whether reducing DUP affects the course of FEP might be seen by comparing FEP outcome in national healthcare sectors with early detection (ED,N=141) and without early detection (no-ED, N=140). Significant findings of this ongoing study are 1) DUP can be decreased in a sector with education and easier treatment access (ED), 2) reducing DUP brings FEP patients in who are younger (average 5 years), less symptomatic (positive/negative/general PANSS symptoms), less compromised (GAF), and in more meaningful activity (QoL), 3) these baseline ED/no-ED differences attenuate at 1 year except for negative symptoms and meaningful activity. Treatments in year 1 are comparable between ED and no-ED patients and unlikely to account for the differences. Implications: Decreasing DUP in FEP may improve long-term prognosis (tertiary prevention) but further follow up is necessary to determine this. PRIME Update: Symptomatic at-risk states predictive of imminent psychosis can be identified reliably and treated to test whether FEP can be prevented. A two-year randomized double-blind (DB), Pbo controlled trial of olanzapine (Olz) in prodromal patients (N=60) is finished. Significant results for the 1 year DB phase are: 1) the ratio of converting to psychosis on Pbo was 4 times that on Olz, adjusting for initial prodromal symptom severity, 2) reduction in severity of positive prodromal symptoms was greater on Olz, 3) weight gain (average 8.8kg) was higher on Olz. In the second no-treatment year, 3 of 9 former Olz patients converted suggesting onset is delayed, not prevented. All study converters (N=21, 35%) received immediate open-label Olz without missing work/school or needing hospitalization. Implications: Prodromal identification and intervention with Olz provides tertiary prevention (less morbidity with psychosis onset), secondary prevention (delayed onset), and causes weight gain. Further research is warranted to formulate treatment recommendations. Support for TIPS is from the National Health Systems of Norway and Denmark and NIMH 01654 (Dr. McGlashan). Support for PRIME was from Eli Lilly, Co. and NIMH 01654.

ARIPIPRAZOLE VERSUS OLANZAPINE IN A 52-WEEK, OPEN-LABEL EXTENSION STUDY

R. McQuade,* D. Kostic, R. Marcus, W. Carson, A. Torbeyns, W. Kerselaers, F. Yocca
Otsuka America Pharmaceutical Inc, Princeton, NJ, USA

The objective of this study was to compare long-term efficacy, safety, and metabolic profile of aripiprazole with olanzapine in patients with chronic schizophrenia. In a 26-week, placebo-controlled trial (Phase I) designed to compare the time to relapse of aripiprazole versus placebo in stabilized patients (n=310) with chronic schizophre-

nia, patients who completed the treatment phase or who met the protocol definition of relapse after at least 2 weeks of double-blind treatment were eligible for a randomized, open-label extension trial of aripiprazole (15–30 mg/day, n=104) versus olanzapine (10–20 mg/day, n=110) for up to 52 weeks (Phase II). Overall, 69% of patients completed the 52-week study. At week 52, mean doses for aripiprazole and olanzapine were 22 mg and 14 mg, respectively. In patients who met Phase I relapse criteria and were randomized into Phase II, PANSS Total reduction (LOCF) was –23.8 with olanzapine and –21.8 for aripiprazole. For patients who completed the 52-week trial, magnitude of improvement was greater and comparable for the two agents (mean change in PANSS total score: aripiprazole = –31.2, olanzapine = –29.6). In patients who completed Phase I of the study and were randomized into Phase II, improvement of symptoms was observed in patients treated with both aripiprazole or olanzapine (PANSS Total reduction (LOCF): –5.5 with olanzapine and –4.6 with aripiprazole); for patients who completed the 52-week trial, improvement was also comparable for the two agents (mean change in PANSS total score: aripiprazole = –7.9, olanzapine = –7.4). Olanzapine led to significantly greater weight gain at all time points in comparison to aripiprazole (week 52 (LOCF): 2.54 kg vs 0.04 kg, respectively; p<0.001). Differences were seen in mean changes from baseline to endpoint in fasting glucose (aripiprazole = –1.4, olanzapine = 12.0 mg/dl), total cholesterol (aripiprazole = 1.6, olanzapine = 17.2 mg/dl), LDL (aripiprazole = –1.5, olanzapine = 13.9 mg/dl), and triglycerides (aripiprazole = 4.9, olanzapine = 24.8 mg/dl). Incidences of EPS and akathisia were comparable for aripiprazole- and olanzapine-treated patients. In both acutely psychotic and stable, chronic patients treated for up to 52 weeks, comparable symptom improvement was observed with both aripiprazole and olanzapine. With regard to weight and metabolic factors, aripiprazole was consistently superior to olanzapine.

IMPROVED SYMPTOM CONTROL AND FUNCTIONING IN PATIENTS WITH PSYCHOTIC DISORDERS FOLLOWING TREATMENT CHANGE FROM OLANZAPINE TO RISPERIDONE LONG-ACTING INJECTABLE

R. Medori,* D. J. Palao Vidal, S. Bleuer, M. Gastpar
Medical Affairs, Janssen-Cilag, Beerse, Belgium

Objective: To investigate the maintained efficacy and safety of a direct change from olanzapine to risperidone long-acting injectable in adults with schizophrenic disorders requiring a treatment change. Methods: Patients with unchanged symptoms while on olanzapine for ≥1 month, received long-acting risperidone, i.m., 25 mg (increased to 37.5 mg or 50 mg, if necessary) every 2 weeks for 6 months. Olanzapine was continued for the first 3 weeks after the first risperidone injection. Results: The analysis included 192 patients (63% male) of mean age 38 years. 70% of patients completed the trial. The most common diagnoses (DSM-IV) were schizophrenia (79%; mostly paranoid) or schizoaffective disorder (15%). Reasons for treatment change were non-compliance (44%), insufficient efficacy (43%) and side effects (19%). At endpoint, 36% of patients received risperidone long-acting injectable 25 mg; 30% and 34% received 37.5 mg and 50 mg, resp. The mean total PANSS score at baseline was 74, which was significantly reduced after 1 month (mean change -5 points); further reductions were observed until treatment endpoint (mean change -8 points) (p<0.001). At all assessments, significant reductions were also seen in all PANSS subscales and in the positive symptoms, negative symptoms, disorganised thoughts and anxiety/depression factors acc. to Marder et al. At endpoint, 32% of patients had a ≥20% improvement from baseline in PANSS total score. By CGI-S, the proportion of patients classified as 'not ill/borderline ill' doubled from 10% at baseline to 20% at endpoint. Mean scores for physical functioning, general health, vitality, social functioning, role emotional and mental health of the SF-36 QoL questionnaire improved significantly from baseline to endpoint (p<0.05) as did the mental component summary score (p< 0.001). GAF scores and patient satisfaction with treatment improved significantly; at endpoint, 31% of patients rated their treatment as 'very good' compared with only 6% at baseline. The baseline median BMI remained unchanged during the study. The ESRS total score was reduced significantly (p<0.001) from baseline to 1 month, and these improvements continued until endpoint. No unexpected side effects were reported. Conclusion: The direct initiation of risperidone long-acting was associated with significant improvements of symptoms and a reduction in movement disorders in patients who were stable on olanzapine, offering a potential to enhance treatment quality.

UNDERSTANDING HOW ANTIPSYCHOTICS IMPROVE PSYCHOSIS: A MULTIDIMENSIONAL PERSPECTIVE

R. Mizrahi,* D. Mamo, R. Bagby, G. Remington, R. Zipursky, S. Kapur
Schizophrenia Department, CAMH, Toronto, ON, Canada

Antipsychotics have been used for more than half a century, and most previous studies measured psychosis as a single symptom or a single dimension. However, several lines of evidence suggest that psychosis itself is a multidimensional phenomenon. At present there is no simple, reliable and validated scale for assessing the dimensions of psychosis in the context of antipsychotic treatment. In the present study, we developed, standardised and applied a scale to assess psychosis from a dimensional perspective and used it to delineate the multidimensional pattern of psychosis resolution. We included 91 patients with schizophrenia (cross-sectional component) and 17 drug free patients (evaluated during the first 6 weeks of antipsychotic treatment -longitudinal component). The patients completed the 15-item, experimenter-administered scale, together with the MINI and PANSS. ICCs were used to determine inter-rater reliability and Cronbach's alpha coefficient was used to evaluate internal consistency. Patients scores were analyzed using factor analysis and general linear models. Inter-raters ICC for each item ranked from 0.76 to 0.9, Cronbach's alpha was above 0.85. The data suggest that four underlying dimensions characterize psychosis: emotional involvement and preoccupation with symptoms; impact of psychosis on behaviour; conviction with the psychotic belief; and external awareness regarding the appropriateness of the belief. There was an improvement in all dimensions over time except for external awareness. The dimension of behavioural impact showed the fastest and major improvement (30% within the first two weeks and 60% at 6 weeks), while improvement in conviction was slower and modest even at six weeks (17 %). Positive symptoms (PANSSP) improvement was intermediate (around 18% within the first two weeks and 40% at 6 weeks), and similar to that of the emotional-preoccupation dimension. The study confirms as a feasible, reliable scale for measuring the dimensions of a psychotic phenomenon, and shows differential sensitivity to change. The dimension of behavioural impact being the most sensitive to early change, more sensitive than the PANSSP scale. Patients show relatively little change in their conviction despite what is traditionally considered good improvement. The implications for the

mechanism of antipsychotic action, and design of more sensitive antipsychotic trials is discussed.

COULD SCHIZOPHRENIC PATIENTS WITH DEPRESSION BENEFIT FROM LITHIUM THERAPY?

S. Mykhnyak,* I. Vlokh
Psychiatric Clinic of Department of Psychiatry, Psychology and Sexology, Lviv National Medical University, Lviv, Ukraine

New form - lithium gamma-hydroglutaminate (LHG) was developed in Lviv Medical University. Experimental animal studies established that this drug evokes number of effects: ability to influence on trifluoperazine-induced catatonia, prevents nicotine tremor, changes duration of sleep and has lower CNS toxicity than in lithium oxybutirate. Multi-center study of LHG and consisted of two phases: 6 and 12 months treatment. The aim of the study was to confirm previously obtained experimental data on LHG, clarifying spectrum of action, selection of optimal doses and establishment of safety and efficacy profile for the new drug. Study included 98 patients with depressive syndrome of different origin- in neurotic patients, bipolar disorder and schizophrenia. Drug was given in doses of 0,3-0,9mg/day up to 1,2 mg/day with following weekly control of lithium blood levels with checking renal and hepatic functions. Data, that were obtained, confirmed drug efficacy in 53% of patients with bipolar depression and in 36% of patients with schizophrenia. LGH was well-tolerated, and safely co-administered with other psychotropics, without causing any side effects or complications, proving to be effective in patients with depressions of different origins.

AN OPEN LABEL PILOT STUDY OF THE EFFECTS OF GALANTAMINE ON DEPRESSIVE SYMPTOMS IN INPATIENTS WITH CHRONIC SCHIZOPHRENIA

M. W. Nelson,* R. L. Benham, S. I. Deutsch, R. B. Rosse
Maryland Psychiatric Research Center, University of Maryland, Baltimore, Baltimore, MD, USA

Depressive symptomatology is common in schizophrenia and is associated with poor outcomes and risk of suicide. Galantamine is an acetylcholinesterase inhibitor with allosteric potentiating properties at nicotinic acetycholine receptors (nAChR) in the brain. Acetylcholinesterase inhibitors have been shown to improve depressive symptoms in patients with Alzheimer's disease. Furthermore, galantamine's action at nAChR has a potential role in the treatment of both schizophrenia and depression. In this pilot study, inpatients with stable, chronic schizophrenia were given galantamine in addition to their existing psychiatric medication regimen in a prospective, open-label design. Subjects were titrated to a dose of 24mg/day over three weeks and maintained at that dose for eight weeks. The primary outcome measure was the Montgomery-Asberg Depression Rating Scale (MADRS). Other measurements included the Brief Psychiatric Rating Scale (BPRS) depression cluster, the Neuropsychiatric Inventory (NPI) depression and depression plus anxiety item scores, and the Clinical Global Impression (CGI) scale. The Wilcoxon Signed-Rank Test was used to analyze changes between baseline and endpoint. Eleven subjects enrolled in the study and seven subjects received study medication. The average decrease in the total MADRS score from baseline was 5.3 +/- 5.5 ($p = 0.075$). A significant decrease in the total BPRS scores and the BPRS depression cluster scores was observed. No significant changes were found in the NPI items or CGI ratings. Galantamine was well tolerated and no subjects have withdrawn from the study due to adverse effects. No worsening of extrapyramidal symptoms or movement disorders was observed. This preliminary data suggests promise for the adjuvant use of galantamine in treating depressive symptoms associated with schizophrenia.

FEASIBILITY OF CARRYING OUT MAINTENANCE OR TARGETED MEDICATION TREATMENT IN FIRST ONSET SCHIZOPHRENIA: THE MESIFOS RCT

F. Nienhuis,* A. Wunderink, D. Wiersma
Dept of Psychiatry, Groningen University Hospital, Groningen, Groningen, Netherlands

The main aim of the guidelines for the treatment with antipsychotics (AP) of patients with a first episode psychosis is to reduce the risk of a relapse. Unfortunately the guidelines vary widely between countries, due to the lack of robust scientific underpinnings. Two approaches in the treatment with AP can be distinguished: targeted and maintenance treatment, both with their own merits. The comparison between targeted and maintenance AP treatment was subject of only a few studies. None of them described in any detail how these strategies were carried out in practice (fidelity to strategy). The Medication Strategies In First Onset Schizophrenia study (MESIFOS) compares targeted treatment and maintenance treatment with regard to Quality of Life (QoL). The target population are patients with a first onset non-affective psychosis, whose positive symptoms remitted within 6 months after commencing AP treatment. After a stable remission phase of 6 months, patients were randomly assigned to either maintenance treatment or targeted treatment with AP. These strategies had to be carried out during 18 months following the remission phase, according to an intention to treat. In the trial 131 patients were included. Among the data that were gathered of these patients were: medication use, side effects, symptom levels, social functioning and quality of life. Also detailed information about prescription and medication use was obtained. Obtaining these data is important, because it was by no means self-evident beforehand that both psychiatrists and patients would adhere to the allotted strategy. We will present the following results about the first nine months of the experimental phase: 1. The extent to which the strategies have been carried out by psychiatrists (fidelity) and followed by patients (compliance). 2. The association of both strategies with Quality of Life, assessed with the WHOQoL-bref.

CLINICAL STATUS AND TOLERABILITY PROFILES OF PREVIOUSLY UNTREATED SCHIZOPHRENIA PATIENTS. 24-MONTH RESULTS FROM THE PAN-EUROPEAN SOHO (SCHIZOPHRENIA OUTPATIENT HEALTH OUTCOMES) STUDY

D. Novick,* J. M. Haro, M. Belger, S. Tzivelekis, J. P. Lepine, J. Alonso, M. G. Bousono, I. Gasquet, H. Kristensen, P. B. Jones, T. Croudace, M. Knapp, V. Mavreas, D. Murray, D. Naber, P. Pancheri, C. J. Slooff, J. M. Texeira
Eli Lilly and Company, Windlesham, United Kingdom

OBJECTIVES: To report the clinical and medication tolerability status of previously untreated schizophrenic patients, after 2 years of

antipsychotic treatment. BACKGROUND: Randomised clinical trials seem to show the superiority of new antipsychotics for the treatment of never-treated patients (1,2). However, limited information exists for routine psychiatric care. The Schizophrenia Outpatient Health Outcomes (SOHO) study is a prospective, outpatient, observational study of health outcomes associated with antipsychotic treatment. METHODS: Never-treated patients were defined as patients who i) had never received antipsychotic treatment for schizophrenia and ii) had not received antipsychotic treatment in the 6 months prior to study inclusion. Clinical severity was assessed with the Clinical Global Impression (CGI) Scale. Dystonia, akathisia and parkinsonism were assessed by participating psychiatrists. Patients were defined as having long-term treatment success if they had i) remained on the same treatment during the first 2 years, ii) responded to treatment as defined by CGI reduction of 2-points when patients were markedly to among the most severely ill or a 1-point reduction when patients were borderline to moderately ill; and iii) remained responding to treatment. RESULTS: 1,009 never-treated patients were enrolled at baseline; 661 had continued treatment after 24 months, of which 505 had remained on their antipsychotic medication started at baseline. Most of the patients were initiated on olanzapine or risperidone. The proportion of patients remaining on their baseline antipsychotic during the 24 months was 82% for olanzapine-treated patients and 76% for risperidone-treated patients. The proportions of patients achieving treatment success, by baseline antipsychotic treatment, were 65% for olanzapine, 51% for risperidone and 56% for oral typicals. Three percent of olanzapine-treated patients had EPS and the mean weight gain over 24 months was 4.3 (sd 6.5) kg. For risperidone, the figures were 18.5% and 3.6 (sd 5.2) kg. CONCLUSIONS: Substantial treatment success was seen from baseline to 24 months among never-treated patients who received either olanzapine, risperidone or oral typical antipsychotics at baseline. Some differences in effectiveness and tolerability were present among the different medications. The results should be interpreted conservatively due to absence of randomization of the treatments and the open label assessment of patients.

THE EFFICACY OF QUETIAPINE IN THE TREATMENT OF DELUSIONAL DISORDER

M. G. Opler,* L. A. Opler, J. A. Mullen
Epidemiology, Columbia University, New York, NY, USA

To determine the efficacy of quetiapine in the treatment of delusional disorder, a separate analysis was conducted on a subset of patients who participated in the Quetiapine Experience With Safety and Tolerability (QUEST) study, a randomized, 4-month, open-label comparison of quetiapine and risperidone in 728 outpatients with a variety of psychotic conditions, including delusional disorder. Patients who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria for delusional disorder were identified from the QUEST study population. The primary rating instrument was the Positive and Negative Syndrome Scale (PANSS). Efficacy was assessed as changes from baseline on the PANSS total score and PANSS subscores for the positive scale, the negative scale, and the delusions item. The statistical significance of treatment-related changes in these scores was analyzed using a 2-tailed *t*-test. Twelve patients with delusional disorder were identified, 10 of whom were treated with quetiapine: 8 men and 2 women (mean age, 46.3 y; mean duration of treatment, 94.7 d; mean dosage, 254 mg/d). Because only 2 patients with delusional disorder received risperidone, no statistical analysis was possible and no results for risperidone were reported. Two of the 10 quetiapine-treated patients were excluded from the analysis because they did not meet illness severity or dosing criteria. The remaining 8 patients showed statistically significant decreases from baseline on the PANSS total score (—19.5, *P*=0.007), and on the subscores for the positive scale (—4.13, P=0.002) and the delusions item (—1.38, *P*=0.028). The mean score on the PANSS negative scale also declined, but the change failed to achieve statistical significance (—3.25, *P*=0.087). This analysis of a subgroup of patients from the QUEST study showed that quetiapine treatment was responsible for significant improvements in symptom severity in 8 patients with delusional disorder. Further studies involving larger numbers of patients treated under blinded conditions are needed to confirm the efficacy of quetiapine in the treatment of delusional disorder.

EFFICACY AND SAFETY OF INTRAMUSCULAR ARIPIPRAZOLE, HALOPERIDOL OR PLACEBO IN ACUTELY AGITATED PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER

D. Oren,* R. Marcus, D. Kostic, R. McQuade, T. Iwamoto, D. Archibald
Bristol-Myers Squibb, Wallingford, CT, USA

This study was to compare the efficacy and safety of intramuscular (IM) aripiprazole to placebo and to establish its non-inferiority to haloperidol IM for the treatment of acutely agitated patients with schizophrenia and schizoaffective disorders. In total, 448 patients ≥18 years of age presenting with acute agitation were randomized to aripiprazole IM (10 mg; n=175), haloperidol IM (6.5 mg; 185) or placebo (n=88) in this 24-hour, multicenter, double-blind study. A second dose of study treatment was permitted ≥2 hours after the initial dose, and a third dose ≥2 hours later. Rescue medication with lorazepam was permitted 60 min after the second dose of study medication. For patients randomized to placebo the third dose contained 10 mg aripiprazole. A repeat dose could be given no later than 20 hours after the first dose. If the 24-hour IM phase was completed, patients entered a 4-day, oral phase (aripiprazole 15 mg, haloperidol 10 mg). PANSS-Excited Components (PEC) and Clinical Global Impression-Improvement (CGI-I) were evaluated at baseline, 30, 45, 60, 90 and 120 min, then 4, 6, 12 and 24 hours after dosing. A rapid reduction of PEC was observed with aripiprazole (10 mg IM) and haloperidol (6.5 mg IM) compared with placebo, and was maintained for the duration of the study. Mean change from baseline PEC at 120 min: aripiprazole IM –7.27, haloperidol IM –7.75, placebo –4.78 (aripiprazole vs placebo & haloperidol vs placebo; p<0.001). In addition, aripiprazole IM and haloperidol IM produced significant improvement in CGI-I scores compared with placebo. Mean change from baseline at 120 min: aripiprazole IM 2.42, haloperidol IM 2.37, placebo 3.10 (aripiprazole vs placebo & haloperidol vs placebo; p<0.001). Incidence of EPS-related adverse events was: aripiprazole 3 (1.7%), haloperidol 23 (12.6%), placebo 2 (2.3%). One patient in the aripiprazole group and 2 patients in the haloperidol treatment group discontinued due to adverse events (AEs) during the 24-hour IM treatment period. Aripiprazole 10 mg IM is an effective treatment for the rapid reduction of acute agitation in patients with schizophrenia and schizoaffective disorders, is not inferior to treatment with haloperidol IM 6.5 mg and shows an incidence of EPS-related adverse events similar to placebo and substantially lower than for haloperidol IM.

PSYCHOMETRIC CHARACTERISTICS OF THE DRUG ATTITUDE INVENTORY

L. Oyewumi,* P. R. Davidson
Psychiatry, Queen, Kingston, ON, Canada

The ten-item version of the Drug Attitude Inventory (DAI-10, Hogan, Awad & Eastwood, 1983) measures attitudes that are predictive of drug compliance in patients with schizophrenia and is widely used in research on schizophrenia (e.g. Hofer et al., 2002). However, little work has been done on the psychometric properties of this short version. The original study examined the reliability of the original thirty item instrument and as a result of the statistical analysis proposed a shortened ten item version that better discriminated between compliers and non-compliers in that sample. Reliability data on the ten item version were not reported. The present study examines the reliability and factor structure of the DAI-10 in a sample of 65 individuals referred for assessment in a first episode psychosis program. Internal consistency of the scale was found to be unacceptably low (alpha = .48). Exploratory factor analysis produced a two-factor solution (Positive Attitudes Factor and Negative Attitudes Factor). Scoring the DAI-10 separating the items on the two factors improved reliability (alphas = .80 and .51 respectively). Normative data are presented and the implications of these reliability estimates for the use of the DAI-10 are discussed. The DAI-10 is a useful instrument in this population and its utility can be enhanced by improving the reliability of the scoring of the instrument. References Hofer, A., Kemmler, G., Eder, U., Honeder, M., Hummer, M., Fleischhacker, W. (2002). Attitudes toward antipsychotics among outpatient clinic attendees with schizophrenia. *Journal of Clinical Psychiatry*, 63, 49-53. Hogan, T.P, Awad, A.G., and Eastwood, R. (1983). A self-report scale predictive of drug compliance in schizophrenics: Reliability and discriminative validity. *Psychological Medicine*, 13, 177-183.

COGNITIVE IMPROVEMENTS IN PATIENTS WITH SCHIZOPHRENIA WITH RISPERIDONE LONG-ACTING INJECTABLE: RELATIONSHIP TO FUNCTIONING?

G. Pandina,* R. Bilder, P. Harvey, R. A. Lasser, S. Rodriguez, I. Turkoz, G. Gharabawi
Janssen Medical Affairs, LLC, Titusville, NJ, USA

Background: Patients with schizophrenia treated with atypical antipsychotics, including risperidone, show improvements in cognition, both when switched from typical agents and treated de novo. Improved functioning has also been observed with atypical agents, however, long-term studies suggest that cognition and functioning may not be related (Addington et al, 2000). Questions remain regarding the relationship between cognition and functioning: 1) is there a minimal level of cognitive change needed to positively impact functioning? 2) is there a need to maintain cognitive improvements over time prior to improvement in functioning, or; 3) are cognition and functioning independent of one another? This preliminary report examines interim results of cognitive and functioning measures from a 12-month study of risperidone long-acting injectable in patients with schizophrenia. Method: Clinically stable adults (N=323) with schizophrenia were randomized to one of two dose levels of long-acting risperidone. A computer-administered cognitive assessment battery (CogTest, LLC) was performed at baseline, 3, 6, and 12 months (measures of attention, motor function, verbal & visual learning/memory, working memory, executive functioning), along with standard clinical assessments and measures of functioning (Strauss-Carpenter Level of Functioning scale (LOF), Personal and Social Performance scale, Schizophrenia Quality of Life Scale). Interim blinded 6-month data on cognitive and functional measures were analyzed (up to n=278 patients). Results: Change at month 6 was assessed for all cognitive measures. Significant improvements were noted in 4 of 7 domains, for example, attention (flanker correct incongruent mean change=2.9; P=0.0010) and verbal learning (word list memory — total learning mean change=3.1, P=0.0003). An exploratory factor analysis combined cognitive data and functioning measures. Significant post-hoc correlations were observed for several factors. For example, total errors on the Cogtest Strategic Target Detection Task, a putative test of executive function, correlated at –0.36 (P<0.001) with the LOF symptomatology subscale. Discussion: Improvements in cognitive functioning were observed in stable patients switched to long-acting risperidone. Modest correlations were observed between cognition and functioning on preliminary analyses at month 6. Further assessment of the relationship between cognition and functioning will be explored using final 12-month data.

A NATURALISTIC COMPARISON OF ATYPICAL (OLANZAPINE, RISPERIDONE) AND CONVENTIONAL (HALOPERIDOL) IN THE ACUTE TREATMENT OF PATIENTS WITH FIRST EPISODE OF PSYCHOSIS

R. Perez,* B. Crespo-Facorro, I. Martinez-Gonzalez, J. M. Pelayo-Teran, C. Gonzalez-Blanch, M. L. Ramirez-Bonilla, J. L. Vazquez-Barquero
HUMV, Santander, Cantabria, Spain

The objective was to compare the efficacy and safety of two atypical neuroleptics (olanzapine and risperidone) and a typical neuroleptic drug (haloperidol) in the acute treatment of drug-naive patients with first-episode psychosis. Subjects with first episode of psychosis were incluided in the study. Inclusion criteria incluided a DSM IV diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder and age range 15-50 years. Exclusion criteria incluided a neuroleptic treatment superior to 12 weeks, DSM IV diagnosis of substance abuse, mental retardation or organic brain disease. Patients were randomly assigned to the three groups of treatment. A naturalistic design was chosen and a flexible-dose was administered to each patient (maximun doses: 20mg olanzapine, 6mg risperidone and 7mg haloperidol). Efficacy measures incluided were BPRS, SANS, SAPS and Clinical Global Impression. Advers effects were assessed by UKU scale, Barnes acathisia scale, Simpson-Angus. All these measures were recorded at baseline, 1, 2, 3, 4 and 6 weeks. Patients who not completed 6 weeks we used last-observation-carried-forward. Between-group comparisons of continous variables were analyzed with analysis of variance (ANOVA). Differences in categoric measures were examined by using chi-square test. From Abril-01 to August-04, 140 patients were incluided in the study 65,7% male and 34,3% female. The mean age was 26,4 years (SD = 6,7). Sixty-two percent of the patient were hospitalized. No statistically significant differences in baseline severity were observed between treatment groups (Table I).Three antipsychotic treatment produced significant symptom reductions as reflected by baseline-to-endpoint total change scores. No differences in efficacy were found between treatment groups. Haloperidol-treated first-episode patients experienced statistically significant more extrapyramidal side effects than atypical antipsychotics treatment groups (Simpson 6w: p=0,003; Barnes 6w: p=0,010). We found that the three treatments

were equaly efficacious in patients with first episode psychosis. Atypical neuroleptic drugs were better tolerated than haloperidol. The main advantage for aypical drugs was lower frecuency of EPS and a decreased use of anticholinergic drugs.

A DOUBLE-BLIND PLACEBO CONTROLLED TRIAL OF MODAFINIL FOR NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

J. Pierre,* J. H. Peloian, D. A. Wirshing, W. C. Wirshing, S. R. Marder
Department of Psychiatry & Biobehavioral Sciences, Geffen School of Medicine at UCLA, Los Angeles, CA, USA

Negative symptoms are core features of schizophrenia that are functionally debilitating, associated with poor outcomes, and resistant to existing pharmacotherapies. This study investigates whether modafinil, a medication approved for the treatment of excessive daytime sleepiness, is effective for the adjunctive treatment of negative symptoms in schizophrenia. Twenty subjects with chronic schizophrenia were randomized to double-blind treatment with modafinil or placebo for 8 weeks, with the option to participate in an additional 8 weeks of open-label treatment. The results of open-label treatment indicate that modafinil was associated with improvements in SANS (mean change score -3.2) and CGI (mean change score -0.5) scores, with minimal change in BPRS scores (mean change score 0.7). Adverse events were infrequent, but included worsening of psychosis (n=1) and insomnia. Modafinil appears to be a promising adjunctive treatment for negative symptoms in schizophrenia. At present, the final patient has not yet completed the study, such that the blind has not yet been broken. However, the double-blind data will be presented at the ICOSR meeting. This research was supported by grants from the Stanley Medical Research Institute, a West Coast College of Biological Society/Janssen Research Foundation Junior Faculty Research Award, and Cephalon, Inc.

A PLACEBO-CONTROLLED STUDY OF RISPERIDONE VS QUETIAPINE FOR SYMPTOM RESPONSE AND READINESS FOR DISCHARGE AMONG AGITATED INPATIENTS WITH SCHIZOPHRENIA

S. G. Potkin,* A. Greenspan, C. Kosik-Gonzalez, C. Bossie, M. Rupnow, Y. Zhu, G. Gharabawi
Psychiatry and Human Behavior, College of Medicine, University of California, Irvine, Irvine, CA, USA

Purpose: A 2-phase 6-week double-blind study assessed the efficacy/effectiveness of risperidone and quetiapine for symptom response and readiness for hospital discharge in acutely agitated inpatients with schizophrenia. Methods: In a 2-week monotherapy phase, patients (18-65 years old) received risperidone (N=153), quetiapine (N=156), or placebo (N=73). In the subsequent 4-week additive-therapy phase, investigators were permitted to prescribe additional psychiatric medications as necessary. Assessments included the PANSS, CGI, medication satisfaction, and a 6-item questionnaire that assessed readiness for discharge from the inpatient setting. Between-group differences for continuous variables were tested by ANCOVA. Results: The 6-week study was completed by 82% of risperidone patients, 74% of quetiapine patients, and 62% of placebo patients. At monotherapy endpoint (LOCF), improvements in mean (±SE) PANSS total scores were significantly greater in patients receiving risperidone (−27.7±1.5) than quetiapine (−20.5±1.5; P<0.001) or placebo (−20.2±2.0; p<0.001). Similar results were observed for the PANSS cluster scores for positive symptoms, disorganized thought, and excitement/hostility. Kaplan-Meier estimates showed a significantly higher probability of readiness for discharge with risperidone (0.63) versus quetiapine (0.45; p=0.011) or placebo (0.42; p=0.024). Differences between quetiapine and placebo were not significant. Mean doses at monotherapy endpoint were 4.3±1.1 mg/day of risperidone and 523.8±168.2 mg/day of quetiapine. During the additive-therapy phase, an additional antipsychotic was received by 33% of risperidone patients and 53% of quetiapine patients; 57% of placebo patients received an antipsychotic (P<0.001; Cochran Mantel Haenzel). Reductions in PANSS total scores at week-6 endpoint (LOCF) were −34.5±1.6 with risperidone, −30.9±1.6 with quetiapine, and −27.9±2.2 with placebo. The only significant between-group difference was between the risperidone and placebo groups (p=0.007). The most common adverse events (≥ 10% in any one group) were headache, sedation, somnolence, dizziness, insomnia, and constipation. Conclusion: Risperidone was associated with greater symptom reduction and readiness for hospital discharge, and less antipsychotic polypharmacy than quetiapine. Funded by Janssen Medical Affairs, L.L.C.

RISPERIDONE VS QUETIAPINE VS FLUPHENAZINE IN TREATMENT-RESISTANT SCHIZOPHRENIA: NEUROPSYCHOLOGICAL OUTCOME

C. M. Richardson,* D. L. Kelly, J. M. Gold, R. McMahon, Y. Yu, R. R. Conley
Maryland Psychiatric Research Center, Catonsville, MD, USA

Schizophrenic patients with treatment-resistant psychosis have also been found to have more severe cognitive deficits than treatment-responsive patients. Atypical antipsychotics may have cognitive advantages over typical agents, but very few studies have examined the impact of atypical versus typical antipsychotics on cognitive functioning in treatment-resistant cohorts. Treatment-resistant schizophrenic patients were treated for 12 weeks in a randomized, double-blind fashion, with risperidone 3 to 5 mg/day, quetiapine 300 to 500 mg/day, or fluphenazine 10 to 15 mg/day, following a six week trial with typical antipsychotics or olanzapine. A neuropsychological battery consisting of nine tests was completed prior to randomization and at study completion. Twenty-five patients completed baseline and endpoint neuropsychological assessments: 11 received risperidone, 6 received quetiapine, and 8 received fluphenazine. There were no differences between the groups in subject age, gender, or race, or the duration of time on the assigned treatment. There were no significant differences between the groups on global change or change in any of six neuropsychological domains. Global scores were essentially unchanged for all groups (z score change = 0.08, 0.11, and 0.15 for risperidone, quetiapine, and fluphenazine, respectively). The

cohort as a whole showed trend improvements on the attention and verbal speed domains, but none of the groups showed significant improvements on any domain. Motor tasks improved most in the quetiapine group. Working memory performance improved most in the fluphenzine group. All groups worsened on memory, with the quetiapine group demonstrating the greatest decrease. Contrary to several published studies, we saw no significant differences in neuropsychological outcome after treatment with atypical vs typical antipsychotics, although the small sample size limits our conclusions. Our modest fluphenazine dose and the absence of routine anticholinergics may have reduced differences seen elsewhere. The modest changes seen with the atypicals is more unusual and may be explained by the greater severity of illness in this cohort, the more optimal and prolonged treatment prior to randomization, and the use of potentially subtherapeutic doses of the atypicals.

COMPARISON OF OLANZAPINE AND RISPERIDONE TREATMENT FOR FIRST EPISODE SCHIZOPHRENIA: FOUR MONTH OUTCOMES

D. G. Robinson,* M. G. Woerner, R. C. Patel, S. M. Sevy, H. Gunduz-Bruce, B. Napolitano, M. Lesser, R. Miller, J. McCormack, B. Lorell, N. Schooler, J. M. Kane
Research, The Zucker Hillside Hospital, Glen Oaks, NY, USA

The study compares the effectiveness of randomly-assigned open-label flexible dosing treatment with olanzapine (2.5 to 20 mg per day) or risperidone (1 to 6 mg) for subjects aged 16 to 40 with a first episode of schizophrenia, schizoaffective disorder, or schizophreniform disorder. Masked assessors conduct all assessments. The study sample consists of 112 subjects. Seventy percent were men. The ethnic background of the subjects was: 54% African-American, 20% Caucasian, 13% Hispanic, 6% Asian and 7%mixed. Overall, subjects were young (mean age 23) and were from lower middle class backgrounds. Most were unemployed at study entry. Subjects had been ill for an extended period before study entry; a mean (SD) of 250 (268) weeks since the onset of any psychiatric symptom and 115 (165) weeks since the onset of psychotic symptoms. Response criteria are: a rating of 3 (mild) or less on the following SADS-C+PD items: severity of delusions; severity of hallucinations; impaired understandability; derailment; illogical thinking; bizarre behavior, and a rating of very much improved or much improved on the CGI improvement item. The acute treatment phase of the trial lasts 16 weeks. Response rates and other outcomes for the acute treatment trial will be presented at the meeting.

ARIPIPRAZOLE VERSUS PERPHENAZINE IN TREATMENT-RESISTANT SCHIZOPHRENIA

R. Sanchez,* H. Y. Meltzer, R. N. Marcus, J. Stringfellow, W. H. Carson, J. M. Kane
Bristol-Myers Squibb, Wallingford, CT, USA

In this multicenter study the efficacy and safety of aripiprazole was assessed compared to perphenazine in patients with treatment-resistant schizophrenia. Patients first entered an initial phase where they underwent 4 to 6 weeks of open-label treatment with either olanzapine or risperidone to confirm resistance to treatment with atypical antipsychotics. Patients shown to be treatment-resistant then entered a 2- to 10-day, single-blind, placebo washout phase, after which they were randomized to double-blind treatment with aripiprazole (15 or 30 mg/day; n=154) or the typical neuroleptic, perphenazine (8–64 mg/day; n=146). Assessment measures included PANSS and CGI rating scales, safety evaluations, and the quality of life scale (QLS). Patients treated with either aripiprazole or perphenazine following failure to respond to olanzapine or risperidone showed improvements from baseline in PANSS Total scores (aripiprazole, –9.8; perphenazine, –10.5), PANSS Negative and Positive subscale scores, and CGI Improvement scores. Overall, 27% of patients responded to aripiprazole therapy and 25% responded to perphenazine (defined as a CGI-I score of 1 or 2 or ≥30% decrease in PANSS Total score). Fewer patients in the aripiprazole group experienced extrapyramidal symptoms, ECG abnormalities, or elevations in plasma prolactin levels than in the perphenazine group. No clinically significant differences in weight were observed between treatments. At least a quarter of patients with schizophrenia who were resistant to treatment with olanzapine or risperidone showed significant improvement with both aripiprazole and perphenazine.

A DOSE-FINDING STUDY OF PREGNENOLONE IN PATIENTS WITH SCHIZOPHRENIA

A. J. Savitz,* K. E. Carpiniello, S. M. Silverstein
Psychiatry, Weill Medical College of Cornell University, White Plains, NY, USA

The neurosteroid, pregnenolone, is enriched in certain regions of the brain and is an indirect agonist of the NMDA receptor. For this reason, the authors hypothesize that it may improve negative and cognitive symptoms of schizophrenia. Method: The primary aim was to determine if patients could tolerate pregnenolone. Under double-blind conditions, patients were randomly assigned to one of four groups: placebo, low dose (100 mg/d), slow titration to high dose (500 mg/d), and rapid escalation to high dose. Patients are on study medication for 8 weeks after a 2-week, single blind lead in. Inclusion criteria included a diagnosis of schizophrenia or schizoaffective disorder, stable medications for 6 weeks, and no substance abuse for 6 months. Pregnenolone was added to existing medications. Symptoms and side effects were measured every two weeks. Cognitive symptoms were assessed at the beginning and end of the study. Steroid levels and blood tests were collected at the beginning, middle, and end of the study. Results: At present 23 of 32 patients have been enrolled. Pregnenolone has been well tolerated. No patients have dropped out of any of the pregnenolone treatment arms. Side effects have been similar across groups except for 3 of 8 patients in the high dose group having mild difficulty falling asleep. There have been no changes in blood levels of medications (valproic acid and clozapine) and no changes in blood counts or basic chemistries. Though analysis of the symptom measures (PANSS and SANS) and cognitive tests await study completion, patients who have been on the higher dose (500 mg/d) have felt better, with an improved sense of energy. Even when blinded to treatment, high-dose patients have asked to remain on pregnenolone. Conclusions: It is expected that the study will be completed in the next 6 months. If the current results hold true, the primary aim of the study will be accomplished in that pregnenolone, even at high dose, is well tolerated in patients with schizophrenia. As more patients complete the study, we will determine if patients on high dose pregnenolone have any change in symptoms or cognition. Qualitatively, patients on 500 mg/d of pregnenolone feel better and ask to remain on study medication. At present, we are continuing patients on an open labeled extension trial of 500 mg/d pregnenolone with continued good tolerance. The study was supported by the Stanley Medical Research Foundation and the GCRC of Weill Medical College.

COGNITIVE IMPROVEMENT IN SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER BY AUGMENTATION OF RISPERIDONE WITH GALANTAMINE

M. H. Schubert,* K. A. Young, S. B. Justice, S. K. Durgam, W. M. Schmitz, M. D. House, P. B. Hicks
Neuropsychiatry Research Program, Central Texas Veterans Health Care System, Waco, TX, USA

Recent studies have shown that cognition directly correlates with functional outcome in patients with schizophrenia or schizoaffective disorder. Cholinesterase inhibitors have been used to treat cognitive deficits in dementia. In this study we add galantamine (24 mg daily), a cholinesterase inhibitor that also has action as an allosteric nicotinic agonist, to risperidone in an 8-week, randomized, double-blind, placebo-controlled trial in schizophrenic or schizoaffective patients. Sixteen patients enrolled in the study with equal numbers being randomized to placebo or galantamine treatment. Cognitive changes with drug treatment were evaluated using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The total RBANS score served as our primary outcome measure. The RBANS includes subset assessments of the cognitive domains of attention, immediate memory, delayed memory, constructional and visuospatial memory, and language. The primary statistical comparison was the mean change of total RBANS score from baseline to week 8. Robust improvement was observed in the total RBANS score from baseline in the galantamine treatment group compared to the placebo control group (X±SEM; 12.1±4.5 vs. -3.3±4.1, respectively, p=0.02). The improvement was most apparent in two domains: attention (10.9±4.4 vs. -5.8±4.4; p=0.02) and delayed memory (12.5±5.1 vs. 9.8±7.1; p=0.02). No improvements were observed in language or visuospatial/constructional domains. These findings suggest that galantamine can be used to improve cognition in patients with schizophrenia or schizoaffective disorder. Support Contributed By: VA Office of Academic Affiliations Post-Residency Fellowship to Max H. Schubert, M.D.

CLINCAL SYMPTOMS AND THE PREDICTION OF CLOZAPINE RESPONSE

C. Shammi,* C. Chung, G. Remington
University of Toronto, Toronto, ON, Canada

It would be helpful to clinicians and patients alike if we could predict clozapine response. Clozapine remains the treatment of choice in refractory schizophrenia, but it is also associated with significant side effects and the need for regular and ongoing hematological monitoring. Being able to predict who might respond to clozapine would strengthen the argument for such a trial despite these concerns. Conversely, knowing that it is unlikely to be effective could prove useful to clinicians in their decision-making regarding the use of other options before moving to clozapine as a last resort, or in a decision to discontinue a trial of clozapine and move to another treatment option. The present study set out to establish if there were early clinical predictors (baseline, week 4) that might be used to predict clozapine response at endpoint (week 12). Sixty-seven patients who were admitted into the Clozapine Program from 1998 to 2004 were examined retrospectively. The program involves a systematic approach to these individuals, involving a 12-week clozapine trial. This includes a standardized titration schedule, as well as a battery of clinical evaluations completed at baseline, week 4, and week 12. No significant differences in baseline Brief Psychiatric Rating Scale (BPRS) total and subscale scores were noted between the responder and nonresponder groups. At week 4, the responder group was found to have significantly greater reductions in BPRS total score and the thought disorder subscale score. Summarizing, we were unable to identify baseline differences in clinical symptoms that might be used to distinguish responders and nonresponders. At one month, the overall prediction rate of response at 12 weeks was 75%. Results indicate that notable clinical improvement can occur in the first month of treatment, and that changes during this interval may prove useful in predicting response at 12 weeks.

EFFICACY AND SAFETY OF ZIPRASIDONE IN FIRST EPISODE PSYCHOSIS

T. Sharma,* V. Kumari, R. Mehrotra, A. Kumar
Psychiatry, Clinical Neuroscience Research Centre, Dartford, Kent, United Kingdom

There is very little data on the efficacy and safety of Ziprasidone in patients with a first episode of psychosis who meet the criteria for schizophrenia or a related psychotic disorder. This study evaluated the effectiveness in acute first episode psychotic patients who were largely neuroleptic naive. Ten patients with first-episode psychosis participated in this 6-week study. Domains measured included psychopathology, neurocognitive functioning, and changes in blood flow using functional magnetic resonance imaging. This report presents data from clinical measures of treatment response, and safety data from the 6 week study evaluating the clinical efficacy. Patients were assessed weekly using clinical scales to assess efficacy and safety in this open label dose finding study. Ziprasidone was associated with substantial baseline to endpoint reductions in symptom severity, as measured by the Positive and Negative Syndrome Scale total score and positive subscale, and by the Clinical Global Impression severity rating. Neuroleptic naive first episode psychotic patients tolerated doses of Ziprasidone up to 80mg daily without any treatment-emergent parkinsonism or akathisia. There were no treatment emergent cardiac abnormalities seen in this patient group. As expected on the basis of previous studies in chronic patients, Ziprasidone was effective in the acute reduction of psychopathological symptoms in this group of patients with first-episode psychosis. Doses above 80mg daily might be tolerated less well by neuroleptic naive first episode psychotic patients.

THE BEHAVIOURAL PROFILE OF ARIPIPRAZOLE IN MODELS OF PSYCHOSIS AND ANXIETY

W. Spooren,* M. Maco, S. Durkin, C. Freichel
PRBD-N, F. Hoffmann-La Roche, Basel, Switzerland

Aripiprazole is a novel antipsychotic with a unique mechanism of action as a partial agonist at the dopamine D2 receptor. In addition, it is a partial 5HT1a receptor agonist and a 5HT2a receptor antagonist. Aripiprazole is claimed to have a broad clinical profile with efficacy on both positive and negative symptoms as well as mood. Despite clinical efficacy, little is known about its pre-clinical profile in animal models. Therefore, we decided to evaluate Aripiprazole in drug-induced (amphetamine and PCP) rodent models of psychosis, i.e. locomotor activity in rats and mice, PPI disruption (rats) and mood (stress-induced hyperthermia, mice). The data indicate that in both rats and mice Aripiprazole (3-30 mg/kg) had no effect on spontaneous locomotor activity but significantly inhibited amphetamine-induced locomotor activity. Aripiprazole also significantly inhibited amphetamine-induced PPI disruption in rats, but was ineffective on PCP-induced PPI disruption. In mood, Aripiprazole was found to

have an anxiolytic-like effect in the stress-induced hyperthermia test in mice. Together, these data indicate that Aripiprazole exhibits antipsychotic-like activity in dopamine based models of psychosis and anxiolytic-like effects in a model of autonomic hyperactivity in anxiety.

OVERALL TREATMENT EFFECTIVENESS AS MEASURED BY TIME CONTINUING ON ANTIPSYCHOTIC THERAPY

V. L. Stauffer,* C. Beasley, H. Liu-Seifert, C. Mitchell, S. Rock, J. Davis, E. Dunayevich
Eli Lilly and Company, Indianapolis, IN, USA

Background: Antipsychotic discontinuation is associated with diminished treatment effectiveness and increased risk of relapse in schizophrenia, and may occur due to patient or physician decisions encompassing lack of efficacy, adverse events, and other factors. All-cause treatment discontinuation captures all of these reasons and has been identified as an important long-term clinical endpoint. Methods: In post-hoc meta-analyses, we examined continuation on antipsychotic therapy in double-blind, randomized clinical trials of olanzapine versus other antipsychotics. Studies were included if they met the following criteria: duration of >12 weeks; double-blind randomized treatment assignment; >20 patients per treatment arm; no protocol-specified definition for mandatory discontinuation prior to 12 weeks; and >2 studies for each antipsychotic comparator. Thirteen studies were identified that met these criteria [olanzapine (n=421) vs. risperidone (n=426): 5; olanzapine (n=550) vs. ziprasidone (n=525): 2; olanzapine (n=537) vs. haloperidol (n=439): 5; olanzapine (n=201) vs. clozapine (n=202): 3]. Patients' diagnoses included (DSM-IV-TR) schizophrenia, schizophreniform disorder, and schizoaffective disorder. Weighted mean hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated based on continuation time; in addition, reasons for discontinuation were analyzed. Four antipsychotics failed to meet the criteria of >2 published studies per comparator: quetiapine, amisulpride, fluphenazine and perphenazine. However, comparable analyses for these studies are included. Results: The HRs for continuation on olanzapine relative to the comparators were: for haloperidol, 1.4 (1.2, 1.7; $p < 0.0001$); for clozapine, 1.2 (0.9, 1.6; $p = 0.312$); for risperidone=1.3 (1.1, 1.6; $p = 0.0047$); and for ziprasidone=1.6 (1.4, 2.0; $p < 0.0001$). Heterogeneity tests for all treatment comparisons were not significant indicating no significant interaction between treatment effect (as measured by HRs) and the respective study. Approximately 54% of olanzapine-treated patients continued through the end of the studies, compared with 46% of risperidone-, 45% of ziprasidone-, 35% of haloperidol-, and 55% of clozapine-treated patients. Conclusions: Olanzapine appears to be associated with significantly longer continuation of treatment relative to haloperidol, risperidone and ziprasidone, but not clozapine.

DIMENSIONS OF POOR INSIGHT AND RISPERIDONE NONADHERENCE IN THE EARLY COURSE OF SCHIZOPHRENIA

K. L. Subotnik,* K. H. Nuechterlein, J. Ventura, M. J. Gitlin, M. J. Aravagiri, S. R. Marder, B. Siegel, M. J. Love, V. Irzhevsky, L. A. Thornton, D. Gretchen-Doorly
Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, University of California, Los Angeles, Los Angeles, CA, USA

Nonadherence to antipsychotic medication treatment remains a major clinical problem despite the development of second-generation antipsychotic medications that have fewer bothersome side effects than earlier antipsychotics. Clearly, this nonadherence to second generation antipsychotics cannot be solely attributed to dislike of medication side effects. Using proportional hazards regression, we examined the role of poor insight in predicting medication nonadherence among recent-onset schizophrenia patients during one year of outpatient treatment with risperidone. The main focus of this longitudinal study (Developmental Processes in Schizophrenic Disorders; PI: Keith Nuechterlein, Ph.D.) was to predict and improve return to work or school for patients recently diagnosed with schizophrenia. Participants received risperidone, group skills training, psychoeducation, and individual case management. Three dimensions of insight (i.e., overall awareness of having a mental disorder, awareness of the beneficial effect of antipsychotic medication, and correctly attributing unusual beliefs to a mental disorder) were measured with the Scale to Assess Unawareness of Mental Disorder. The degree of antipsychotic medication nonadherence was assessed weekly for up to 12 months following initial stabilization on risperidone, using all available sources of information, including pill counts, monthly risperidone blood plasma assays, patient self-reports, and clinician reports. Risperidone nonadherence was defined as missing 25% or more of prescribed medication for at least two consecutive weeks during the 12-month follow-through period or leaving treatment (58% of participants). A proportional hazards regression model using all three dimensions of poor insight predicted medication nonadherence during the 12-month follow-through period (X^2 (df = 3, N = 43) = 7.8, $p = .05$). However, only the dimension assessing the correctness of the attributions about unusual beliefs (i.e., relabeling) contributed significantly to predicting medication nonadherence ($\beta = .74$, df = 1, $p = .007$, Hazard Ratio = 2.1). Our findings support the conceptualization of poor insight as multidimensional. Interestingly, awareness of the beneficial effects of risperidone did not itself predict later adherence. However, this awareness was assessed early in treatment and might become a more meaningful dimension as treatment progresses.

USE OF QUETIAPINE IN TREATING NONPSYCHOTIC ANXIETY AND DEPRESSIVE DISORDER

S. Targum,* H. Hassman, B. Bastani, M. Bari
PharmaStar, Wayne, PA, USA

This open-label study evaluated the anxiolytic, antidepressive, and sleep effects and safety of quetiapine in patients with major depressive disorder (MDD) on stable doses of selective serotonin reuptake inhibitors (SSRIs) who presented with persistent anxiety. Three sites participated in a 4-week open-label trial of quetiapine added to existing SSRIs. Eligible, consenting subjects (ages 18–60) met DSM-IV criteria for MDD, were taking stable doses of an SSRI (or venlafaxine) for at least 6 weeks prior to baseline, had a Hamilton Anxiety scale (HAM-A) score ≥20 and a Hamilton Depression scale (HAM-D) score ≤17 at screening and baseline. Ratings included the HAM-A, HAM-D, Zung Anxiety scale, Clinical Global Impression-Severity of Illness scale (CGI-SI), CGI-Improvement scale, Pittsburgh Sleep Quality Index (PSQI), Barnes Akathisia Rating Scale (BAS), and Simpson-Angus Scale (SAS). Quetiapine was initiated at 25 mg on day 1, increased to 25 mg twice daily on day 2, and increased afterward based upon clinical response. The antidepressant dose remained unchanged. Twenty-two subjects met inclusion/exclusion criteria and were started on study medication. Antidepressants included sertraline (4), fluoxetine (3), citalopram (7), paroxetine (3), and venlafaxine (5). Seventeen subjects (77%) completed the study.

Stable quetiapine doses (mean 105.9±65.6 mg/d; range, 25–300 mg/d) were achieved between weeks 1 and 2. The mean HAM-A score improved significantly, from 25.6±5.5 at baseline to 9.2±5.5 at endpoint (P<0.001). Similarly, there were significant improvements on the Zung Scale (P<0.001), CGI-SI (P<0.001), and PSQI (P<0.001). The HAM-D improved from 15.0±1.8 at baseline to 7.2±5.0 at endpoint (P<0.001), with changes noted primarily in the anxiety, somatic, and sleep items. Nine subjects described sedative-like effects that were mostly transient within the first week of treatment. Five subjects withdrew from the study within the first week. However, 13 of the remaining 17 subjects (76%) had HAM-A scores drop >50% from baseline. No extrapyramidal symptoms were noted on either the BAS or SAS. Supplemental quetiapine significantly reduced persistent anxiety, reduced depressive symptoms, and improved sleep in treated depressed patients who had been taking stable doses of SSRIs or venlafaxine. These results need to be interpreted with caution given the open-label nature of the study and lack of a control group.

THE OPUS TRIAL: GENDER DIFFERENCES IN A SAMPLE OF 547 FIRST-EPISODE PSYCHOTIC PATIENTS

A. Thorup,* L. Petersen, P. Jeppesen, T. Christensen, M. Nordentoft
Psyhiatric, Bispebjerg, Frederiksberg, Denmark

Objective: Gender differences in first episode psychotic patients reveal important information about the caracteristics and needs for these patients. Methods: We randomised 547 first-episode psychosis patients to integrated treatment or standard treatment. Patients were assessed after one and two years by independent investigators. Data concerninig gender differences and psychopathology, misuse, social network and functioning and self-esteem were analysed. Results: Males and females had similar ages of onset and similar duration of untreated psychosis. Significant differences were found in terms of misuse and psychopathology, were males tend to have more severe negative and disorganised symptoms than females. Females had better social networks and social functioning but poorer self-esteem.The development over time showed some of the same trends. Conclusion: When the future treatment for young first-episode is being planned take into account the gender differences that indicate that while males have trouble with negative symptoms and social contact, women suffer from poor self-esteem in spite of better social functioning.

PATIENTS WITH SCHIZOPHRENIA TAKING TYPICAL OR ATYPICAL ANTIPSYCHOTICS: EVALUATING SYMPTOMS WITH BRIEF PSYCHIATRY RATING SCALE

S. Uzun,* O. Kozumplik, N. Mimica, V. Jukic, V. Folnegovic-Smalc
University Department, PH Vrapce, Zagreb, Croatia

Objective: To evaluate changes in symptoms in patients with schizophrenia taking typical and atypical antipsychotics, using Brief Psychiatry Rating Scale (BPRS). Methods: BPRS was used in order to evaluate changes in symptoms in 96 patients with paranoid schizophrenia (49 male, 47 female, mean age/years 37.6) according to DSM-IV-TR criteria. Previous to inclusion in our study, all patients were treated with typical or atypical antipsychotics for a period of at least three months. Out of total number, 43 patients were treated with typical and 53 with atypical antipsychotics. The first assessment (baseline) was made upon the inclusion. The other assessments were made every three months during one year. Results were statistically analysed using methods of descriptive statistics and chi-square test. Statistical significance was set to p<0.05. During investigation there were 9 cases of therapy discontinuation due to side effects (restlessness, tremor) in the group of patients treated with typical antipsychotics, and 6 cases in the group of patients treated with atypical antipsychotics (sedation, hyperprolactinemia, weight gain). The patients who discontinued the therapy were assessed on the last day of therapy, and their results were added to the results of other patients from the group. Results: At baseline, there was no significant difference between two groups of patients on the BPRS items. After six months of continuous treatment, patients treated with atypical antipsychotics scored significantly better in BPRS items regarding emotional withdrawal, depressive mood and uncooperativeness. After one year of continuous treatment, patients treated with atypical antipsychotics scored significantly better in BPRS items regarding emotional withdrawal, depressive mood, uncooperativeness, and blunted affect. Conclusion: Results indicate superiority of atypical over typical antipsychotics in reducing negative and general symptoms of schizophrenia measured by BPRS. References: 1. Overall JE, Gorham DR 1962 The Brief Psychiatric Rating Scale. *Psychol Rep* 10:799-812. 2. Folnegovic-Smalc V, Jukic V, Kozumplik O, Uzun S, Mimica N. Side effect profile of atypical antipsychotic agents and comparison to conventional antipsychotics. *Soc psihijatrija* 2003;31:19-22.

BIOAVAILABILITY OF AN ORAL SOLUTION OF THE ANTIPSYCHOTIC ARIPIPRAZOLE

N. Vachharajani,* T. Vanderslice, G. Kollia, D. Boulton, S. Mallikaarjun, T. Iwamoto, D. Kornhauser
Bristol-Myers Squibb, Lawrenceville, NJ, USA

The objective of this study was to estimate the relative bioavailability of aripiprazole when administered as an oral solution compared to the tablet formulation. Healthy adult subjects received aripiprazole administered in oral solution and tablet formulations as single doses of 5, 10, 15, and 30 mg in two open-label, randomized, crossover studies. Serial blood samples were collected for pharmacokinetic assessments up to 384 hours (17 days) post-dose. The bioavailability of aripiprazole from the oral solution as compared to the tablet was determined and the doses of aripiprazole needed to achieve C_{max} and AUC comparable to those from the same tablet dose were estimated. Safety was also monitored throughout the study. C_{max} and AUC satisfied the criterion for dose proportionality for oral solution doses of 5, 10, and 15 mg. Peak plasma concentrations of aripiprazole from the solution were higher than with the tablets at equivalent doses, and the solution systemic exposures were slightly higher than the tablets. For 30 mg doses, the oral solution to tablet ratio of geometric mean C_{max} values for aripiprazole was 1.22, and that of AUC_{∞} was 1.14. Aripiprazole is well absorbed when administered orally as a solution. The peak and systemic exposures to aripiprazole from oral solution are somewhat greater than those from tablets.

FACIAL AFFECT RECOGNITION IN ADOLESCENTS WITH FIRST-EPISODE SCHIZOPHRENIA—A PILOT STUDY OF A REMEDIATION PROGRAM

S. Werneck-Rohrrer,* J. Edwards, A. Schweitzer, M. Schloegelhofer, G. P. Amminger
Department of Neuropsychiatry of Childhood and Adolescence, Medical University of Vienna, Vienna, Austria

Recognizing facial affects is of great importance for the social functioning of the individual. Patients with schizophrenia have problems in the perception of emotional affects, mainly in the recognition of fear and sadness. It is suggested that this impairment is more severe in patients who also have psychopathic traits (Blair et al., 2003). We used a training program for the remediation of facial-affect recognition (TAR) by Frommann, Streit and Woelwer (2003). The TAR is a 12-session program which uses restitution and compensation strategies and the principles of errorless learning. The TAR shows good feasibility in adults with schizophrenia, and our purpose was to examine its suitability for the use in adolescents with first-episode schizophrenia. Assessments were made at baseline, before treatment, at the end of the treatment, and at a follow-up examination after three months. We used a computerized task for recognition of facial affect (PFA)and the task four of a facial recognition assessment (FACT), which was developed by Edwards et al. (2001), who replicated and extended the tasks of Feinberg et al. (1986). The Training of Affect Recognition (TAR) was carried out in pairs. The intervention follows a detailed treatment manual provided by Frommann and colleagues (2003).The pattern of the results generally suggests an improvement between baseline and end of treatment and stabilization between end of treatment and three months follow-up after the intervention. At baseline the mean-value of right answers(PFA-Test) was 14.75. At the end of treatment it was 21.71, and at the follow up assessment the mean value of right answers was 20.5. The TAR appears suitable for the use with adolescents with first-episode schizophrenia but with minor modifications. The evaluation of the effectiveness of the training requires further investigation. Blair, R. J. R. et al. (2003). Theory of mind and psychopathy: can psychopathic individuals read the language of the eyes? *Neuropsychologia* 41, 523-526; Edwards, J. et al. (2001). Facial affect and affective prosody recognition in first-episode schizophrenia. *Schizophrenia Research* 48, 235-253; Frommann, N. et al. W. (2003). Remediation of facial affect recognition impairments in patients with schizophrenia: a new training program in: *Psychiatry research* 117, 281-284.

LONG-TERM OUTCOMES IN TREATED VERSUS UNTREATED GERIATRIC SCHIZOPHRENIA

L. White,* J. I. Friedman, M. M. Evers, P. D. Harvey, M. J. Parrella, K. L. Davis
Clinical Neuroscience Center, Pilgrim Psychiatric Center, West Brentwood, NY, USA

Purpose: Some groups have reported the longitudinal course of elderly poor outcome schizophrenic patients to be characterized by progressive decline in cognitive functions and functional capacity. Additionally, many of these poor outcome patients remain severely symptomatic despite antipsychotic treatment. Although these patients experience minimal reduction of psychotic symptoms there may be beneficial effects of antipsychotic treatments on cognitive functions and functional capacity. This study compared the longitudinal course of psychotic symptoms, cognitive functions and functional impairment in geriatric schizophrenic patients treated and not treated with antipsychotic medications. Methods: 683 schizophrenic patients over the age of 60 were assessed multiple times over an average six year interval on measures of symptom severity, cognitive abilities and basic self-care functions. Mixed effects linear regression analyses were used to examine the effects of time, treatment vs. no treatment and the interaction of time by treatment group. Results: 168 patients received no antipsychotic treatment and 515 patients received some form of antipsychotic treatment for the entire follow-up period. At baseline Positive and Negative Syndrome Scale (PANSS) positive symptoms were more severe in the patients treated with antipsychotics (mean 18.8 vs. 16.7; t=3.03, p=0.003). Over time the effect of treatment on positive symptoms was non significant (MMLE=0.21, p=0.43). However the group not treated with antipsychotics demonstrated a more rapid deterioration of cognitive functions compared to the treated group as measured by the Alzheimer's Disease Assessment Scale Late- Stage-Cognitive (ADAS-L- COG) (MMLE=0.78, p=0.04). Conclusion: Although antipsychotics failed to have a beneficial effect on psychotic symptoms in these chronic geriatric patients with schizophrenia, antipsychotics appear to exert some protective effect against the deterioration of cognitive abilities.

CHANGES IN PANSS MEASURED INSIGHT DURING THE FIRST YEAR OF TREATMENT FOR SCHIZOPHRENIA

D. Whitehorn,* R. Vogler, K. P. Good, Q. Rui, H. Milliken, L. C. Kopala
Nova Scotia Early Psychosis Program, Capital District Mental Health Program, Dartmouth, NS, Canada

Objective: Insight is rated as one item in the widely used Positive and Negative Syndrome Scale (PANSS). A recent study (Mintz et al, *Schiz Res* 67:213-17:2004) reported that amongst patients treated in an Early Psychosis program (EPP) many who lacked insight at initial assessment appeared to gain insight during the first year of treatment. The current study set out to test and extend these findings using a clinical population from another EPP. Methods: 105 patients (67% male, age 21.9 years +/-5.6) presenting to the Nova Scotia EPP with a schizophrenia spectrum disorder and no previous treatment with antipsychotic medication were rated with the PANSS at initial assessment. After 6 and 12 months of continuous treatment with one of three atypical antipsychotic agents, 53/105 and 45/105 respectively had follow up ratings completed. 35 patients had ratings at initial assessment, 6 and 12 months. A rating of 4 or greater on PANSS item G12 (lack of judgement and insight) was used to indicate a lack of insight. Results: At initial assessment 62% of patients were rated as lacking insight. At 6 and 12 months, 10% and 15% respectively lacked insight. For the 35 patients who had ratings at all three time points, insight was lacking in 57% at baseline, 3% at 6 months and 14% at 12 months. Considering all patients over the 12 month period, 38% maintained insight throughout, 48% gained while 3% lost insight and 11% consistently lacked insight. At all three assessment time points patients lacking insight had significantly higher total PANSS scores. Insight at initial assessment did not predict remission of positive or negative symptoms (no relevant PANSS item rated greater than 3) at either 6 or 12 months. Conclusions: The results confirmed that, for many patients, PANSS rated insight changes over the first year of treatment. While 60% were rated as lacking insight at initial assessment, only 10-15% continued to have this deficit after one year. This suggests that there are two subgroups; those with a

primary lack of insight which persists despite treatment, and those with a secondary lack of insight, possibly related to lack of knowledge or the impact of acute psychosis, who develop, or regain illness awareness with treatment. The therapeutic issues involved with these two groups are clearly different. Caution should be taken, as well, in making associations with the presence or absence of insight based on ratings taken only at initial assessment.

TREATMENT DELAY, SHORT-TERM RESPONSE AND OUTCOME OF TWO MEDICATION TREATMENT STRATEGIES IN A FIRST ONSET SCHIZOPHRENIA STUDY: THE MESIFOS RCT

L. Wunderink,* F. J. Nienhuis, D. Wiersma, T. C. Boonstra
Psychiatry, Groningen University Medical Center, Groningen, Netherlands

Trials on relapse rates after a first psychotic episode support long-term antipsychotic treatment. However, relapse prevention is not the sole contributor to quality of life and social functioning. The Mesifos RCT is designed to compare outcome of targeted versus maintenance treatment on quality of life in stably remitted patients after a first psychotic episode. From October 2001 until January 2003 we included all first psychotic episode patients (n=157) fulfilling the trial criteria in a catchment area of 3.1 million inhabitants. Patients (n=131) who remitted within 6 months after starting antipsychotics and who remained stable for another 6 months were actually assigned to either maintenance or targeted treatment. The first nine months of treatment according to both strategies have been completed. First results will be discussed, while another nine month follow-up is still ongoing. Duration of untreated psychosis (DUP) was significantly related to time to remission (TTR), a finding reported by several but not all studies. But is DUP an independent predictor of outcome? The analysis presented is focused on 1) prediction of time to remission (short-term response) by duration of untreated psychosis (DUP), and conceivable confounders: duration of prodromal symptoms, diagnosis, gender, age of onset, family history, substance abuse, pretreatment functioning and sociodemographic factors; and 2) prediction of outcome in terms of persisting psychopathology, functioning and quality of life after 6 months of stable remission and 9 months of either maintenance or targeted treatment strategy (15 months-outcome) by DUP, covariates and treatment strategy. Its implications will be discussed.

EFFECT OF OMEGA-3 FATTY ACID ON CLINICALLY-STABLE SCHIZOPHRENIC PATIENTS WITH A HIGH RISK FOR CORONARY ARTERY DISEASE

J. K. Yao,* S. Magan, J. Gurklis, A. Sonel, R. Reddy
Medical Research Service, VA Pittsburgh Healthcare System, Pittsburgh, PA, USA

There is excess and premature mortality in schizophrenia, from both natural and unnatural causes, when compared to the general population. Of the deaths from natural causes, those due to coronary artery disease (CAD) are particularly common, likely due to a higher incidence of risk factors associated with CAD. Many CAD risk factors are modifiable. Studies suggest that the omega-3 fatty acid may be beneficial in reducing CAD risk as well as symptom severity in schizophrenic patients. In this study, we tested whether eicosapentaenoic acid (EPA) supplementation can regulate plasma cholesterol pathways and thereby, lead to reductions in key risk factors of CAD and concurrently improve the psychiatric status. Sixteen patients with neuroleptic-treated schizophrenia at high risk for CAD were treated with EPA (2 g of ethyl-EPA in 4 x 500 mg capsules) daily for 6 months using an open-label design. Lipid profile and clinical assessments were monitored at baseline, 1-, 3- and 6-month. The EPA levels were elevated more than 5-fold in RBC membranes of all patients after supplementation, indicating a high degree of compliance. The increases of RBC-EPA were closely correlated to increased levels of a metabolite of EPA, docosapentadienoic acid (DPA). Moreover, a 12-60% increase in HDL-cholesterol was observed in 9 of 16 patients. Concomitantly, there were significantly reduced levels of plasma triglycerides. With regard to psychiatric status, there were reductions (16-46%) in PANSS negative symptoms subscale scores in 8 of 16 patients. No significant worsening was seen in the remaining patients. Previously, we have demonstrated that EPA treatment may be beneficial for reducing the severity of psychopathology in patients by increasing the physiologic response mediated through the platelet 5-HT receptor complex. The present data further support that EPA supplementation may reduce CAD risk by increasing HDL-cholesterol and decreasing plasma triglyceride levels. Future randomized controlled trials are needed to confirm the beneficial effects of EPA supplementation observed in this study.

SUBJECTIVE RESPONSE TO ATYPICAL AND TYPICAL ANTIPSYCHOTICS IN SCHIZOPHRENIC OUTPATIENTS

B. Yoon,* H. Jung, J. Kim, Y. Sea
Naju National Hospital, Naju City, Jeonnam, South Korea

Objective: Drug Attitude Inventory (DAI) was used to compare the subjective response and attitude to antipsychotics among schizophrenic outpatients receiving atypical and typical antipsychotic medications. Methods: One hundred ten patients meeting selection criteria and receiving risperidone (N=30), olanzapine (N=30), clozapine (N=20) and haloperidol (N=30) for a period of 6 months or longer were included. They were all stabilized outpatient clinic attendees. Subjective response and attitude toward neuroleptics was evaluated using 10-items of Drug Attitude Inventory (DAI-10). Demographic and clinical data were also compared between the four medication groups using various rating rating scales: the Positive and Negative Syndrome Scale (PANSS), Extrapyramidal Symptom Rating Scale (ESRS), Korean modified version of Subjective Wellbeing under Neuroleptic treatment (KmSWN), Global Assessment of Functioning scale (GAF). Results: Patients receiving olanzapine were younger and had shorter duration of current medication than those of haloperidol. Although there were no differences on the medication compliance, GAF and KmSWN, patients receiving olanzapine showed less severe psychopathlogy on the positive, general psychopathology, and total scores of PANSS and better score on dyskinesia subscale of ESRS than those of haloperidol and clozapine. Only the patients receiving olanzapine showed better scores on the positive subjective feelings and the final score of DAI than those of haloperidol. These effects were still present after controlling the variables such as age, psychopathlogies and dyskinesia subscale as the covariates. Conclusion: Although olanzapine showed the favorable outcomes, these results suggest that we may not conclude the general notion that the novel antipsychotics are uniformly better tolerated as indicated by the measures of subjective responses, side effects, and a subjective quality of life in schizophrenic outpatients.

INCREASED TIME TO ALL-CAUSE ANTIPSYCHOTIC TRIAL DISCONTINUATION IS ASSOCIATED WITH BETTER SCHIZOPHRENIA TREATMENT OUTCOMES

F. Zhao,* H. Ascher-Svanum, C. P. Mitchell, G. A. Phillips, E. Dunayevich
Eli Lilly and Company, Indianapolis, IN, USA

Background: Time to all-cause medication discontinuation is recognized as an important outcome measure in the treatment of schizophrenia because it integrates clinician and patient judgments about the treatment's efficacy and tolerability. This study assessed whether longer antipsychotic trial participation is associated with more efficacious outcomes and with better quality of life for patients with schizophrenia. Methods: Patients diagnosed with schizophrenia, schizophreniform disorder, or schizoaffective disorders were pooled from double-blind, randomized studies of at least 24 weeks in duration comparing olanzapine with other antipsychotics. Participants were treated with haloperidol, risperidone, olanzapine, quetiapine, or ziprasidone. Post-hoc, Pearson partial correlations were conducted at the 24-28 week timepoint to examine the relationships between time to all-cause study discontinuation and improvements on the Positive and Negative Syndrome Scale (PANSS) and the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), adjusting for baseline outcome measure scores. Outcome measures were also contrasted for patients who completed the study treatment period with patients who did not. Results: Longer time to drug discontinuation was significantly associated with greater improvements in PANSS total score ($r=-0.519$, $p<0.0001$), positive symptoms ($r=-0.502$, $p<0.0001$), and negative symptoms ($r=-0.424$, $p<0.0001$). Longer time to discontinuation was also associated with greater improvements on the SF-36 Mental Component Summary (MCS) ($r=0.325$, $p<0.0001$) and Physical Component Summary ($r=0.0792$, $p=0.0036$) scores, and on all other SF-36 subscales ($r=.12-.28$, $p<.0001$). Compared with patients who did not complete the study treatment period, the completers experienced significantly greater improvements in efficacy outcome measures, including symptom severity (the difference in mean change between completers and non-completers on the PANSS total score ranged from -12.39 ~ -29.03 across studies, $p < 0.0001$ in all studies). Completers also showed significantly greater improvement than non-completers on several health outcome measures, including SF-36 MCS (mean change on MCS score: 8.32 vs. 1.43, $p<.0001$). Conclusions: In the treatment of patients with schizophrenia, longer duration of participation in an antipsychotic trial is associated with significantly greater improvement in clinical symptomatology and in health-related quality of life.

A RANDOMIZED DOUBLE-BLIND STUDY OF QUETIAPINE AND RISPERIDONE IN THE TREATMENT OF SCHIZOPHRENIA

K. Zhong,* P. Harvey, M. Brecher, D. Sweitzer
Clinical Research, Neuroscience, AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA

This study compared the efficacy and tolerability of quetiapine and risperidone in treating schizophrenia and assessed the effects of both agents on cognitive and social functioning. In this double-blind, randomized, flexible-dose study, patients who met DSM–IV criteria for schizophrenia with PANSS scores of ≥60 were randomized to either quetiapine (200–800 mg/d) or risperidone (2–8 mg/d) for 8 weeks. The primary efficacy measure was change from baseline on PANSS total scores. Secondary efficacy outcomes included response rate (proportion of patients with either ≥40% reduction in PANSS scores or rated ≤3 on CGI-C scores), and change from baseline on cognitive and social functioning assessments. Treatment-emergent AEs and change from baseline on weight, glucose, and prolactin were assessed. A total of 673 patients were randomized to quetiapine (338) or risperidone (335). Baseline characteristics were comparable; mean daily doses were 525 mg and 5.2 mg for quetiapine and risperidone, respectively. No statistically significant between-group difference was found on change from baseline to endpoint in PANSS total scores. In each group, similar proportions of patients showed ≥40% reduction in PANSS total and subscales, and a similar percentage were rated "much" or "very much" improved on CGI-C. As to cognitive improvement, both agents significantly improved episodic memory, verbal fluency, and social skills performance. Improvements in executive functioning and total learning were associated with social skills performance in both quetiapine- and risperidone-treated patients. Completion rates were similar for quetiapine (46%) and risperidone (50%); AE-related withdrawals were 6% and 8% for quetiapine and risperidone, respectively. Glucose and weight changes were similar between groups. EPS-related AEs were significantly higher with risperidone (22%) vs quetiapine (12.7%). Plasma prolactin levels increased markedly by end of study in risperidone-treated patients, but decreased in quetiapine-treated patients. In this study, quetiapine and risperidone were equally efficacious in treating schizophrenia, both improved cognitive and social functioning, and both had minimal effects on weight and glucose. Risperidone-treated patients, however, had a significantly higher incidence of EPS-related AEs and significantly higher elevations of prolactin plasma levels vs quetiapine-treated patients.

19. Therapeutics: Pharmacologic Probes

TRANSDERMAL NICOTINE EFFECTS ON ATTENTION IN SCHIZOPHRENIA

C. G. Allen,* P. G. Nestor, M. A. Niznikiewicz, T. Cunningham, J. Adams, M. E. Shenton, R. W. McCarley
Clinical Psychology, University of Massachusetts–Boston, Boston, MA, USA

Use of cigarettes in persons with schizophrenia is greater than in any other clinical or general population. A myriad of health risks are associated with cigarette smoking including coronary heart disease, stroke, and lung cancer; many of which are increased in schizophrenia. Recent evidence has pointed to particular abnormalities in schizophrenia of nicotinic acetylcholine receptors (e.g., alpha4beta2 and alpha7 subunits). Prior research suggests that nicotine administration provides neuropsychological benefits for persons including those with schizophrenia on sustained attention tasks, while abstinence leads to impairment. This study utilized a novel methodological tool in the assessment of potential attentional benefits from nicotine in schizophrenia. Male heavy smokers with schizophrenia and male normal comparison smokers were recruited. All subjects completed the Posner Attention Network Test, designed to measure alerting, orienting and executive networks of attention. Reaction time and accuracy rates were measured. Each task was completed during three nicotine conditions, including baseline (without recent nicotine use), early withdrawal (overnight abstinence) and nicotine administration (following a 2-hour 21mg nicotine patch application). Subjects provided saliva samples for cotinine analysis at each testing period. Alerting, orienting and executive networks of attention are expected to be impaired during baseline assessment in comparison to normal control subjects. Alerting attention in schizophrenia will be particularly impaired, given known deficits in sustained attention. Following an early withdrawal period, networks of attention are hypothesized to be significantly impaired in relation to baseline functioning. Administration of a nicotine patch is expected to ameliorate deficits of early withdrawal and may demonstrate improved functioning in comparison to baseline assessment. Cotinine levels are expected to correspond to each nicotine condition. Results provide insight into continued evaluation of the relationship between nicotine and attention functioning in schizophrenia.

A DOUBLE-BLIND SHAM CONTROLLED TRIAL OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION IN THE TREATMENT OF REFRACTORY AUDITORY HALLUCINATIONS

J. Benitez,* P. B. Fitzgerald, N. Marston, A. R. de Castella, J. Kulkarni
School of Psychology, Psychiatry & Psychological Medicine, Monash University, Clayton, VIC, Australia

Background Previous research suggests that repetitive transcranial magnetic stimulation applied to temporoparietal cortex may have therapeutic benefit for patients with schizophrenia and treatment resistant auditory hallucinations. We aimed to test this hypothesis in a randomised double blind trial. Method 33 patients with treatment resistant auditory hallucinations entered a randomised sham controlled double-blind trial. rTMS was applied for 10 consecutive week days, for 15 minutes at 1Hz and 90% of the resting motor threshold. We assessed clinical symptoms and cognitive function. Results rTMS was safe with no adverse effects on memory and cognitive parameters assessed. Overall, active treatment did not result in a greater therapeutic effect than sham on the severity of hallucinations. Active treatment did result in a reduction of the loudness of hallucinations greater than the sham group. In a small number of active treatment responders, the effect of treatment persisted for over one month. Patients with persistent voices during treatment appeared to respond more poorly to rTMS. Conclusions The study does not support the clinical effectiveness of rTMS using the stimulation parameters provided. However, it does suggest that rTMS methods may have a therapeutic role and indicates the need for further exploration of alternative stimulation methods. It also supports the involvement of the temporoparietal cortex in the pathogenesis of hallucinations.

INVERSE AGONIST PROFILING OF ANTIPSYCHOTICS AT THE HUMAN D2 DOPAMINE RECEPTOR

E. S. Burstein,* J. Ma, S. Wong, D. M. Weiner, M. R. Brann
ACADIA Pharmaceuticals, San Diego, CA, USA

Drugs that antagonize D2-like G-protein coupled receptors (GPCRs) are efficacious for a variety of CNS disorders, particularly schizophrenia. The impact of inverse agonism upon the clinical properties of these compounds is not fully understood in part because the low sensitivity of many functional assays prevents reliable measurements of constitutive activity. Using a cell-based functional assay we have found that overexpression of GalphaO induced constitutive activity of the human D2 dopamine receptor. Over 30 antipsychotics, representing several chemical classes, including both typical and atypical antipsychotics, as well as several reference compounds were profiled for intrinsic activity at this receptor. Virtually all of the antipsychotics tested were inverse agonists, displaying a range of efficacies, from partial to full inverse agonism. In contrast, very few compounds, including aripiprazole were partial agonists. The clinical implications of these findings will be discussed.

NICOTINE REDUCES DEFICITS IN CORTICAL INFORMATION PROCESSING AND COGNITIVE FUNCTION PRODUCED BY KETAMINE IN HUMANS

H. Cho,* D. Mathalon, E. B. Perry, N. Boutros, L. Jacobsen, R. Gueorguieva, R. K. Blais, L. Donahue, D. C. D'Souza, J. H. Krystal
Psychiatry, Yale University School of Medicine, New Haven, CT, USA

The administration of NMDA glutamate receptor antagonists to healthy human subjects produces impairments in cognitive functions and symptoms that resemble endogenous psychoses. Nicotine is known to enhance attention and information processing and this may explain extraordinary high rates of smoking in schizophrenic patients. In animal studies, nicotine reduced some deficits produced by NMDA antagonist drugs. However, the interactions of nicotinic and NMDA receptor function have not been studied in humans. The purpose of the current study was to determine whether nicotine attenuates the deficits in cortical information processing and cognitive functions produced by ketamine. Eight psychiatrically healthy, nontreatment seeking smokers with overnight abstinence completed 4 test days each, separated by at least 3 days during which they received

ketamine (bolus 0.26mg/kg and constant infusion 0.65mg/kg/hr) or placebo followed by two injections of nicotine or placebo in a double-blind counterbalanced design: ketamine, nicotine, ketamine and nicotine, and placebo. Nicotine was delivered intravenously twice at a dose of 1.0 mg/kg/min over 10 minutes to model the amount of nicotine delivered by a typical cigarette. Information processing was measured using event related potentials (P50, mismatch negativity and P300, with auditory stimuli). Attention (CPT), working memory and PANSS/CADSS/visual analog scale for mood were also measured. The above outcome measures were applied after the injection nicotine or placebo. Nicotine attenuated ketamine-induced MMN and P3 abnormalities and decrease in correct responses of AX-CPT without affecting P50 and working memory performance. This may be consistent with an attenuation of ketmine-induced increases in scores of PANSS and CADSS by nicotine. These data provide the first clinical evidence that stimulation of nicotine receptors may reduce the impact of deficits in NMDA receptor function on cortical information processing. This study is supported by a NARSAD Young Investigator Award (H-S Cho).

THE EFFECT OF HIGH FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) ON NEGATIVE SYMPTOMS AND ELECTROPHYSIOLOGICAL CORRELATES IN SCHIZOPHRENIA

J. Cordes,* J. Brinkmeyer, G. Kotrotsios, M. Arends, A. Mobascher, M. Jaenner, M. W. Agelink, W. Woelwer
Psychiatry and Psychotherapy, Heinrich-Heine-University, Duesseldorf, Germany

Deficits in the recognition of facial expressions of emotions in schizophrenia have been widely described in the literature. The electrophysiological activity of early components (P100, N170, N240) might represent specific cerebral processes underlying decoding of facial expressions. Disturbed facial affect recognition in schizophrenic patients might be a result of hypoactivity in inferior prefrontal areas (Streit 1999, 2001). rTMS shows increasing evidence of successful treatment in schizophrenia. Most results demonstrate a reduction of negative symptoms following high frequency rTMS. This study was realized to evaluate the effect of left prefrontal high frequency rTMS on facial affect recognition deficit and negative symptoms in schizophrenia. By using a sham-controlled randomized design 17 schizophrenic patients (rTMS = 11, sham = 6) were treated with 10 Hz rTMS of the dorsolateral prefrontal cortex over 10 days at 110 % of motor threshold. The Positive and Negative Symptoms Scale (PANSS) was used to assess schizophrenic symptomatic before the first and after the 10th session with rTMS. The ability to recognise emotional expressions of faces was tested. 32 electrodes EEG was recorded during the facial affect recognition task, and a 5 minutes baseline (qEEG). The measurements were made before the first and after the 10th session of rTMS. There was a significant improvement of negative (p=0,016) and positive symptoms (p=0,029) in both groups. The reduction of negative symptoms was more pronounced under rTMS compared to sham stimulation. There was no effect of rTMS in the positive symptom subscale in relation to sham stimulation. After the verum rTMS treatment subjects showed a significant increased alpha-Power at the fronto-temporal electrodes that differentiated them from the sham-patients. Identification rate of facial expressions significantly improved (p<0,05) in patients who received verum rTMS treatment. Interestingly we also found significantly increased amplitudes at about 170ms (N170) and 240 ms (P240) after the verum rTMS treatment. No effect was observed at the sham group. A deficit in dopamine transmission in the prefrontal cortex might implicated in the cognitive impairments and negative symptoms of schizophrenia. High frequency rTMS over the left dorsolateral prefrontal cortex may be a therapeutic approach to improve negative symptoms and the recognition deficit in patients with schizophrenia.

DISRUPTION OF OREXIN/HYPOCRETIN SIGNALING BLOCKS THE EFFECTS OF CLOZAPINE ON THE PREFRONTAL CORTEX

A. Y. Deutch,* L. L. Jackson, M. Bubser
Psychiatry and Pharmacology, Vanderbilt University Medical Center, Nashville, TN, USA

The mechanisms of action of clozapine and other atypical antipsychotic drugs (APDs) remain incompletely understood. Among the effects of clozapine reported in animal studies are an increase in both basal and evoked extracellular dopamine levels in the prefrontal cortex (PFC) and an induction of the immediate-early gene c-fos in the PFC; typical APDs such as haloperidol do not result in these effects. The mechanisms through which clozapine evokes increased Fos expression in the cortex and increased dopamine release remain poorly understood. Several recent case studies have suggested that modafanil, which is used to treat narcolepsy and is thought to act by increasing release of orexin, can reduce the sedation that accompanies clozapine treatment. Modafanil has recently been shown to improve attention and other cognitive deficits in schizophrenia. We previously reported that clozapine activates a subset of orexin neurons that project to the PFC, and that orexin evokes monoamine release in the PFC. We therefore examined the effects of lesions of the orexin neurons in the lateral hypothalamus and contiguous perifornical area (LH/PFA) on clozapine-induced Fos expression in the PFC. Ibotenic acid lesions of this area sharply reduced clozapine-evoked Fos expression in the PFC; there was an inconsistent effect on clozapine-induced Fos in the medial thalamus, but clozapine-induced Fos in the nucleus accumbens did not appear to be affected. Because lesions of the LH/PFA targeted cells that do not express orexin as well as orexin, we also examined the effects of pretreatment with an orexin OR1X antagonist on clozapine-induced Fos expression. The orexin antagonist blocked the ability of clozapine to induce Fos in the PFC. Consistent with recent data suggesting that orexin plays a central role in attention and other cognitive domains, and that orexin increase catecholamine release in the PFC, our data point to an important role for orexin in subserving the effects of atypical APDs on cognitive deficits in schizophrenia. Supported in part by MH-45124 and MH-57795 and the National Parkinson Foundation Center of Excellence at Vanderbilt University.

N-DESMETHYLCLOZAPINE IN SCHIZOPHRENIA

J. B. Eamma,* D. M. Weiner, E. Taylor, K. E. Vanover, M. R. Brann, R. E. Davis, A. Preda, C. A. Tamminga
Psychiatry, UT Southwestern Medical Center at Dallas, Dallas, TX, USA

Of all the conventional and new antipsychotic medications that have been administered in the treatment of schizophrenia, clozapine distinguishes itself by being the only antipsychotic that demonstrates superior antipsychotic efficacy. The major metabolite of clozapine,

N-desmethylclozapine (NDMC), in vitro shows an analogous receptor profile to that of clozapine. This suggests that NDMC shares many of the clinical properties and characteristics of clozapine with one intriguing exception. Clozapine, as well as many other major antipsychotics, exerts antagonistic actions at M1 muscarinic cholinergic receptors, while its major metabolite, NDMC, exerts agonistic actions. It is widely believed that antagonistic actions at muscarinic receptors are associated with working memory impairments in patients treated with antipsychotics. NDMC administered to patients alone would display unopposed agonist actions at the muscarinic receptor with selectivity for M1/M5. Therefore, the possibility exists that, by administering NDMC to patients by itself, NDMC could have the same superior antipsychotic efficacy as clozapine without producing memory dysfunction. It is postulated that NDMC could even improve cognition in treated patients. In clinical studies, serum levels of NDMC following oral dosing of clozapine approximate 70% of clozapine levels themselves. So, although NDMC has never been given to humans by itself, NDMC has received extensive human exposure. Currently, a clinical study is being conducted to administer NDMC by itself to humans for the first time. This study will demonstrate the safety, tolerability, and pharmacokinetics of NDMC. Pharmacokinetic data will be reported.

SEX DIFFERENCES AND INDIVIDUAL DIFFERENCES IN COGNITIVE PERFORMANCE AND THEIR RELATIONSHIP TO ENDOGENOUS GONADAL HORMONES AND GONADOTROPINS IMPLICATIONS FOR SCHIZOPHRENIA

R. Halari,* M. Hines, V. Kumari, R. Mehrotra, M. Wheeler, G. Ng, T. Sharma
Institute of Psychiatry, London, London, United Kingdom

We examined associations of endogenous levels of gonadal hormones and gonadotropins to performance on a sexually dimorphic cognitive battery in a sample of healthy men (n = 42) and women (n = 42) aged 18-35 years. Serum blood samples (10ml) were collected between 0900 and 1030, and concentrations of testosterone (T), estradiol (E), progesterone (PROG), luteinizing hormone (LH), follicle-stimulating hormone (FSH) and sex hormone binding globulin (SHBG) were measured. In women, these samples were collected during the follicular phase of the menstrual cycle. Participants completed three spatial tasks (mental rotation, modified judgement of line orientation and computerized Benton judgement of line orientation), two verbal tasks (letter and category fluency), an inhibition task, and two control measures (a working memory task and a vocabulary test). Results demonstrated significant sex differences favoring men on all the spatial tasks and the inhibition task, and differences favoring women on the category fluency task. There were sex differences on specific conditions of the working memory task, some favoring men and some women, and no sex difference on the vocabulary test. The only significant relationships between hormones and cognitive performance were not predicted, and were no longer significant following Bonferroni corrections for multiple comparisons. These results suggest there are few if any consistent and substantial relationships between individual differences in endogenous and non-fluctuating levels of gonadal hormones or gonadotropins and these cognitive abilities in men or women.

SOME LINGUISTIC SIGNS OF KETAMINE-INDUCED COGNITIVE IMPAIRMENT

C. He,* M. A. Covington, J. Semple, J. Brown
Artificial Intelligence Center, University of Georgia, Athens, GA, USA

This experiment is a study of the effects of sub-anesthetic doses of ketamine upon speech, as ketamine-influenced speech may reflect the cognitive impairment that ketamine produces in healthy volunteers similar to that observed in schizophrenia (e.g., Malhotra et al. 1996; Adler et al. 1998; Lahti et al. 2001). During the placebo-controlled, double-blind experiment, 20 healthy subjects were asked to describe some pictures from the Thematic Apperception Test (TAT, Murray 1943/1971) both after ketamine and placebo. Their speech was recorded and a statistical analysis was done to the recordings. We focus on quantitative linguistic properties that are objectively measurable, rather than those widely adopted criteria based on subjective ratings such as derailment and incoherence. An immediate consequence is that we were able to discover some characteristics of ketamine-influenced speech that easily elude even the trained ear. The most prominent result of the experiment was that ketamine resulted in a significantly lowered proportion of verb tokens in speech. At the same time, ketamine significantly increased the percentage of nouns. Subjects exhibited impaired verbal retrieval and a tendency to name objects without describing their actions. Discoursewise, ketamine significantly increased the use of fillers like um, uh. Filled pauses increase the latency of response and are a sign of speech poverty — a representative symptom of negative schizophrenia. Ketamine also affected the percentage of questions and the percentage of first person pronoun I. Such changes may be due to self-centeredness and impaired "Theory of Mind" commonly found in schizophrenia. We conclude that ketamine-induced cognitive impairment results in deviations in terms of vocabulary use. Results from a preliminary experiment on schizophrenic speech have shown the same linguistic characteristics. This research was supported by GlaxoSmithKline Research & Development Ltd.

EFFECTS OF MODAFINIL ON PREFRONTAL FUNCTION AND VOLUNTARY BEHAVIOUR IN CHRONIC SCHIZOPHRENIA

M. Hunter,* V. S. Ganesan, S. A. Spence
Academic Clinical Psychiatry, University of Sheffield, Sheffield, United Kingdom

Introduction: Poverty and stereotypy of voluntary motor behaviour are central in the deficit state of chronic schizophrenia and are likely to result from dysfunction of the prefrontal cortex. Modafinil is a putative cognitive enhancing drug that might be of utility in the treatment of chronic schizophrenia. We used functional magnetic resonance imaging to investigate the acute effects of modafinil on the neural and behavioural correlates of voluntary motor behaviour in chronic schizophrenia. Methods: Stable outpatients (n=12; mean age=37 years) with DSM-IV diagnoses of schizophrenia and negative symptoms (mean total SANS score=11.5; mean duration of illness=14 years) participated. Patients were studied on 2 days, a week apart. In a randomized double-blind placebo-controlled crossover design, patients received either modafinil 100mg or placebo prior to functional brain imaging. Inside the scanner, patients were required to generate sequences of spontaneous motor-action by deciding when to perform button-pressing movements with the first finger of their right hand. Patients were instructed to attempt random (variable and

unpredictable) responding; randomness was quantified by calculation of the coefficient of variation (standard deviation to mean inter-response interval ratio). Following scanning, each patient was fitted with a wrist-worn accelerometer that recorded motor activity over the next 4 hours (peak plasma levels of modafinil occur 2-4 hours post dosing). Results: Imaging data were analyzed using a random effects model. Compared with placebo, the administration of modafinil was associated with significantly greater group-level activation of bilateral dorsolateral prefrontal cortex during the performance of voluntary movements (Brodmann's areas 9 and 46; $t>2.42$; $p<0.05$). At the individual level, increased activation of left dorsolateral prefrontal cortex (area 46) correlated with reduced stereotypy in the timing of such movements ($r=0.65$; $p<0.05$) and positively predicted increased total motor activity following scanning ($r=0.50$; $p<0.05$). Conclusions: Modafinil can enhance prefrontal activation in patients with chronic schizophrenia. The physiological response of left dorsolateral prefrontal cortex to modafinil predicts the drug's effects on voluntary behaviour both inside and outside the scanner. Functional magnetic resonance imaging may be helpful in evaluating the potential benefit of modafinil for individual patients with chronic schizophrenia.

NEUROCOGNITIVE IMPROVEMENT WITH NORMALIZATION OF SERUM SODIUM IN PATIENTS WITH CHRONIC HYPONATREMIA

M. Jessani,* A. E. Silverman, R. A. Shaughnessy, J. Kaminski, L. R. Falconero, R. Josiassen
Arthur P. Noyes Research Foundation, Norristown, PA, USA

OBJECTIVE: Hyponatremia (serum sodium <135 mmol/L) is an electrolyte abnormality that occurs frequently in long-term psychiatric patients (Siegler, et al., 1995). Most cases are mild, but if serum sodium levels fall abruptly below 130 mmol/L abnormal movements (Nagaratnam, Icano and Peric, 1997) delirium, seizures, and even death (Illowski and Kirch, 1988) are potential consequences. Few treatments exist beyond the combination of fluid restriction and hypertonic saline. However, the recent development of compounds that directly inhibit arginine vasopressin (AVP) represents a promising treatment option (Wong & Verbalis, 2001). The purpose of this case series was to explore whether normalized serum sodium levels had beneficial effects in motor and cognitive functioning in adult schizophrenic patients with hyponatremia. METHODS: Ten adult hyponatremic schizophrenic patients (mean 51.2 years) had been enrolled in efficacy studies of two experimental compounds that directly inhibit AVP activity. With one compound only V2 receptors are blocked at the kidney (Yamamura et al., 1991), while V1a (primarily distributed in the vasculature) and V2 receptors are affected equally with the other compound (Decaux, 2001). Although the double-blind outcome studies were focused on improving serum sodium and potential side effects, additional clinical observations were obtained. While the investigators remained blinded to study drug (placebo versus AVP antagonist), they were not blinded to serum sodium levels. RESULTS: Matched pairs t-test comparison of baseline and Day 30 serum sodium values was statistically significant ($p<0.005$). Group mean scores from the Brief Assessment of Cognition in Schizophrenia were improved between baseline and Day 30 (all $p<0.05$). ANOVA comparisons of "low" and "corrected" sub-groups suggested an association between corrected sodium levels and specific cognitive measures. In two patients, clinical examination of motor function revealed a reduction in fine tremors, and in one case moderate ataxia that was resolved. CONCLUSIONS: Hyponatremia is a significant cause of morbidity and mortality. Unfortunately, current available treatments are suboptimal. Recent studies with experimental compounds that directly inhibit the action of AVP have yielded positive results on serum sodium levels, which may also have beneficial effects on motor and cognitive functioning.

PRELIMINARY EVIDENCE OF ATTENUATION OF THE DISRUPTIVE EFFECTS OF THE NMDA GLUTAMATE RECEPTOR ANTAGONIST, KETAMINE, ON WORKING MEMORY BY PRETREATMENT WITH THE GROUP II METABOTROPIC GLUTAMATE RECEPTOR (MGLUR) AGONIST, LY354740, IN HEALTHY HUMAN SUBJECTS

J. H. Krystal,* E. Perry, W. Abi-Saab, D. C. D'Souza, N. Liu, R. Gueorguieva, L. MacDougall, T. Hunsberger, A. Belger, L. Levine, A. Breier
Psychiatry, Yale University School of Medicine, New Haven, CT, USA

A component of the behavioral consequences of deficits in N-methyl-D-aspartate (NMDA) glutamate receptor function is thought to arise from disinhibition of cortical glutamatergic circuitry through preferential inhibition of GABAergic interneurons over the activity of principal neurons within limbic and cortical circuitry. This study evaluated whether pretreatment with a drug that reduces glutamatergic activation, the group II metabotropic glutamate receptor (mGluR) agonist, LY354740, reduced the cognitive effects of the NMDA glutamate receptor antagonist, ketamine, in healthy human subjects. Nineteen healthy human subjects completed 3 test days during which LY354740 (matched placebo, 100 mg, 400 mg) was administered under double-blind conditions 4 hours prior to the single-blind intravenous administration of saline and 5.7 hours prior to ketamine administration (bolus of 0.26 mg/kg over 1 minute, infusion of 0.65 mg/kg/hr for 100 minutes). Thus on each test day each subject received a single dose of LY354740 (or its matched placebo) and both saline and ketamine infusions. Ketamine impaired attention, working memory, and delayed recall. It also produced positive and negative symptoms, perceptual changes, and dysphoric mood. LY354740 did not have a significant effect on working memory on the placebo day; however, it produced a significant dose-related improvement in working memory during ketamine infusion. LY354740 did not produce demonstrable effects on the behavioral outcomes in this study independent of its interaction with ketamine. These data provide preliminary and suggestive evidence that LY354740 or other group II mGluR agonists might play a role in treating working memory impairment related to deficits in NMDA receptor function. The authors thank Eli Lilly and Company for the provision of LY354740 and administrative and scientific support of the study. The authors also acknowledge support from NARSAD (W.A.), the Department of Veterans Affairs (Alcohol Research Center, Schizophrenia Biological Research Center, National Center for PTSD), the National Institute of Mental Health (5P50 MH44866-12), and the National Institute on Alcohol Abuse and Alcoholism (KO2 AA 00261-01).

ESTROGEN TREATMENT IN WOMEN WITH SCHIZOPHRENIA

J. Kulkarni,* A. de Castella
Psychiatry Research, The Alfred Hospital, Melbourne, VIC, Australia

This study is a clinical trial that builds on preliminary trials and explores the estrogen hypothesis of schizophrenia, which suggests

that estrogen may have a protective effect against schizophrenia in women (1,2). Estrogen has been shown in animal studies to modulate both the dopamine and serotonin neurotransmitter systems - the main neurotransmitters implicated in the pathogenesis of schizophrenia. Estrogen has also been reported to positively affect aspects of cognition and psychopathology in women, both normal and with psychosis. We conducted a double-blind, 28-day, placebo controlled adjunct study with two groups of women of child-bearing age - one receiving standardised anti-psychotic medication plus 100mcg transdermal estradiol or transdermal placebo (n=90). The two groups were well matched in age, diagnosis, medication dosage and menstrual cycle phase at baseline. Analysis shows that women receiving 100mcg estradiol made significantly greater improvements in schizophrenia symptoms than those receiving placebo - using the PANSS rating scale ($p<0.001$). Significant improvements were demonstrated in the positive, negative and general symptomatology PANSS subscales in the estrogen group. Estrogen, LH, FSH, progesterone, prolactin and testosterone levels were analysed using 5 (time) by 2 (treatment condition) repeated measures ANOVA. LH levels were suppressed significantly in the estrogen group demonstrating a pituitary effect for the administration of 100mcg transdermal estradiol. There were significant improvements for women receiving adjunctive estradiol in the cognitive functional areas of verbal memory. This same group worsened with respect to visual memory compared to the placebo group. The addition of 100mcg adjunctive transdermal estrogen significantly enhanced treatment responsivity of acute, severe psychotic symptoms in women with schizophrenia. The positive impact of estrogen treatment via direct actions on dopamine and serotonin systems or via an indirect prolactin medicated effect may prove clinically useful in the overall treatment of women with schizophrenia. 1. Hafner H, Behrens S, De Vry J, Gattaz WF. An animal model for the effects of estradiol on dopamine-mediated behaviour: implications for sex differences in schizophrenia. *Psychiatry Res* 1991:38(2);125-34. 2. Seeman MV, Lang M. The role of estrogens in schizophrenia gender differences. *Schizophrenia Bull* 1990:16;185-195.

FUNCTIONAL EFFECTS OF HALOPERIDOL AND OLANZAPINE DURING A 6-WEEK TREATMENT PERIOD AND RELATIONS TO CLINICAL RESPONSE

A. C. Lahti,* H. H. Holcomb, L. Beason-Held, C. A. Tamminga, M. A. Weiler
Psychiatry, Maryland Psychiatric Research Center, Baltimore, MD, USA

Using PET with ^{15}O, we characterized the rCBF changes induced by haloperidol and olanzapine after 1 and 6 weeks of treatment during resting and task-activated states in schizophrenia volunteers (SV). We hypothesized that resting rCBF with these drugs would be different in basal ganglia. Haloperidol, in contrast to olanzapine, would increase rCBF in the dorsal striatum. We also hypothesized that both drugs would reduce resting rCBF in limbic regions and that these changes would correlate with psychosis improvement. Finally, we hypothesized that task-activated rCBF patterns in ACC would be increased with antipsychotic drug treatment. After a two-week medication withdrawal, SV were blindly randomized to treatment with haloperidol (n=12) or olanzapine (n=17). Each SV was scanned off-medication and after 1 and 6 weeks of treatment. They were scanned during three conditions: rest, control task (CT) and decision task (DEC). To evaluate the effect of drugs on resting rCBF, contrasts were made between the Off-drug and Week 6 scans, and the Off-drug and Week 1 scans. In these contrasts, rCBF values were extracted from significant ACC and hippocampal clusters and correlated with BPRS psychosis improvement. To evaluate the effect of each drug on task activated rCBF patterns in ACC, we performed the contrast: Week 6 (DEC –CT)–Off-drug (DEC–CT). At rest, while significantly more activation was seen in the dorsal striatum with haloperidol compared to olanzapine, both drugs showed significant activation of the ventral striatum. Both drugs significantly decreased rCBF in the ACC, and this decrease was correlated positively with psychosis improvement. rCBF changes in the hippocampus did not predict psychosis improvement in either group. Middle frontal and parietal cortices were significantly activated with olanzapine. During task performance, rCBF in ACC was more activated with both drugs. These results indicate that cortico-subcortical and limbic neuronal networks are affected by both first and second-generation antipsychotics. It may be that blockade of limbic DA projections is key to antipsychotic action and that this blockade is followed by neuronal events affecting the ACC. Reduced resting ACC activity may be associated with the successful response to antipsychotic treatment. This, in turn, may promote a more adaptive response to task demands. Activation of a cortical network subserving executive function could be linked to the effect of olanzapine on cognition.

QUETIAPINE HAS NO IMPACT ON TOBACCO SMOKING IN SCHIZOPHRENIA, DESPITE IMPROVEMENTS IN SYMPTOMATOLOGY: AN INTERIM ANALYSIS

N. Legare,* S. Potvin, R. H. Bouchard, A. Mancini-Marie, P. Barabe, O. Lipp, J. Y. Roy, E. Stip
Psychiatry, Centre de Recherche Fernand-Seguin, Louis-H Lafontaine Hospital, University of Montreal, Montreal, QC, Canada

Up to 90% of schizophrenia patients smoke tobacco. Despite this high prevalence, the pharmacological treatment of tobacco addiction in schizophrenia has received little attention from research. Recently, clozapine has shown promising results in dual diagnosis patients, where it was reported to decrease tobacco smoking. Quetiapine is a pharmacological analogue of clozapine (similar 5-HT2A/D2 ratio, fast kick off from D2, 5-HT1A partial agonism, etc.). We hypothesized that quetiapine would relieve tobacco smoking by improving the key symptoms that schizophrenia patients try to self-medicate with tobacco, namely: cognition, negative symptoms, depression and extra-pyramidal symptoms (EPS). Fifteen dual diagnosis schizophrenia patients (DSM-IV) were switched from their previous antipsychotic drug(s) to quetiapine in a 12-week open-label trial. Concomitant drugs were allowed (mainly antidepressant drugs; no other antipsychotics). Schizophrenia symptoms (PANSS), depressive symptoms (Calgary scale), and EPS (ESRS) were assessed on weeks 0 (baseline) and 12 (end of study). Tobacco addiction was measured with the Fagerstrom questionnaire. Carbon monoxide (CO) blood levels were also gathered. Paired T tests showed significant ($p < 0.05$) improvements in positive, negative, cognitive and general symptoms (PANSS), and also depression and parkinsonian signs. However, no changes in tobacco smoking and addiction were noticed during the study, either with the Fagerstrom questionnaire or the CO levels. This is the first study to show that quetiapine retains its clinical efficacy in dual diagnosis schizophrenia patients. However, there was no significant impact on tobacco smoking as a result of symptom improvement. The current results cast some doubt on

the self-medication hypothesis of tobacco smoking in schizophrenia. Funding: This study was funded by AstraZeneca.

INFLUENCE OF HIGH FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS) ON CARDIOVAGAL MODULATION AND MONOAMINERGIC ACTIVITY IN SCHIZOPHRENIA

A. Mobascher,* M. W. Agelink, M. Arends, J. Brinkmeyer, M. Jaenner, U. Henning, A. Klimke, J. Cordes
Psychiatry and Psychotherapy, Heinrich-Heine-University, Duesseldorf, Germany

In schizophrenia the parasympathic activity is significantly decreased, when the psychotic states are more pronounced (Toichi 1999). Plasma and serum indices of monoaminergic activity reflect partly the illness of schizophrenia (Oades, 2002). In healthy human subjects after slow rTMS heart rate variability (HRV) was significantly increased (Yoshida 2001). The effect of rTMS on dopaminergic activity might be of particular relevance to elucidate its mechanism of action (Strafella, 2001). This study was realized to evaluate the effects of rTMS on serum monoamines and autonomic nervous system in schizophrenia. By using a sham-controlled randomised design 17 patients with schizophrenia were treated with 10 Hz rTMS of the dorsolateral prefrontal cortex over 10 days at 110 % of motor threshold. The severity of schizophrenic symptoms was assessed by the positive and negative syndrome scale (PANSS). Homovanillic acid (HVA) and 3-methoxy-4-hydroxy phenyl glycol (MHPG), the major metabolites of dopamine and noradrenaline and the 5-minute resting HRV including spectral analysis were measured in both groups before and after the third rTMS session. Preliminary results suggest a significant increase in absolute high-frequency and low-frequency power and a decrease of the catecholamine metabolite homovanillic acid (HVA) during the course of a rTMS trial in schizophrenic patients. In the sham group the parasympathic activity is decreased and the noradrenaline metabolite HVA is increased. Newer studies confirmed an autonomic neurocardiac imbalance in patients with schizophrenia. Increased HVA levels were shown to be associated with negative symptoms (Zhang 2001). In the literature during antipsychotic treatment the concentrations of HVA and MHPG were significantly reduced only in the schizphrenics who responded to the treatment (Nagaoka 1997). Our data suggest an association of psychopathological improvement to rTMS with corresponding changes of autonomic nervous system function and decrease of HVA. In the sham group the increase of noradrenaline and HVA may reflect particularly an unspecific sympathetic activation by rTMS.

PROOF OF PRINCIPLE OF EFFECTS OF THE ALPHA7 NICOTINIC CHOLINERGIC RECEPTOR AGONIST DMXB-A IN SCHIZOPHRENIA—NEUROPSYCHOLOGICAL AND NEUROPHYSIOLOGICAL EFFECTS OF A SINGLE DAY ADMINISTRATION

A. Olincy,* J. G. Harris, L. L. Johnson, V. Pender, L. F. Martin, S. Kongs, D. Allensworth, G. O. Zerbe, R. Freedman
Psychiatry, University of Colorado Health Sciences Center, Denver, CO, USA

Introduction: The rate of smoking is elevated in schizophrenia and may be an attempt at self-medication to overcome deficiencies in cholinergic neurotransmission. Nicotine normalizes the P50 deficit and improves coginitive dysfunction in schizophrenia. However, less potentially toxic and more chronically effective cholinergic treatments are needed such as 3-(2,4 dimethoxybenzylidine) anabaseine (DMXBA). This study assessed DMXBA's ability to normalize the P50 and attentional difficulties in schizophrenia. Methods: Twelve non-smoking outpatients with schizophrenia received on three seperate days 150 mg then 75 mg DMXBA, 75 mg then 37.5 mg DMXBA and placebo. The subject's P50 was recorded at baseline, 45 minutes and 1.5 hours after first dose, and 1.75 hours after second dose. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was used to measure learning, memory, visuospatial/constructional, language and attention. The RBANS scale was administered 45 minutes after the second dose. The Brief Psychiatric Rating Scale (BPRS) and adverse events checklist was administered at baseline, 1.75 hours after first drug administration, 2.15 hours after second drug administration and at discharge. All data were analyzed by a repeated measures, mixed effects Analysis of Variance. Results: No significant changes in P50 suppression were found by drug regimen. Total RBANS Score and the Attention Index showed a significant difference between placebo and low dose DMXBA. There was also a significant effect of DMXBA on the Total BPRS Score 3 hours after the high dose. Toxicity was minimal. Discussion: 75 mg of DMXBA in a single dose administration improves cognition in schizophrenia.

COMPARATIVE AND INTERACTIVE HUMAN PSYCHOPHARMACOLOGIC EFFECTS OF KETAMINE AND AMPHETAMINE: IMPLICATIONS FOR GLUTAMATERGIC AND DOPAMINERGIC MODEL PSYCHOSES AND COGNITIVE FUNCTION

E. B. Perry,* D. C. D'Souza, R. Gueorguieva, A. Belger, S. H. Madonick, A. Abi-Dargham, T. B. Cooper, L. MacDougall, W. Abi-Saab, J. H. Krystal
Schizophrenia Biological Research Center, VA Connecticut Healthcare System, West Haven, CT, USA

Ketamine and amphetamine produce in healthy human subjects cognitive, behavioral, and subjective effects resembling endogenous psychoses. The purpose of this study was to directly compare the effects of ketamine and amphetamine and to explore their interactive effects within subjects. In this placebo-controlled randomized double-blind trial, 27 healthy human subjects completed 4 test days. On each test day, each subject received amphetamine (a one-minute infusion of amphetamine 0.25 mg/kg or saline) as well as ketamine (a one-minute intravenous infusion that contained ketamine 0.23 mg/kg followed by a one-hour infusion of 0.5 mg/kg or an identical saline bolus and infusion). The order of amphetamine and ketamine infusion was randomized across subjects. At the doses studied, ketamine and amphetamine produced positive symptoms and euphoria. However, hallucinatory effects were produced only by ketamine, while hostility, grandiosity, and somatic concern were produced only by amphetamine. Similarly, both amphetamine and ketamine produced conceptual disorganization, but only ketamine produced concrete ideation and unusual mannerisms. Ketamine, but not amphetamine, produced negative symptoms and disrupted delayed recall. Ketamine and amphetamine showed three types of interactive effects: 1) amphetamine attenuated the impairment of working memory produced by ketamine, 2) amphetamine and ketamine had additive interactive effects on thought disorder, level of arousal, and, to some

extent, euphoria, and 3) amphetamine and ketamine had less than additive interactive effects on psychosis and total PANSS scores. The partial overlap between the acute cognitive and behavioral effects of ketamine and amphetamine in healthy human subjects and their less than additive interactive effects on psychosis were consistent with models that implicate both NMDA glutamate receptors and dopamine systems in psychosis. However, glutamate and dopamine may differentially contribute to features of psychosis and may participate in distinct and additive ways to the production of thought disorder and euphoria. With respect to medication development for cognitive dysfunction, the pattern of the interactive effects of ketamine and amphetamine was consistent with the hypothesis that facilitation of prefrontal cortical dopamine levels would attenuate some cognitive impairments associated with deficits in NMDA receptor function.

HIGH FREQUENCY RTMS IN THE TREATMENT OF NEGATIVE SYMPTOMS OF SCHIZOPHRENIA: CASE STUDY

R. Prikryl,* T. Kasparek, H. Kucerova, E. Ceskova, S. Skotakova
Psychiatry, Masaryk University, Brno, Czech Republic

a) Negative symptoms are one of the basic characteristics of schizophrenia. They are regarded as the most persistent, refractory, and disabling component of the disorder. Negative symptoms do not respond to therapy with antipsychotics of the 1st generation and the effect of antipsychotics of the 2nd generation remains problematic. Repetitive transcranial magnetic stimulation (rTMS) presents a new opportunity for influencing negative symptoms of schizophrenia. A theoretical justification of the effect of rTMS on negative schizophrenic symptoms can be seen in the fact that high-frequency rTMS has an activating effect on cortex neurons. Negative correlation between activity of the frontal cortex and severity of negative symptoms has been proved repeatedly. Another important fact is that dopamine can be released in the mezolimbic and mezostriatal brain systems by high-frequency stimulation of the frontal cortex (Strafella et al. 2001). b) Thirty four years old schizophrenic patient (paranoid subtype) with prominent negative symptoms was included into the study. He has been suffering from schizophrenia for 64 months. Stimulation was applied to the left dorsolateral prefrontal cortex using a Magstim Super Rapid stimulator equipped with a focal figure 8-shaped coil that allowed continuous air cooling to prevent overheating during stimulation. Stimulation frequency was 10Hz. Stimulation intensity was 110% of the motor threshold intensity. Patient received 15 rTMS sessions on 15 consecutive working days. Each daily session consisted of 15 trains of 10 seconds duration and 30 seconds intertrains intervals. It means 1500 stimuli per session. Psychopathology was rated by PANSS before and after stimulation. c) The mean negative PANSS score was 29 before and 17 after stimulation (total PANSS: 76 and 44, positive PANSS: 10 and 9, general PANSS: 37 and 28). rTMS has led to 42% reduction of negative PANSS score (43% total, 10% positive and 25% general PANSS score). d) In conclusion, our result supports the therapeutic potential of rTMS at higher frequency for negative symptoms of schizophrenia. Strafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *J Neurosci*, 2001, 21, 157:1-4. The study was supported by grant No. NR 7986/ 2004 supported by Ministry of Health of Czech Republic.

PHARMACOLOGICAL CHARACTERIZATION OF N-DESMETHYLCLOZAPINE (ACP-104), A POTENT M1 RECEPTOR AGONIST

S. Risso Bradley,* J. Lameh, T. Son, L. Pounds, A. Bajpai, T. A. Spalding, F. Ek, J. Ohlsson, R. Olsson, B. R. Tolf, U. Hacksell, D. M. Weiner, M. R. Brann, R. E. Davis
ACADIA Pharmaceuticals, San Diego, CA, USA

Clozapine shows a unique antipsychotic clinical profile in that it improves both positive and negative symptoms of schizophrenia in patients not responding to typical antipsychotic agents, with a low propensity to induce extrapyramidal side effects. Further, clozapine demonstrates a cognitive profile superior to that of other antipsychotic drugs. Clozapine also has unique untoward effects such as seizures, agranulocytosis and sailorrhea. These characteristics of clozapine prompted us to determine the potential mechanisms that contribute to this unique antipsychotic drug profile. Our previous work profiling a large library of clinically relevant drugs revealed that N-desmethylclozapine (ACP-104), the active metabolite of clozapine, was a potent and efficacious M1 muscarinic receptor agonist in vitro, suggesting that activation of muscarinic M1 receptors may contribute to the unique clinical profile of clozapine. In order to provide further characterization, the pharmacological activity of ACP-104 was investigated at M1-M5 receptors and other monoaminergic receptors using multiple different in vitro and ex vivo assays. Moreover, several chemical analogs of ACP-104 have been profiled in order to identify more potent or efficacious compounds acting through this mechanism. Through this effort, we have expanded our understanding of the muscarinic mechanisms underlying the unique clinical profile of clozapine and its major metabolite. These data support the development of ACP-104 as a novel therapy for schizophrenia.

PHARMACOSENSITIVITY OF THE COGTEST BATTERY IN CLINICAL TRIALS OF SCHIZOPHRENIA

A. Small,* P. Barua, R. Bilder, T. Sharma
Clinical Neuroscience Research Centre, Dartford, United Kingdom

Cogtest (Cogtest plc, London) is a computerized neurocognitive test battery of 16 subtests currently being used in over 300 organizations across 16 countries. It is designed for use with a variety of clinical populations and in clinical trials. The platform allows for accurate recording of reaction time data, enhanced standardization relative to examiner administered tests and is easily adapted for implementation in functional neuroimaging environments. Its internet data capture and web reporting facilities makes it unique amongst current cognitive test providers. Additionally, its multiple parallel forms make it amenable to repeated testing sessions across time making it an excellent tool for clinical trials. In order to verify the sensitivity of the Cogtest system to pharmaceutical interventions, we administered a single 0.3mg subcutaneous dose of scopolamine to N=8 elderly study participants. Scopolamine has been routinely used to induce cognitive dysfunction in a bid to mimic the loss of acetylcholine transmission seen in cognitive disorders like Alzheimers disease. All participants were tested on a battery of three Cogtest assessments, a test of continuous performance, one of strategic rule learning and a word-learning task. Participants were assessed 1-hour prior to drug administration and then 0:45, 1:45, 3:45 and 7:5 hours after drug. Consistent with the known effects of scopolamine, a decline in performance

was seen on each task 1.45 hours after drug administration. Also consistent with known effects, cognitive decline was most marked on the word memory task, with performance falling from a mean total trials score of 10.1 (SE 1.16) to 5.9 (SE 0.8). Also consistent with our knowledge of the effects of scopolamine, performance at 7.5 hours was restored to baseline levels 9.9 (SE 1.2). This effect was found to be statistically significant when analyzed by ANOVA (F=3.75, P=0.01). The results of this study reaffirm our understanding of the dementia-mimetic properties of scopolamine. The study also confirms the capacity of the Cogtest battery to the detect scopolamine induced memory impairments in small groups of normal volunteers and its application in clinical trials in schizophrenia.

REDUCTION OF HALOPERIDOL-INDUCED SIDE EFFECTS BY ACP-103 IN HEALTHY VOLUNTEERS

K. E. Vanover,* D. M. Weiner, L. G. Nilsson, A. Grahnen, B. R. Tolf, U. Hacksell, M. R. Brann, R. E. Davis
ACADIA Pharmaceuticals, San Diego, CA, USA

ACP-103 is a novel serotonin2A (5-HT2A) receptor inverse agonist. An exploratory clinical pharmacology study of the potential of ACP-103 to inhibit central nervous system side effects produced by haloperidol was conducted using a randomized, double blind, placebo-controlled, single dose crossover study design in healthy male volunteers. The subjects participated in two randomized consecutive study periods. In one period, one half of the subjects received 7.5 mg haloperidol plus placebo as single doses and the other half received 7.5 mg haloperidol plus 100 mg ACP-103 as single doses. Following a washout period of at least 14 days, subjects returned for a second period and were crossed over to the opposite treatment from that received in the first period. Haloperidol caused measurable akathisia in 11 of 18 subjects and induced approximately a 3-fold increase in prolactin secretion. ACP-103 treatment caused a clear and consistent decrease in haloperidol-induced akathisia compared to placebo treated subjects as measured by the Barnes Akathisia rating scale. Further, ACP-103 significantly reduced haloperidol-induced hyperprolactinemia. The plasma levels associated with a single administration of 100 mg ACP-103 are comparable to those achieved at steady state following chronic once daily administration of a 20 mg dose of ACP-103. Importantly, the pharmacokinetics of haloperidol and ACP-103 were not affected by their co-administration, indicating a lack of drug-drug interaction. No serious adverse events were reported. Taken together, these data suggest that ACP-103, when combined with existing antipsychotic drugs, may reduce the side effects associated with these drugs and expand their range of efficacy. ACP-103 is being developed as an adjunctive therapy for schizophrenia and as a therapy for treatment-induced dysfunction in Parkinson's disease.

THE ROLE OF M1 MUSCARINIC RECEPTOR AGONISM OF N-DESMETHYLCLOZAPINE (ACP-104) IN ANTIPSYCHOTIC AND COGNITIVE PARADIGMS IN MICE

I. Veinbergs,* D. M. Weiner, T. M. Olafson, M. B. Thygesen, N. Schlienger, R. Olsson, B. R. Tolf, M. R. Brann, R. E. Davis, K. E. Vanover
Pharmacology, ACADIA Pharmaceuticals, San Diego, CA, USA

Comprehensive in vitro functional profiling of antipsychotics at human monoamine receptors revealed that N-desmethylclozapine (ACP-104), the principal metabolite of clozapine, is a potent and efficacious muscarinic receptor agonist. This finding may explain the unique profile of clozapine as an antipsychotic, with efficacy against the positive symptoms in treatment-resistant schizophrenic patients, and the ability to improve cognition and treat the negative symptoms characteristic of this disease. The purpose of the present study was to characterize ACP-104 in antipsychotic and cognitive paradigms in mice. ACP-104 attenuated amphetamine- and MK-801-induced hyperactivity consistent with antipsychotic-like efficacy at doses that did not reduce spontaneous locomotor activity and did not produce neuroleptic-like side effects. ACP-104 also improved spatial memory performance of hippocampally deficient mice in the Morris water maze. Further, confirmation of central m1 receptor activation was demonstrated by a regionally selective and dose-dependent increase in MAPK activation in brain following systemic administration in mice an effect that was blocked by scopolamine, confirming central M1 muscarinic receptor agonist activity in vivo. The present study shows the muscarinic receptor agonist activities of ACP-104 are unique among antipsychotics, and provide a possible molecular basis for the superior clinical effects of clozapine. Furthermore this data suggests that ACP-104 alone may be an effective treatment of the psychotic and cognitive symptoms in schizophrenia.

DOPAMINE D2 RECEPTOR OCCUPANCY IN HEALTHY ADULT MALE HUMAN BEINGS TREATED WITH SM-13496 USING POSITRON EMISSION TOMOGRAPHY

D. F. Wong,* J. R. Brasic, H. Kuwabara, M. Alexander, A. Maini, A. K. Srivastava, R. Kassem, M. Ogasa
Radiology, Johns Hopkins Medical Institutions, Baltimore, MD, USA

SM-13496 is an atypical antipsychotic under development. The objectives of this study of healthy adult male humans are (1) to determine the dopamine D_2 receptor occupancy of SM-13496 at five single oral doses ranging from 10 to 80 mg, and (2) to investigate the relationship of the serum concentrations of SM-13496 to the brain dopamine D_2 receptor occupancy of SM-13496. Twenty healthy male humans, 18-35 years of age, underwent positron emission tomography (PET) for 90 min after the intravenous (IV) administration of [^{11}C]raclopride before and 90 min following dosing with SM-13496. Pharmacokinetic analyses were performed to determine serum concentrations of SM-13496 in samples on the day of dosing at the following times: prior to dosing, and 0.5, 1, 1.5, 2, 2.5 and 3 hours after dosing. Increased percent D_2 receptor occupancy in the putamen, caudate nucleus, and ventral striatum, is observed with each increase in SM-13496 dose up to 60 mg. Dose dependent increases in mean D_2 receptor occupancies were observed. Serum concentrations of SM-13496 increase in a dose-dependent manner peaking at 60 mg. Administration of SM-13496 result in dose-dependent receptor occupancy rates with the maximal receptor occupancy occurring in the 60 mg group. A relationship between serum concentration and D_2 receptor occupancy is demonstrated for both the parent drug and its major metabolite. The lowest dose of SM-13496, 10 mg, results in an average concentration of 3.36 ng/mL and occupancy rates of approximately 40%. The 60 mg dose group exhibits maximal receptor occupancies within the 75% to 85% range, while rates in the 80 mg group are somewhat lower, but still within the 70%-80% range. We conclude that in healthy adult male humans (1) mean occupancy of D_2 receptors correlates well with average peak serum concentrations of SM-13496 at doses up to 60 mg, (2) the mean D_2 receptor occupancy correlates better with the area under the curve (AUC) than with the

peak and average concentrations of SM-13496, (3) the mean concentrations of SM-13496 are proportional to the AUC of SM-13496, (4) the mean concentrations of SM-13496 are more stable than the peak concentrations of SM-13496, (5) at doses of 10 to 80 mg, SM-13496 occupies approximately 30 to 90% of D_2 receptors in the putamen, caudate nucleus, and ventral striatum regions. Sumitomo Pharmaceuticals America, Ltd. provides research funding.

20. Therapeutics: Psychosocial Trials

EARLY INTERVENTION IN ANTIPSYCHOTIC-INDUCED WEIGHT GAIN IN FIRST EPISODE PSYCHOSIS

M. Alvarez,* C. Gonzalez-Blanch, R. Perez-Iglesias, T. Perez-Pardal, O. Martinez-Garcia, B. Crespo-Facorro, J. L. Vazquez-Barquero
Department of Psychiatry, University Hospital Marques de Vadecilla, Santander, Cantabria, Spain

The aim of the study is to test the effectiveness of an early behavioural intervention in preventing antipsychotic weigh gain in a first episode psychosis sample that hadn't been previously treated with antipsychotic medication. In this clinical trial 61 patients, aged 16-45 years, whom had already been randomized to three different antipsychotic treatments (risperidone (N=23), olanzapine (N=18) and haloperidol (N=21)) were randomly allocated to either, an early behavioural intervention in weight gain (EBI, N=35) or routine care (RC, N=27). The EBI was specifically designed to address weight gain in first episode psychosis. It consisted on 8 flexible modules of treatment that included strategies to manage the main causes of weight gain. The different modules were progressively used depending on the initial assessment evaluation. The RC consisted on non-structured information and informal advice regarding weight gain. Weight and body mass index were calculated on a weekly basis for 12 weeks since the beginning of the pharmacological treatment. The outcomes were analysed by using two criteria: weight gain at 12 weeks, and proportion of patients that increase more than 7% of the initial weight at 12 weeks. At the completion of the study there were significant differences between the two groups in weigh gain by using both outcome measures. The average of weigh gain in the RC group was 4.1 kg whereas in the SBI group was 6.8 kg (p=0,01). In terms of percentage of weigh gain, 77.1% of the patients allocated to the RC group gained more that 7% of their initial weight in opposition to 40.7% of the patients in the SBI group (p=0,04). In the analysis carried out among pharmacological treatment groups we obtained similar findings. In the olanzapine group, 100% of the patients allocated to the RC group gained more that 7% of the initial weight compared to 66.7% in the EBI group (p=0,05). In the risperidone group 84.6% of the patients of the RC group gained more than 7% of weight against 30% in the EBI group (p=0,008). Finally, in the haloperidol group 53.8 of the patients in the RC group and 25% in the SBI gained more than 7% of their initial weight (p=0,195). Even though both groups showed weight gain, this increase is significantly smaller in the behavioural management group compare to ordinary advice regarding weight gain. The EBI intervention is effective in preventing weight gain independently from the pharmacological treatment.

EXERCISE IN PERSONS WITH SCHIZOPHRENIA

L. H. Beebe,* S. S. Allen, A. A. Goodwin, N. B. Morris, L. Tian, J. Kuldau
College of Nursing, Univ of FL, Gainesville, FL, USA

A pilot study of effects of 16-weeks of treadmill walking for veterans with schizophrenia. Subjects recruited from an outpatient clinic in the southeast. Inclusion criteria-diagnosis of schizophrenia, and medical clearance. Exclusion criteria-disorders that would prevent safe participation. Measures-six minute walking distance, body mass index, percent body fat and Positive and negative syndrome scale. Attendance-43% to 91%. 75% attended more than half of sessions. Exercisers had improvements in exercise capacity, reductions in body mass index and reductions in psychiatric symptoms. Exercisers experienced significant reductions in body fat ($p = 0.03$) as compared to nonexercisers. More research is needed to identify the most effective exercise interventions and the most feasible delivery modalities for persons with schizophrenia in community settings. This study supported by National Institute for Nursing Research through the Biobehavioral Research Center at the University of Florida College of Nursing.

Characteristics of veterans with schizohprenia (N= 10).

FUNCTIONAL OUTCOMES FROM A RCT OF COGNITIVE TRAINING AND WORK THERAPY: 12 MONTH FOLLOW-UP

M. D. Bell,* G. Bryson, T. C. Greig, J. M. Fiszdon, B. E. Wexler
Rehabilitation Research and Development Service, Department of Veterans Affairs, West Haven, CT, USA

Background: Cognitive deficits in schizophrenia are strongly associated with functional impairment. Neurocognitive enhancement therapy (NET) involves computerized cognitive training and other methods to improve attention, memory and executive function. Previous studies found that NET improved neuropsychological test performance and that gains were sustained six-months after training(1). Objective: The present study examines work outcomes when NET was added to a 6-month work rehabilitation program. Design: Randomized clinical trial. Setting: VA outpatient work rehabilitation program. Patients:145 outpatients with diagnoses of schizophrenia or schizoaffective disorder recruited from VA mental hygiene clinic and from a community mental health center. Interventions: 6-month paid Work Therapy (WT) and NET+WT. Main Outcome Measures: Hours worked, work status and Instrumental Functioning (QLS;2) for 6 months prior to intake, for 6 months of active rehabilitation, and for

6 months following rehabilitation. Results: Mixed random effects analyses revealed significant increase in hours worked over time for both conditions ($p < .0001$). NET+WT worked more hours than WT alone ($p < .05$), with differences greatest during 6 months after rehabilitation. Patients in NET+WT who reached normal-range digit recall performance after training worked the most during follow-up ($p < .01$). These responders to NET worked on average 390 hours during the 6 months following the intervention as compared to an average of 130 hours for WT subjects with normal-range digit recall ($p < .0001$). NET+WT responders showed a trend toward more competitive employment (odds ratio = 2.44, $p = .15$). Instrumental functioning showed significant improvement over time ($p < .0001$), but no differences were found between condition. Improvement in instrumental functioning in both conditions was sustained during follow-up. Conclusions: WT outcomes were enhanced after patients received NET training. Responders to cognitive training did best. Findings are consistent with models of neuroplasticity that predict gradual experience-based changes in brain function. Findings support efficacy of cognitive training when integrated into broader rehabilitation programs. 1. Bell MD et al. Neurocognitive enhancement therapy with work therapy: effects on neuropsychological test performance. *Arch Gen Psych*. 2001, 58:763-768. 2. Heinrichs DW et al. The Quality of Life Scale. 1984, *Schiz Bull* 10:388-398. Funded by VA RR&D.

BEHAVIORAL TREATMENT FOR SUBSTANCE ABUSE IN SEVERE AND PERSISTENT MENTAL ILLNESS

A. S. Bellack,* M. E. Bennett, J. S. Gearon
Psychiatry, University of Maryland, Baltimore, Baltimore, MD, USA

The purpose of this study was to evaluate a new intervention for drug abuse in patients with schizophrenia and other forms of severe mental illness. There is a broad consensus on a number of principles required for effective treatment of comborbid drug abuse, but there is a dearth of empirical data on effective techniques for producing change, and no approach meets criteria for an evidence based practice. We have developed a new, multifaceted treatment for substance abuse in dual disordered patients that addresses the specific problems and needs of this population: Behavioral Treatment for Substance Abuse in Severe and Persistent Mental Illness (BTSAS). This manualized intervention includes a urinalysis contingency, behavioral goal setting, social skills training, psychoeducation, and relapse prevention and problem solving training. It is administered in small groups, twice per week for 6-months. We have recently completed a randomized clinical trial to compare BTSAS with a standardized reference treatment, Supportive Treatment in Addiction Recovery (STAR). Subjects were 126 stabilized outpatients meeting criteria for serious mental Illness (SMI) (42.86% schizophrenia/schizoaffective, 50% Major Affective Disorder), and current dependence on cocaine (67.5%), heroin (24.6%), or cannabis (7.94%). The data provide strong support for the efficacy of BTSAS. It was significantly more effective than STAR in keeping subjects in treatment and having them attend sessions regularly, an important outcome for this population. Survival in BTSAS was 54% vs 32% in STAR (p=0.0282), and BTSAS subjects attended a mean of 54.4% of sessions, vs 35% for STAR (p=0.0042). Most importantly, subjects in BTSAS had significantly less drug use during the 6-month treatment period as evidenced by urinalysis conducted in each session. BTSAS subjects had a mean of 70% clean urines vs a mean of 51% clean urines for STAR subjects (p= 0.434). Subjects in BTSAS also had a significantly greater number of 4-week and 8-week periods of abstinence (4-week: BTSAS= 44.12% vs STAR= 8.82%, p=0.001; 8-week: BTSAS= 29.41% vs STAR= 2.94%, p=0.003). The data lend strong support for the efficacy of BTSAS. The in session urinalysis data are comparable or superior to findings from major clinical trials of drug abusing patients without comborbid psychiatric illness, and suggest the clinical importance of these findings. Plans for future research on BTSAS will be discussed.

THE MED-EMONITOR™ FOR IMPROVING ADHERENCE TO ORAL MEDICATION IN SCHIZOPHRENIA

S. Bendle,* D. I. Velligan, J. L. Mueller, B. V. Davis, J. L. Ritch, A. L. Miller
Psychiatry, UTHSCSA, San Antonio, TX, USA

Adherence to oral antipsychotic medication is important in preventing symptom exacerbation and rehospitalization for patients with schizophrenia. Unfortunately, adherence rates to even the novel antipsychotic medications are poor. The Med-eMonitor™(MM; InforMedix, Inc.) is a recently developed portable electronic device capable of storing a month′s supply of up to five different medications. The device prompts users when to take medication, reminds the patients of the goal of taking each medication, alerts them if they are taking the wrong medication or taking it at the wrong time, records when containers are opened, asks if medication has been taken following the opening of a compartment, and automatically downloads data to a secure web site when placed into a cradle connected to a telephone line. The monitor can also serve as an electronic patient diary, by asking a number of questions about side effects, symptoms, and quality-of-life on a regular basis. The web site provides daily reports of medication adherence, and patients′ responses to queries. Through these daily reports, if problem adherence and/or clinical deterioration are identified, treatment providers can intervene quickly. We provided this device to 10 schizophrenia outpatients for a period of one to two months. Adherence improved for all patients using the device. Subjects took an average of 90% of prescribed medications accurately compared to less than 50% when patients were followed without intervention. Queries as to the usefulness of the device were made regularly for each patient and a total of 67 queries were available for analysis. In 87% of these, patients reported that the MM was ″a lot helpful″ and in an additional 10% of queries, patients reported that the monitor was ″a little helpful.″ The Med-eMonitor may be a feasible way to improve adherence to medication and to assess medication compliance in schizophrenia patients. Potential uses include both clinical care and pharmaceutical research studies of novel medications. Funded by: R01 MH61775-04 and R01 MH62850-05.

RANDOMIZED CONTROLLED TRIAL OF TWO-YEARS INTEGRATED TREATMENT VERSUS STANDARD TREATMENT OF PATIENTS WITH FIRST-EPISODE OF SCHIZOPHRENIA OR PSYCHOSIS, FIVE YEARS FOLLOW-UP: THE OPUS TRIAL

M. Bertelsen
E, Bispebjerg Hospital, Copenhagen, Denmark

The trial is a single-blinded randomized clinical trial, comparing two-years integrated psycho-social treatment (IT) with standard treatment (ST) aimed at young people with first-episode of schizophrenia or psychosis. The integrated treatment consists of ACT (assertive

community treatment) specialized for first-episode patients. One- and two-year follow up of the cohort (n=547 patients) have demonstrated good effects on symptoms, abuse, housing situation, and education in the IT group compared with the ST group. There are evidence that psychotic symptoms develop differently and independently of each other during the course of the illness, and that the severity of negative symptoms and cognitive dysfunction have a greater impact on the outcome, than psychotic symptoms. According to the internationally operationalized criteria for the outcome of schizophrenia, I hypothesize in the five year follow up of the cohort, that a greater part of patients in the IT group have reached social recovery (no abuse, GAF score higher than 60, employment or working at an education, living independently or with parents) or full recovery(the same criteria and no symptoms at all for the last two years) compared to patients in the ST group. The results are preliminary.

A PSYCHIATRIC REHABILITATION APPROACH TO WEIGHT LOSS

C. Brown,* J. Goetz, A. Van Sciver
Occupational Therapy Education, University of Kansas Medical Center, Kansas City, KS, USA

Healthy People 2010 indicates that 65% of the adults in the United Stares are overweight or obese. (U.S. Department of Health and Human Services (USDHHS), 2000). People with serious mental illness are at greater risk for obesity due to poverty, limited access to health care, poor health behaviors and the side effects of antipsychotic medications (Allison et al, 1999; Dixon et al, 2000; Holmberg & Kane, 1999). This study examines the efficacy of a weight loss program for people with serious mental illness. The program innovation combines evidenced based weight loss strategies with psychiatric rehabilitation principles. The manualized program is designed to be easily implemented by mental health programs such as community mental health centers, community support programs, psychiatric rehabilitation programs and clubhouses. Baseline data for participants in the intervention pilot study indicates the need for such programs. Of those participating in the pilot study (n=44), 4.5% were categorized as normal weight, 11.4% overweight, 41.0% obese, and 43.2% extremely obese according to the guidelines outlined by the World Health Organization. The number of obese individuals is considerably higher than a national sample (84.2% vs. 30.5%) (Flegal, Carroll, Ogden & Johnson, 2002). Dietary analysis of 24-hour recall revealed that the typical diet of individuals participating in the pilot study was higher in fat, saturated fat, and sodium than is generally recommended. Further, the intake of fruits and vegetables was limited. Many of the participants were taking medications that are associated with an increased risk of obesity and diabetes: 83% were taking a new generation antipsychotic, 23% were on a selective serotonin reuptake inhibitor and 17% were on a mood stabilizer. A statistically significant difference was found between the two groups for weight loss. The intervention group lost a mean of 2.7 kg and the control group gained 0.7 kg. Seventeen (77%) of the intervention participants lost weight, and 6 (27%) participants had a weight loss > 5 kg. The reduction in energy intake for the intervention group was 405 kcal, close to the recommended 500 kcal for weight loss. Analyses also explored changes in behavior to determine the factors that contributed to weight loss.

PREDICTORS OF ENGAGEMENT IN SUBSTANCE ABUSE TREATMENT AMONG PATIENTS WITH SEVERE AND PERSISTENT MENTAL ILLNESS

C. H. Brown,* M. E. Bennett, A. S. Bellack, Y. Yang, V. Iannone
Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, MD, USA

Patients with severe and persistent mental illness (SPMI) show alarmingly high rates of substance use disorders. Although efforts are being made to develop and test treatments that are designed for this multiply-impaired population, treatment engagement, attendance, and adherence are considerably affected by dual diagnosis. A lack of research and variable assessment from study to study prevent drawing general conclusions about engagement failure. Specific areas of deficit experienced by SPMI patients that may contribute to engagement failure include: symptom severity, cognitive impairment, longstanding treatment and substance abuse histories, low motivation to change behavior, and extremely poor social functioning. This study examines the relationship of the above factors to engagement using data from an ongoing randomized stage 1b treatment development trial comparing two substance abuse treatment programs: one, a multi-faceted behavioral intervention and the other, a standardized "supportive" reference treatment. Patients treated at several sites including a VA hospital, had a substance abuse disorder and at least one other psychiatric disorder, with or without psychosis. Engagement is defined as attending at least 3 treatment group sessions. To date, out of 126 patients with current drug dependence who completed baseline assessments, 46% failed to become engaged. Preliminary analysis using a multiple logistic regression prediction model indicates an increased relative odds of engagement (adjusted odds ratio, [95% conf. intvl.]) for patients who: were randomized to the reference versus the behavioral intervention (2.6, [1.1, 6.2]), received treatment at a clinic other than the VA hospital clinic (2.9,[1.2, 7.1]), did not experience increased temptation due to negative symptoms (2.7, [1.1, 6.6]), visit friends rarely or never (1.6,[1.1, 2.4]), report a positive general feeling about their family (2.3,[1.1, 4.5]), and frequently get together with family members (1.4, [1.0, 2.0].) These results suggest that relationships with family and peers, negative symptoms, coordination among health providers, clinic, and patient, and characteristics of the treatment itself all influence engagement in dually diagnosed SPMI patients. One way to reduce obstacles to engagement, therefore, is to enlist the help of a family member or "concerned significant other" (CSO) and provide them with a skills-training/education program.

NEUROPSYCHOLOGICAL OUTCOMES FROM A RCT OF COGNITIVE TRAINING AND WORK THERAPY: 12 MONTH FOLLOW-UP

G. J. Bryson,* M. D. Bell, T. C. Greig, B. E. Wexler
Psychology, VACT Healthcare System, Newington, CT, USA

Background: Neurocognitive enhancement therapy (NET) involves computerized cognitive training and other methods to improve attention, memory and executive function. Previous studies found that NET improved neuropsychological test performance at the conclusion of six-months of training (Bell et al, 2001). Objective: The present study examines neuropsychological outcomes 6-month after the conclusion of rehabilitation. Design: Randomized clinical trial. Setting: VA outpatient work rehabilitation program. Patients: 145 out-

patients with diagnoses of schizophrenia or schizoaffective disorder recruited from a VA and a community mental health center. Interventions: 6-month paid Work Therapy (WT) and NET+WT. Main Outcome Measures: Neuropsychological performance at baseline, after 6 months of rehabilitation, and at 6 months follow-up. Results: Repeated measures MANOVA revealed greater neuropsychological improvements on working memory measures ($p < .02$) and on executive function measures ($p < .02$) for the NET+WT condition. Comparison of conditions using linear trend analyses of individual variables showed significantly greater improvement over time for NET+WT on Digits Backwards ($p < .05$), Digit Symbol ($p < .05$) WCST Percent Conceptual Level ($p < .002$) and WCST Categories Complete ($p < .05$). Both conditions showed significant improvement over time on verbal memory ($p < .005$) and visual memory ($p < .000$) but there was no condition by time effect. Individual variables showing significant linear trends for both groups over time were Logical Memory (LM) I ($p < .000$) LM II ($p < .000$), Hopkins Verbal Learning Test (HVLT) 1 ($p < .000$), HVLT 3 ($p < .000$) and Visual Reproduction II ($p < .000$). Plots of all variables where NET+WT showed greater improvements than WT had a similar pattern of rapid improvement during rehabilitation and plateau or small continued increases for the NET+WT condition during follow-up. Conclusions: NET+WT yielded greater neuropsychological benefits than WT on working memory and executive function. Verbal and visual memory significantly improved with work therapy whether or not it was combined with NET. Improvements generally endured six-months after rehabilitation was completed. Findings support efficacy of cognitive training of neuropsychological functioning and indicate the durability of effects over time. It is possible that work therapy alone may also produce verbal and visual memory improvements. Funded by VA RR&D.

IS THERE A LINK BETWEEN COMPLIANCE, INSIGHT, AND ATTITUDE TOWARD TREATMENT IN SCHIZOPHRENIA?

C. Buhl,* E. Corruble, P. Hardy
94, CHU Bicetre- AP-HP, Kremlin-Bicetre, France

Rationale: Non compliance is one of the most important variables contributing to relapse in schizophrenia[1]. In schizophrenia, compliance and attitude toward treatment are strongly linked to each other [2][3]. Besides these results, the link between insight and compliance to antipsychotics remain uncertain. The goal of our study is to investigate, if these three dimensions (i.e. insight, attitude toward treatment and compliance) are linked to each other. Methods: In a transversal study, 50 patients with schizophrenia or schizo-affective disorder (DSM-IV) were assessed for insight, subjective attitude towards antipsychotics and compliance. The insight measures used were David's Schedule of Assessment of Insight (SAI-E)[4] and the «lack of judgment» PANSS item. Subjective attitude towards treatment was rated using the Drug Attitude Inventory(DAI)[5]. Compliance was rated using a semi-quantitative four point auto-evaluation scale. Spearman correlations were performed between these variables. Results: Results are shown in Table 1. Our results failed to evidence a correlation between drug attitude and insight. Patients assessed compliance correlated with DAI scores but not with insight measures. Conclusion: Insight and drug attitude may not be linked in schizophrenia. Our results may be due to methodological reasons. If our results were to be replicated, improving insight would not be an efficient strategy to improve attitude toward treatment and compliance to antipsychotics. Factors influencing compliance in schizophrenia need further investigations. References 1. Marder S.R., Overview of partial compliance, *J Clin Psychiatry*, 2003;64[S16]:3-9. 2. Fleischhacker W.W., Oehl A.A., Hummer M.: Factors influencing compliance in schizophrenia patients, *J Clin Psychiatry*, 2003; 645[S 16]: 10-13. 3. Cabeze IG, Amador M.S., Lopez C.A., Gonzalez de Chavez M.: Subjective response to antipsychotics in schizophrenic patients: clinical implications and related factors. *Schizophr Res*, 2000; 41(2): 349-355. 4. David AS et al: The assessment of insight, *Br J Psychiatry*, 1992; 161: 599-602. 5. Hogan et al: A self report scale predicitive of drug compliance in schizophrenics, reliability and discriminative validity, *Psychol Med*, 1983; 13:177-183.

Table 1: Results

THE EFFECTIVENESS OF SUPPORT GROUPS FOR PEOPLE SUFFERING FROM PSYCHOSIS: A MULTI-CENTER RANDOMIZED CONTROLLED TRIAL

S. Castelein,* R. Bruggeman, J. T. van Busschbach, M. van der Gaag, P. J. Mulder, H. Knegtering, D. Wiersma
Psychiatry, University Hospital Groningen, Groningen, Netherlands

Patients suffering from psychosis often display the need of peer support groups to learn to cope with daily life problems. In recent years we developed a method using group sessions with only minimal professional guidance. Aim of the present study is to investigate the effectiveness of these peer support groups on social support, social contacts, self-efficacy, self-esteem and quality of life. In addition, patients and professional evaluated the prescribed methodology. This multi-center randomised controlled trial compares five peer support groups with waiting-list comparison groups over a 8 months period. Social support, social contacts, self-efficacy (Mental Health Confidence Scale, MHCS), self-esteem (Rosenberg) and quality of life (WHO-Qol BREF) are assessed before the beginning and again at the end of a series of 16 sessions. Group processes are registered by the professionals. Long-term effects will be evaluated in a follow-up study. One-hundred-nineteen patients have been included: 78 men and 41 women (mean age: 39 yrs; mean duration of illness: 10 yrs). Of these patients 17 % had suffered from 1 psychosis, 51% two psychosis and 32% had three or more psychosis. Of this ongoing study, we here describe the preliminary results of two of the experimental groups and their controls (n=50). In the peer support group patients reported significantly more social contacts ($p=0.035$) and experienced more social support in comparison with the control group. At the end of the study participants of the peer support group reported improvement or much improvement in insight and knowledge in problems of fellow-sufferers (82- 89%), in solidarity (64%), in recognition (79%), and in insight in their illness (67%). On the MHCS in the experimental group the domain advocacy had increased significantly within the group ($p=0.007$, n=27), but not in comparison with the control group. As yet, differences on quality of life and self-esteem were not found in either condition. Evaluation of the methodology underscored the importance of professional guidance for the continuance of the group process (92%, n=25). With regard to the

methods used in this intervention patients reported an overall satisfaction. This study was granted by ZONMW, The Netherlands Organisation for Health Research and Development.

PSYCHOEDUCATION FOR FAMILY MEMBERS OF FIRST EPISODE PSYCHOSIS: THE OPINION OF RELATIVES

A. C. Chaves,* R. F. Cabral
Psychiatry, Federal University of Sao Paulo UNIFESP-EPM, Sao Paulo, Brazil

background: Patient's family members are considered an important part of evaluation, treatment and recovery in psychosis. Family Psychoeducation interventionsin schizophrenia have improved psychiatric treatment compliance and have reduced the psychosis relapse rate. Nonetheless, in first episode psychosis, the family interventions studies have shown contradictory results. Differences in sample criteria and study design make the comparison between difficult. Moreover, there is no agreement in the literature which information should be delivered and what participants think about intervention content and utility. Methods: From January 2002 to June 2003, 65 family members of 46 first episode patients were involved in psychoeducational family intervention as a part of an outpatient first episode psychosis program in Sao Paulo, Brazil. To evaluate the relatives view and satisfactions with the intervention, they answered a questionnaire after six weely sessions. Results: Thirty-one women (77.5%) and 9 (22.5%) men answered the questionnaire. Most of them (82.5%) had daily contact with the patient and 19 (47.5%) were mothers. In relation to knowledge acquisition, around one-third did not improve their understanding about the illness, about symptoms definitions and their relationship with the patient's behavior. Ninety percent of the participants felt the meetings useful to cope better with their ill relative and found helpful to hear other families talk about their experiences. Conclusions: the results showed that the nonspsecific aspects of the intervention as to give help and support were approved by most of the sample. However, the specific psychoeduaction components did not have the same approval. Before conducting a randomized controlled trial the treatment team should improvr these intervention issues.

PRACTICAL PATIENT CENTEREDNESS IN SCHIZOPHRENIA RESEARCH-REFLECTIONS ON THE SONAR STUDY

A. M. Cheetham,* T. G. Calton
Psychiatry, Nottinghamshire Healthcare NHS Trust, Nottingham, Nottinghamshire, United Kingdom

Background: The concept of patient centeredness within mental health has been incorporated into both UK and international governmental policy on mental health provision. Our group's research suggests most schizophrenia research is not patient centered. If patient centeredness is to be embraced it should be reflected in both the CONTENT and PROCESS of research. This abstract reflects on measures taken during the SONAR study to promote patient centeredness. *The SONAR study*: The Study Of Nottingham youth At Risk cleaves to the 'high risk' paradigm employing clinical, neuropsychological and neurophysiological assessments (EEG & fMRI) to elucidate risk factors for adolescent onset schizophrenia. The study compares young people with a diagnosis of schizophrenia, their 'high risk' siblings and healthy controls with the aim of identifying specific risk indices. *Practical patient centeredness* Empowerment and choice: interviews take place at weekends and evenings at patients' convenience. Breaks are encouraged and rest facilities provided. Options for travel are provided e.g. refunded taxi or collection by investigator. The emphasis here is to constantly strive to ensure that participants feel in control of the research experience. Investigator empathy: all investigators have undergone EEGs and fMRI scans to allow them to fully inform the patient as to the nature of these experiences. This 'humanises' the research technology and fosters trust. Language:medical jargon is eliminated and real-world examples are used e.g. drawing analogies between EEGs and heart traces seen on television. This helps to demystify the research process and grounds it in everyday experience. Information and feedback: in addition to verbal and written information, a participant-orientated website has been set up. Information is provided in a sensitive and participatory manner, guided by the patient's existing knowledge. This is particularly important given the ethical issues inhering on the subject of risk. Participants are invited to seek feedback at every stage, thereby increasing their sense of ownership of the research. Peer referee system: selected participants have been asked to act as peer referees to provide information to potential participants. This consolidates trust and treats the participants as experts. Being reflective and reflexive: we invite participants to complete a questionnaire about their experience of undergoing EEG and fMRI, and have used this to improve practice.

AN EDUCATIONAL INTERVENTION DESIGNED TO IMPROVE TREATMENT ADHERENCE IN SCHIZOPHRENIA

A. A. Collins,* G. J. Remington
Schizophrenia Program, Centre for Addiction and Mental Health, Toronto, ON, Canada

Poor medication adherence, which is reported to occur in up to 80% of outpatients, is one of the major determinants of outcome in schizophrenia. Notably, Bauml et al. (1993) found that patient adherence could be improved by 30% and first year readmission rates reduced by 20% after employing a series of eight educational sessions. Thus, there is reason to believe that adherence improving strategies like education have potential for reducing health care costs and the personal suffering that schizophrenia imposes. Subjects for this study were individuals with prospectively confirmed schizophrenia or schizoaffective disorder using SCID, who agreed to participate in the project. Subjects were between the ages of 18-65, taking oral antipsychotics, and competent to consent voluntarily to participate. Exclusion criteria included: patients treated with clozapine, any physicial condition which could compromise neurocognitive function and/or depot antipsychotic use within the last 6 months. Following initial screening and pre treatment assessment, eligible subjects were randomly assigned to receive either standard care or standard care plus education. The educational intervention consisted of 1.5 hour meetings each week for a total of 6 weeks. Each presentation provided didactic information, in combination with case material to highlight key points. Results indicate that there were no significant between group differences at baseline on any of the variables. However, it is noteworthy that at the 3 month follow up, patients who participated in the education group were significantly more adherent and less symptomatic than those who received standard care.

INTERACTION OF THERAPEUTIC ALLIANCE AND WORK PERFORMANCE IN SCHIZOPHRENIA

L. W. Davis,* P. Lysaker
Roudebush VA Medical Center, Indianapolis, IN, USA

While therapeutic alliance in schizophrenia has been linked with treatment adherence and outcome, less is known about whether it is related to outcome in rehabilitation. To examine this question we compared the work performance of twenty-six persons with SCID-I confirmed diagnoses of schizophrenia or schizoaffective disorder in a six-month vocational rehabilitation program with higher vs. lower levels of therapeutic alliance in individual cognitive behavior psychotherapy. Trained raters blind to work performance observed and rated a mid-program videotaped therapy session using the Working Alliance Inventory, Short Form (WAI-S) to assess therapeutic alliance. Work performance was measured at three time points: week 1, week 11 and week 23 of the rehabilitation program. Trained raters blind to therapeutic alliance obtained rated five dimensions of participants' work behavior at each time point using the Work Behavior Inventory: Social Skills, Cooperativeness, Personal Presentation, Work Habits and Work Quality. Participants were placed into a higher or lower therapeutic alliance group based on a median split on the WAI-S resulting in 13 participants per group. Using a repeated measures analysis of variance group effects were found for Work Quality ($F=3.49, p<.05$) and Personal Presentation ($F=4.6, p<.05$) with the higher therapeutic alliance having overall better work performance on both. Time effects were found for Work Quality ($F=3.47, p<.05$) and Personal Presentation ($F=7.2, p<.05$) with the sample overall showing improvement over the course of rehabilitation. Interactions were found for Cooperativeness ($F=3.46, P<.05$) and Work Quality ($F=5.8, p<.05$) with the higher therapeutic alliance group showing steady increases in these domains and the lower therapeutic alliance group showing initial improvement followed by a decline. Results suggest that therapeutic alliance is linked to performance in rehabilitation. There are three possible interpretations, none of which are mutually exclusive. It may be that stronger therapeutic alliance assists persons to sustain initial gains and to continue to improve in rehabilitation. It is also possible that counselors form strong therapeutic relationships with persons who also do well in rehabilitation. It is thirdly possible that the observed relationships here are the results of other factors not measured. Future research employing more frequent assessments of therapeutic alliance and rehabilitation outcome is planned.

AN OBJECTIVE ASSESSMENT OF FUNCTIONAL OUTCOME IN SCHIZOPHRENIA

S. Dube,* L. Frank, L. Kleinman, L. Matza, D. Revicki, Y. Zhao, L. Bowman, B. Kinon, R. Mohs
Eli Lilly and Company, Indianapolis, IN, USA

Recent studies demonstrate that symptomatic and cognitive impairments seen in patients with schizophrenia impair multiple domains of function such as social functioning, employment status, living status, and instrumental activities of daily living (Addington & Addington 2000; Bell & Bryson 2001; Bryson & Bell 2003; Bryson et al. 1998; Green et al. 2000; Kasckow et al. 2001; McGurk et al. 2003; Palmer et al. 2002; Sharma & Antonova 2003). None of existing instruments (e.g., Level of Function Scale and Quality of Life Scale) used for assessing various aspects of functional status in schizophrenia (Cramer et al. 2000; Heinrichs et al. 1984) are optimal. While those relying on self-report may be unreliable (Fitzgerald et al. 2001; Khatri et al. 2001), many others are influenced by schizophrenia symptomatology itself. Few, if any, address objective indices of functioning, and none are designed to measure change in function over time. Because cognitive deficits are correlated with functional outcomes (Green et al. 2000) and cognitive benefits are a target for developing newer treatments for schizophrenia (Purdon et al. 2000), it is important that future clinical trials assess the functional implications of these cognitive improvements. We are developing a new, objective measure of functioning for patients with schizophrenia in long-term clinical trial settings. Aiming to objectively document the actual level of functioning, as opposed to capacity of function or qualitative judgments of the level of function, the instrument is evolved from existing scales used in patients with schizophrenia but extends them by quantifying objective, observable functioning along specific domains. This process included a review of literature on measurement of functional status in schizophrenia, expert panels, and review of clinical relevance. The instrument focuses on four key domains: living situation, self care/instrumental activities, productive activities/role functioning, and social functioning. Each domain is rated on a global score of 0 to 100 with higher scores indicating better functioning. Prior to completing the global rating, several dimensions (such as competence, independence, stability, degree of assistance) are evaluated for each domain, using a semi-structured interview format with patients, informants and any other source of information including patients charts, and scored with closed-ended Likert scaled items.

VALIDATION OF A PHYSICAL ACTIVITY ASSESSMENT TOOL FOR INDIVIDUALS WITH SCHIZOPHRENIA

G. E. Faulkner,* T. Cohn, G. Remington
Faculty of Physical Education and Health, University of Toronto, Toronto, ON, Canada

In adopting a behavioural epidemiological framework to understanding physical activity in individuals with schizophrenia, the critical first step is to develop methods for accurately measuring physical activity. There is a need to develop low cost, practical and accurate measures of physical activity in individuals with schizophrenia and self-report is one promising methodology. However, no validated tool currently exists for assessing physi-

cal activity in this population. The purpose of this study was to assess the reliability and validity of the International Physical Activity Questionnaire (IPAQ) Short-Form (Craig et al., 2003) using standard validation procedures. Participants were thirty individuals with diagnosed schizophrenia recruited from outpatient services at the Centre for Addiction and Mental Health, Toronto. To assess reliability, participants completed the IPAQ twice over a one week period (test-retest repeatability). Validation of self-reported activity levels used objective data collected by RT3 Tri-axial research trackers (motion detectors). To assess criterion validity, the physical activity from the self-report IPAQ was compared with the RT3 objective measure of physical activity recorded over seven days. Additionally, participants were asked to recall their physical activity over 7, 3 and 1 day periods. Accelerometers were found to be a suitable tool for measuring physical activity in individuals with schizophrenia and their use supported previous studies suggesting that this population is less active than the general population. Preliminary results found adequate reliability and validity coefficients for the IPAQ in terms of repeatability (Spearman's correlation coefficient > 0.8) and in comparing self-report and objective levels of physical activity (Spearman's correlation coefficient > 0.4). However, validity coefficients worsened from the one day to the seven day recall format. Overall, our data indicate that the IPAQ short-form has adequate reliability and validity to use in research on physical activity in individuals with schizophrenia over three day recall periods. References Craig, C.L, Marshall, A.L., Sjostrom, M., et al. (2003). International physical activity questionnaire: 12-country reliability and validity. *Medicine and Science in Sports and Exercise*, 35, 1381-1395. This research is supported by a pilot project grant funded by The Canadian Institutes of Health Research (CIHR).

DIFFERENCES BETWEEN FAMILIES WHO STAY INVOLVED VS. THOSE WHO DO NOT FOR PATIENTS WITH SCHIZOPHRENIA

S. M. Feldman,* D. L. Kelly, Y. Yu, E. Gale, R. R. Conley
TRP, Maryland Psychiatric Research Center, Baltimore, MD, USA

It is known that family relationships and education concerning mental illness may play a significant role in course of illness and utilization of services. Patients whose families refuse to become involved have been shown to have higher rates of noncompliance. This study examined factors associated with the involvement of family members in the lives of an individual who has schizophrenia. Participants in this study were inpatients who were divided into two cohorts: involved(N=29) or non-involved families(N=9)based on scores on the Quality of Life scale. Patients who had involved families were 11 years younger than the non-involved group (P=0.05). Twenty-eight percent of the patients with involved families were female as were 33% of the group with non-involved families. Female patients had less contact with family and Caucasian patients were 10% more likely to have an involved family. Families who were involved tended to have a greater frequency of psychiatric illness and medication use within their families. Those involved also were more likely to have completed high school compared to the non-involved families. This study confirms that education seems to play a role in families' ability to remain involved in the lives of their ill relatives and that this involvement leads to improved clinical outcomes for the patient with schizophrenia.

COGNITIVE TRAINING OF VERBAL MEMORY USING A DICHOTIC LISTENING PARADIGM: IMPACT ON SYMPTOMS AND COGNITION

J. Fiszdon,* H. Whelahan, G. J. Bryson, B. E. Wexler, M. D. Bell
Rehabilitation Research and Development Service, VA Connecticut Healthcare System, West Haven, CT, USA

The goal of the current study was to investigate the impact of a verbal memory training task on psychiatric symptoms and cognition in schizophrenia. Since successful performance on the dichotic listening (DL) task requires selectively and willfully ignoring distracters and attending to verbal information, we reasoned that training would be associated with greater improvements in psychiatric symptoms, hallucinations specifically. Additionally, since the task requires selective attention and accurate verbal recall of story material, we hypothesized that training would be associated with improvements on a measure of attention and a measure of verbal story recall. As part of a larger, 6-month cognitive remediation program, 57 patients with schizophrenia were randomly assigned to receive performance-based, hierarchical training on a verbal memory task based on a dichotic listening with distracter paradigm. These patients were compared to 68 patients who had been randomly assigned to a control condition of the protocol. Analyses of covariance, with pre-post training difference score as a between-subjects variable, indicated no group effects for either general psychopathology as assessed by the PANSS ($F(123, 1) = .97$, $p = .33$), nor for auditory hallucinations specifically, as assessed by the SAPS auditory hallucinations item ($F(123, 1) = .32$, $p = .57$). A significant group effect was found for the verbal memory measure ($F(124, 1) = 4.01$, $p = .04$), but not the attention measure ($F(123, 1) = 1.48$, $p = .23$). The current investigation adds to the growing literature on the effectiveness of cognitive remediation training and indicates that training on the DL task enhances verbal episodic memory. The results do not, however, support the use of DL training as a method for reducing auditory hallucinations, as training was not significantly associated with symptomatic changes. Future studies of cognitive training interventions for auditory hallucinations may benefit by examining not only symptom intensity, but also the ability to willfully divert attention away from auditory hallucinations and toward appropriate stimuli. Research supported by grant from the Veterans Administration RR&D Service.

COGNITIVE-BEHAVIORAL TREATMENT APPLICATIONS IN INDIVIDUALS WITH CHRONIC SCHIZOPHRENIA

M. L. Gaither,* D. Nazzaro, S. Huegel, A. Jacoby, G. Haas
VA Pittsburgh Healthcare System, Pittsburgh, PA, USA

Purpose: In recent years, cognitive-behavioral interventions have been adapted for treatment of positive symptoms in schizophrenia. The purpose of the current study was to evaluate a brief, cognitive-behavioral intervention (COPE-Adapt) for the chronic phase of schizophrenia. The COPE treatment incorporates cognitive-behavioral techniques that target individualized goals and subjective well being. It was hypothesized that this brief treatment would potentially reduce patients' subjective psychiatric distress. Experimental design and methods: To date, 47 outpatients diagnosed with schizophrenia or schizoaffective disorder have been randomly assigned to either: (1) COPE-Adapt or (2) a Current Events (CE) control condition. Participants in both conditions meet weekly for 30-minute sessions over 15 weeks. Clinical assessments (SAPS, SANS, BDI, GAS,

CGI, SCL90-R, QLS, HAM-D, BPRS, SUM-D, ISOM) are conducted at baseline, week 8, week 15, and 3-month follow-up. Preliminary results: To date, preliminary results have been analyzed for the first twenty-four subjects. Repeated measures analyses of variance indicate a significant decrease in depressive symptoms (on the BDI) from baseline to 8 weeks ($p<.03$), and from baseline to 15 weeks ($p<.001$) Likewise, BPRS ratings showed a significant decline in symptomatology from baseline to 15 weeks ($p<.05$). Interestingly, there was no treatment effect on any of the symptom domains. Conclusions: Although we did not find treatment effects as hypothesized, we did find that brief (15-week), minimal contact (30 minutes) interventions, whether COPE or CE, were associated with significant decreases in symptom severity. Additionally, relevant research (Sensky et al., 2000) on cognitive interventions in schizophrenia have shown that overall gains in symptoms may not appear until several months after treatment onset. This project was supported by funds from the VISN 4 Competitive Pilot Project Fund and the VISN 4 Mental Illness, Research, Education, and Clinical Center (MIRECC), Department of Veterans Affairs. References Sensky, T., Turkington, D., Kingdon, D., Scott, J. L., Scott, J., Siddle, R., O'Carroll, M., & Barnes, T. R. E. (2000). A randomized controlled trial of cognitive-behavioral therapy for persistent symptoms in schizophrenia resistant to medication. *Archives of General Psychiatry*, 57, 165-172.

EFFECTS OF COGNITIVE REMEDIATION ON SUPPORTED EMPLOYMENT: A RANDOMIZED CLINICAL TRIAL

T. C. Greig,* W. Zito, B. Wexler, M. D. Bell
Psychiatry, Yale University, New Haven, CT, USA

The purpose of this study is to determine if cognitive remediation leads to improvement in work outcomes in a comprehensive rehabilitation program for people with schizophrenia. Participants (N=64) were randomly assigned to one of two conditions: Neurogcognitive Enhancement Therapy (NET; 1) plus Supported Employment (SE) or SE alone. NET is comprised of 3 parts: 1) Cognitive remediation in which particpants are paid minimum wage to engage in up to 10hrs/wk of computer-based cognitive training exercises targeting attention, memory, and executive function. 2) A work group in which job specialists from SE provide individualized structured feedback using the Work Behavior Inventory (WBI; 2). 3) A Social Information Processing (SIP) group in which members are required to make oral presentations, ask questions and provide constructive feedback to the speaker. In contrast, the participants assigned to the SE group attend 2 non-cognitive groups per week and participate in the same SE program as NET participants, working up to 20 hrs/wk for 1 year in a community setting and receiving minimum wage. ANCOVAs were used to compare initial WBI ratings with ratings at the end of the active intervention. There was significantly greater improvement for the NET+SE condition on the WBI total score ($F(1,51)=4.10$, $p<.05$) and three of the WBI subscales: social skills ($F(1,51)=4.49$, $p<.05$), cooperativeness ($F(1,51)=3.95$, $p<.05$), and personal presentation ($F(1,51)=3.93$, $p<.05$). At the end of 1 year there were no significant differences between conditions in hours worked. At the end of 2 years, there were group differences in work hours. with NET+SE working significantly more hours than SE ($F(1,40)=4.39$, $p<.05$). These findings suggest that a comprehensive rehabilitation program including NET yields greater functional improvements than SE alone. Greater work performance improvements in the first year were followed by more work hours in the second year for the NET+SE group suggesting that the rehabilitation benefits of NET are maintained even after the active intervention ends. In keeping with models of neuroplasticity that posit activity-induced brain changes, cognitive training may need to be intensive and prolonged to be effective, but benefits may continue after training is completed. 1. Bell MD et al. NET with work therapy: *Arch Gen Psych*. 2001, 58:763-768. 2. Bryson et al. WBI. *Psychi Rehab J*. 11997 20:47-55. Funded by grants from VA RR&D and NIMH to Dr. Bell.

PERFORMANCE-BASED FUNDING OF SUPPORTED-EMPLOYMENT: A MULTI-SITE CONTROLLED TRIAL

M. E. Griss,* J. H. McGrew, J. K. Johannesen, D. L. Born, C. Katuin
Psychology, Indiana University Purdue University Indianapolis, Indianapolis, IN, USA

Background: Supported Employment (SE) has been identified as an evidence-based practice in the treatment of individuals with severe mental illness. Although SE is generally more effective than other vocational models, there is considerable variability in outcomes and in the faithfulness of implementation of SE across programs. Evaluations of SE services in Indiana have identified 2 critical problem areas in client outcomes: (1) individuals were increasingly being employed in service jobs and decreasingly in career-oriented jobs, and (2) job placements tended to be short term, with few lasting as long as 9 months. To help foster better long-term outcomes, the SECT center, Vocational Rehabilitation Services (VRS), and the Indiana Division of Mental Health and Addictions (DMHA) proposed the implementation of a results-based funding (RBF) system, in which providers received payment only when clients successfully attained each of 5 employment milestones. We present the results of a multi-site controlled trial of RBF vs. a traditional fee-for-service (FFS) model. Method: The sample included N = 122 (RBF = 81, FFS = 41) consumers of SE (52% schizophrenia, 35% mood disorder). Assessments of clinical and life outcomes were conducted quarterly across 12 months. Results: Although time required to attain employment was equivalent between conditions, those in RBF were more likely to attain each milestone, particularly completion of a person-centered plan and 9-months of employment. However, there were few differences between those in RBF and FFS on non-milestone employment variables (e.g., job match, wages) or on most clinical measures (e.g., quality of life, functioning). Two meaningful differences include identification of more barriers to employment and greater clinical service use outside of SE for those in FFS, both of which negatively correlated with milestone attainment across the entire sample. Consistent with findings on the importance of accelerated employment placements, there was a trend for RBF consumers to more rapidly achieve a person-centered plan and 5 days of employment. Conclusions: Results indicate that RBF produces better overall milestone outcomes. However, vocational improvements with RBF were limited to those specified (e.g., 9 months of employment) and did not generalize to changes in broader areas targeted by psychiatric rehabilitation.

VARIABLES INFLUENCING PATIENT OUTCOMES IN SCHIZOPHRENIA

A. Hofer,* S. Baumgartner, M. Edlinger, M. Hummer, G. Kemmler, M. A. Rettenbacher, W. W. Fleischhacker
Biological Psychiatry, Medical University Innsbruck, Innsbruck, Austria

The present study examined the relationships of psychopathology, side effects, and sociodemographic factors with treatment outcomes

in terms of patients' functioning, needs and quality of life (QOL). Sixty outpatients with schizophrenia who had a duration of illness over two years and had been treated with either clozapine or olanzapine for at least six months were investigated. Apart from the registration of demographic data, various rating scales were used: the Positive and Negative Syndrome Scale, the UKU Side Effect Rating Scale, the Drug Attitude Inventory, the Berliner Beduerfnisinventar, and the WHOQOL-BREF. Most psychopathological symptoms as well as psychic side effects, weight gain, and female sex were negatively associated with QOL, while cognitive symptoms and treatment with olanzapine correlated with higher QOL. Age, education, depression/anxiety, negative symptoms, and psychic side effects were predictors of patients' needs for care. Older patients more often lived in a stable partnership and/or independently. Female sex, cognitive symptoms, and parkinsonism negatively influenced the patients' occupational functioning. Living independently was negatively associated with negative symptoms. Our results highlight the complex nature of patient outcomes in schizophrenia. They reemphasize the need of targeting effectiveness, i.e. both symptomatic improvement as well as drug safety, in such patients.

RESEARCH INTERVIEWS AND THEIR THERAPEUTIC EFFECT: A POSSIBLE CONFOUNDING ELEMENT IN PSYCHIATRIC RESEARCH METHODOLOGY

D. C. Kelly,* K. Elkins, S. Leicester, M. Dell'Olio, L. Tennakoon, C. Stanford, L. Phillips
PACE Clinic, ORYGEN, MARIBYRNONG, VIC, Australia

Background: There is a paucity of research into the suggestion that interviews conducted by postgraduates with a background in psychological practice and/or in possession of rapport building skills will confound investigations into the benefits of particular therapies. Research interviews often depend on techniques akin to so-called befriending and cognitively based therapies, particularly in long-term investigations. In monitoring and reflecting upon their experiences, research participants are often asked therapeutically significant questions such as their level of distress or reactions to stimuli. Objectives: To highlight the dynamics of relationships between research interviewers and research participants, and how such a rapport may affect larger research questions. Method: At this point a review of limited literature in the field and the subjective opinions of those involved in research at the ORYGEN Research centre in Melbourne will serve as our starting point. Interviews with researchers and participants are expected. Discussion: The possibility that the results of any research projects in which interviews are conducted on a regular basis independent of therapeutic inquiries may confound the research aims is worthy of further inquiry. As yet, there seems to be little data on the reality of such a suggestion despite anecdotal support. Personally, researchers have acknowledged the reality of such concerns, along with concomitant emotional burden often experienced by other therapists or investigators involved in official treatment of clients participating in research. Also, clients can often make little distinction concerning the qualifications or roles of those staff they come into contact with, despite attempts to highlight this differentiation. Such circumstances can give rise to confounding elements such as a potential for alliances, splitting and conflicting data. Another variable may be a psychologically trained interviewers difficulty in remaining neutral when confronted with client distress, passivity or distortion.

EXTENSIONS OF ERRORLESS LEARNING FOR SOCIAL PROBLEM-SOLVING DEFICITS IN SCHIZOPHRENIA

R. Kern,* M. F. Green, S. S. Mitchell, A. Kopelowicz, J. Mintz, R. P. Liberman
Psychiatry and Biobehavioral Sciences, UCLA, Los Angeles, CA, USA

There is a clear need to develop psychosocial rehabilitation methods that compensate for neurocognitive deficits common to persons with severe and persistent mental illness. Errorless learning (EL), a compensatory training intervention, has been successful for teaching entry-level job tasks. However, EL's applicability to broader, more complex functions is unknown. The present study tested the extension of EL to social problem-solving skill deficits in schizophrenia. Sixty clinically stable outpatients with schizophrenia or schizoaffective disorder were stratified by gender and level of memory impairment prior to randomization to training group (EL vs. symptom management). Groups were matched for training time, format and structure of training, and types of teaching aids used. Social problem-solving ability, measured by the Assessment of Interpersonal Problem-Solving Skills (AIPSS), was assessed at baseline, within two days after training, and three months later. Dependent measures were AIPSS scores for Receiving, Processing, and Sending skills. A repeated measures ANCOVA was conducted for each dependent measure with baseline AIPSS scores entered as covariates. For all three skills, there was a significant training group effect favoring EL. Durability of EL training effects extended to the three-month follow-up for Processing and Sending, but not Receiving skills. Results support the extension of EL to complex skills such as social problem-solving in the rehabilitation of persons with schizophrenia.

THE ACE PROJECT: A RANDOMISED CONTROLLED TRIAL OF CBT VERSUS BEFRIENDING FOR ACUTE FIRST EPISODE PSYCHOSIS: ACUTE PHASE RESULTS

E. Killackey,* H. Jackson, P. McGorry, S. Bendall, K. Allott, T. Johnson, J. Gleeson, S. Harrigan
ORYGEN Research Centre, Melbourne, VIC, Australia

Aims: The ACE project was a RCT involving 62 patients with a first episode of psychosis who were registered with ORYGEN. They were randomly assigned to either a Befriending condition or a CBT intervention known as Active Cognitive Therapy for Early Psychosis (ACE). The aim of the study was to determine whether treating patients in the acute treatment phase with CBT would lead to a faster decrement and more sustained improvement in positive and negative symptoms, and improvement in quality of life, as well as lead to a reduction in relapse as measured at 1-year follow up. Methods: All patients were treated within the ORYGEN service and medication was standardised across both conditions. All patients received the same range of treatment services, including low dose medication and case management. Two therapists treated patients across both conditions and patients could not receive any more than 20 sessions within 10-14 weeks. Patients were assessed by an independent rater on a range of measures of symptoms and adjustment - at baseline, the middle, the end of treatment and at 1 year follow up. An independent pair of raters assessed treatment fidelity. Results: Data at the midpoint assessment showed positive effects on the eight primary measures and all favouring ACE, although the results did not always achieve statistical significance. Effect sizes were in the moderate to

large range (.4-.8). At 10-12 weeks once treatment had been completed, although there were still positive effects favouring ACE, they were less significant statistically. Discussion and Conclusions: The results support the efficacy of CBT approaches in the acute phase of first episode psychosis, and more specifically, in the first half of the acute treatment phase. In the current study, ACE accelerated recovery in the first 5-6 weeks of the acute treatment phase.

GROUP CBT FOR PERSECUTORY DELUSIONS: WILL LEARNING TO PROCESS INFORMATION DIFFERENTLY REDUCE PARANOID IDEATION?

Y. Landa,* S. Silverstein, K. Carpiniello, A. Savitz
Psychiatry, Cornell University Medical College, White Plains, NY, USA

In recent years, much insight was gained in the etiology and maintenance of persecutory delusions and specific attentional, attributional, and reasoning biases were identified (Bentall, 2001; Freeman & Garety, 2003). Future progress will depend on the development of treatment interventions based on the empirically proven psychological models of paranoid symptom onset and maintenance. Studies shown that patients with persecutory delusions: (1) selectively attend to the threatening information, particularly the information related to the self, (2) attribute negative events to external personal causes, (3) jump to conclusions on the basis of insufficient information, (4) have difficulties interpreting others' motivations and intentions, and (5) use safety behaviours (e.g. isolation) that contribute to persistence of persecutory delusions. We developed targeted interventions to address the above cognitive biases. We used a group format, since our previous study of group CBT for delusions showed that the group format was particularly beneficial for paranoid patients. At baseline all patients admitted to the group (N=5) reported persecutory delusions. Pre and post measures include: EBS, IPSAQ, HT, SQ, CDRS and PSYRATS. Patients meet weekly for an hour and will attend 20 sessions. Treatment interventions are focused on: (1) collaboratively developing a model of persecutory delusions formation and maintenance for each patient, (2) learning to identify cognitive biases contributing to paranoid thoughts, (3) increasing awareness of the triggers and consequences of persecutory thoughts, (4) learning to evaluate beliefs by examining the evidence for and against them, (5) learning to shift attention from the "persecutor" and to identify the source of their own frustration, (6) practicing understanding others' intentions and motivations. At present the treatment is half completed and all patients remain in the group. Patients report reduction in delusional conviction and intensity of distress, increased awareness of irrationality of beliefs, increased ability to dismiss a paranoid thought, and decreased safety behaviors. The study will demonstrate whether targeting specific cognitive biases produce changes in information processing in paranoid patients, and whether these changes (if any) contribute to the reduction of paranoid ideation.

GENERALIZATION EFFECTS OF TRAINING ON THE WISCONSIN CARD SORTING TEST AND SOCIAL SKILLS OUTCOME IN SCHIZOPHRENIA

W. W. Leung,* W. Tenhula, A. S. Bellack
Psychology, University of Maryland at College Park, College Park, MD, USA

Although considerable evidence has demonstrated that social skills training (SST) is associated with improved clinical outcome in schizophrenia, little is known regarding the factors that predict skill acquisition and generalization. Neuropsychological indices may be one important predictor of the extent to which patients are able to benefit from SST. Specifically, executive functioning may have particular relevance to the acquisition and generalization of social skills in SST, given the prominent deficits in *social* problem solving (e.g., generating and implementing effective solutions) in individuals with schizophrenia. This poster will utilize data from an ongoing study to examine the degree to which learning and generalization on two tests of reasoning and problem solving can predict the capacity to benefit from SST. Other neuropsychological variables that may limit the generalization of skills training will also be identified. A sample of participants meeting DSM-IV criteria for schizophrenia or schizoaffective disorder (n = 60) participated in five stages of this study. First, subjects completed a neuropsychological battery and a social functioning assessment (MASC) at baseline. Second, subjects were reassessed on two executive functioning tests following WCST training. Third, subjects participated in a 4-week follow-up assessment which included the WCST and Halstead Category Test (CT). Finally, subjects participated in a social skills training and a post-SST assessment on the MASC. It is hypothesized that improved performance on the WCST will produce improvements (i.e., generalization) on other executive functioning tasks (i.e., the CT). It is also predicted that changes in executive functioning will be maintained after 4-weeks. Further, the generalization across executive functioning tasks will predict MASC performance post-SST (i.e. capacity to benefit from SST). In addition, it is hypothesized that baseline measures of executive functioning, working memory, verbal memory, and general cognitive ability will predict SST outcome. Findings and implications will be discussed. This research is supported by a VA Merit Review Entry Program (MREP) grant to Dr. Tenhula.

COGNITIVE BEHAVIOR THERAPY AND FUNCTIONAL OUTCOME IN SCHIZOPHRENIA

P. Lysaker,* L. W. Davis, G. J. Bryson, M. D. Bell
Roudebush VA Med Center, Indianapolis, IN, USA

Many with schizophrenia wish to work, yet enter vocational rehabilitation with expectations of failure. These beliefs represent a barrier to desired levels of function. Cognitive behavior therapy (CBT) has proven to be useful to persons with schizophrenia and could be adapted to enhance vocational outcomes. Accordingly, we adapted existing technology to create a manualized program, the Indianapolis Vocational Intervention Program (IVIP), which is intended as an adjunct to work therapy programs that offer participants paid work placements. The IVIP was initially developed working with 20 participants with schizophrenia spectrum disorders actively engaged in 20 hours per week of work activity. The IVIP is designed as a 6-month program and includes weekly group and individual CBT interventions. To test the effectiveness of the IVIP, 46 participants with diagnoses of schizophrenia or schizoaffective disorder were randomly assigned to receive a 6-month work placement and IVIP (n = 23) or a work placement and standard services (n = 23). Hours of work were assessed weekly and work performance was assessed biweekly using the Work Behavior Inventory for both groups. Work performance scores were averaged across 3 points in time: weeks 3-9, weeks 11-17, and weeks 19-25. Beliefs about self were assessed at baseline and after 5 months of treatment using the Beck Hopelessness Scale and the Rosenberg Self-Esteem Schedule. Metacognition was assessed using the Metacognition Assessment Scale as applied to unstructured narratives of self and illness collected at baseline and follow-up and transcribed verbatim. Level of metacogntion

was it emerged within narratives was assessed by raters blind to condition and assessment time. T-tests revealed participants randomly assigned to IVIP worked more weeks ($t = 2.5$, $p < .05$) and demonstrated better work performance from weeks 3-9 ($t = 2.3$, $p < .05$) and weeks 19-25 ($t = 2.1$, $p < .05$). CBT participants also demonstrated more hope ($f = 8.7$, $p < .01$) and self-esteem ($f = 8.9$, $p < .01$) at five-month follow-up, and higher levels of metacognition ($f = 4.20$, $p < .05$) in ANCOVA controlling for equivalent scores at baseline. With replication results suggest CBT may assist some with schizophrenia to achieve better work outcomes.

COGNITIVE ADAPTATION TRAINING AND ADHERENCE TO MEDICATION

N. J. Maples,* D. I. Velligan, M. Wang, J. Lopez, D. A. Castillo, A. M. Dassori
Psychiatry, UTHSCSA, San Antonio, TX, USA

Cognitive Adaptation Training (CAT) uses environmental supports such as signs, checklists, and alarms to cue and sequence appropriate behavior in the home environment. The effect of CAT on medication adherence was investigated in 42 schizophrenia patients seen for a nine-month period. Patients were assessed after hospital discharge and a 3-month naturalistic follow-up period during which they received no intervention. This period allowed baseline medication adherence to be assessed prior to intervention. Medication adherence was assessed at unannounced in-home pill counting visits that occurred at approximate 3-month intervals. Patients taking 0-29% of their medication at baseline were classified as non-adherent, those taking 30-69% were classified as partially adherent and those taking 70% or more were classified as adherent. Following assessment, patients were randomly assigned to either Full-CAT (CAT treatment focused on many aspects of functioning including medication adherence), Pharm-CAT (CAT treatment focused only on medication and appointment adherence) or follow-up only. Subjects were classified as adherent, partially adherent, or non-adherent following 6 months of treatment. Data were analyzed using the Cochran-Mantel Hanszel test to examine group (CAT or Pharm-CAT versus Control) by endpoint adherence relationships for three different strata (baseline adherence levels). This analysis controlled for problems with regression to the mean. Results were similar for the 3 strata (Breslow-Day; $p<0.40$). For the sample as a whole, patients in CAT groups were significantly more likely to be adherent at the end of treatment than those in the control condition ($Q_{CMH(1)} = 4.00$; $p<.04$; $est.\theta_{MH} = 4.75$). Environmental supports improve adherence to medication for patients with schizophrenia. Funded by: R01 MH62850-05.

MEASURING CLINICIAN BEHAVIOR AND ITS RELATIONSHIP TO PATIENT AND FAMILY OUTCOMES IN A FAMILY PSYCHO-EDUCATION AND SUPPORT INTERVENTION FOR SCHIZOPHRENIA

M. G. McDonell,* M. L. Rodgers, R. A. Short, D. Norell, L. Pinter, D. G. Dyck
Department of Psychiatry and Behavioral Sciences, University of Washington, Medical School, Lakewood, WA, USA

Family psycho-education interventions are a best practice in the treatment of schizophrenia. Despite empirical support, well-developed treatment manuals, and dissemination, little is know about the relationship between clinician adherence to these interventions and treatment outcomes. The Multiple Family Group-Adherence and Competence Checklist (MFG-ACC) was developed to measure clinician adherence and competence in multiple family group treatment (MFGT), an empirically supported family intervention (McFarlane, 2002). It was hypothesized that the MFG-ACC would demonstrate adequate psychometric properties and that high adherence to MFGT would be associated with significant reductions in ratings of patient symptoms and a positive impact on family psychological resources and distress. Seven clinician dyads administered MFGT to a total of 53 participants with psychotic disorders in a two year randomized trial. Using the MFG-ACC, three raters examined 42 videotaped sessions (6/dyad). Thirty sessions were examined by two raters to assess inter-rater reliability. Based on MFG-ACC scores, patients were grouped into those who received low/moderate and high quality MFGT. The relationship between MFGT quality and patient and caregiver outcomes was then examined. The MFG-ACC demonstrated adequate internal consistency and inter-rater reliability. The tool was able to discriminate between clinicians who attained low, moderate, and high levels of adherence and competence. Accounting for baseline levels of psychiatric symptoms and MFGT session attendance, patients who received low/moderate quality MFGT had significantly higher rates of negative symptoms, $F(1,34)=4.43$, $p<.05$, and overall psychiatric symptoms, $F(1,34)=8.17$, $p<.01$, across the two year intervention, relative to those who received high quality MFGT. MFGT quality was not associated with family outcomes. Results suggest that the MFG-ACC is an adequate tool for research and clinical supervision. Improvements to the tool are suggested. The MFG-ACC is also a valuable tool for predicting patient outcomes, as those who received high quality MFGT had lower rates of psychiatric symptoms, relative to those receiving low/moderate quality MFGT. The differential impact of clinician adherence on patient and family outcomes is discussed. This study highlights the importance of measuring clinician adherence and competence when investigating and disseminating psychosocial interventions.

COGNITIVE SKILLS TRAINING IN INPATIENTS WITH SCHIZOPHRENIA

S. McGurk,* J. P. Lindenmayer, A. Khan, D. Wance, N. Bernstein, B. Simon
Pilgrim Psychiatric Center, West Brentwood, NY, USA

Background: Cognitive impairments in schizophrenia are strongly associated with functional impairment. In fact, cognitive functions, more so than positive symptoms, are the major determinant of employment and related outcomes (Jaeger et al.,1992; Goldman et al.,1993; Hagger et al.,1993; Meltzer & McGurk, 1999). Cognitive skills training programs have had success in improving cognitive and functional deficits in inpatients (e.g., Spaulding et al.). Aim: The present study is a randomized controlled 12 week trial comparing clinical, functional and neurocognitive outcomes of a cognitive skills program to a control condition. Methods: Inpatients with DSM IV schizophrenia from a tertiary care psychiatric center are randomized to either the computerized cognitive skills training program or the control condition. The program used is COGPACK (Marker and Olbrich, 1998). In this program patients use 12 different exercises that practice the areas of problem solving skills, memory, and psychomotor speed with each exercise having 10 levels of difficulty. When the subject is able to provide 90% of the correct responses for that level of difficulty, the practice is automatically increased to the next level of difficulty. The cognitive skills training program is implemented over

24 hours of computerized cognitive training and weekly group discussions covering a period of 12 weeks. The control group receives similar hours of staff and computer exposure, but without cognitive training exercises. All patients are on antipsychotic medication and are assessed at baseline and endpoint with a comprehensive neuropsychological test battery, the PANSS, the SAS and the Social Adaptive Functioning Scale (SAFE). Results: Preliminary results are presented as the study is ongoing. Due to low power, initial analyses (within-group t-tests) are limited to patients who have received treatment (N=15). Significant improvements were found in measures of attention and motor speed (Trail Making, t= 2.5, p<0.05) and executive functioning (Wisconsin Card Sorting Test Total Categories t= 2.0, p< 0.05). Conclusion: Results thus far support the feasibility and efficacy of implementing a cognitive skills training program in an inpatient setting.

PREDICTORS OF RESPONSE TO COGNITIVE REMEDIATION IN A COMMUNITY PSYCHIATRIC PROGRAM

A. Medalia,* J. Choi
Psychiatry, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

The aim of this study was to examine factors that may be associated with a positive response to cognitive remediation rendered in a community psychiatric program. Implementing a cognitive remediation program in a community clinic presents unique challenges due to a lack of participant motivation for treatment. The Neuropsychological Educational Approach to Remediation (NEAR) is a unique computer-assisted cognitive remediation program that addresses those challenges by encouraging active engagement and intrinsic motivation to facilitate the transfer of learned cognitive skills to everyday situations. The study was quasi-experimental with no random assignment or control condition since all participants referred for cognitive remediation were required to be included in treatment per agency guidelines. Forty-eight adult psychiatric outpatients (26 participants diagnosed with schizophrenia) from a large community mental health agency in New York City completed 26 hours of NEAR. Since the goal of cognitive remediation is to not merely improve behaviors seen during remediation training but rather behaviors outside of the treatment setting, remediation success was measured by improvement in attention as applied to common clerical duties, and by looking at behaviors relevant to successful employment. Results showed significant post-treatment improvement on functional measures of attention and work behavior. Notably, there was a threshold of motivation with no treatment effect on the attention measure below a certain level. Specifically, participants with low motivation did not obtain any cognitive benefits while a high level of motivation was associated with a very large treatment effect (ES = 0.90). The findings suggest that NEAR is an effective modality of cognitive remediation for use in community-based programs since it creates an environment that significantly enhances motivation and the learning process. In addition, behaviors developed from NEAR can be readily applied to meaningful vocational goals. This study demonstrates how participants with persistent mental illness can make practical behavioral improvements once sufficiently motivated to engage in cognitive training, and in so doing, maximize treatment outcome. This study underscores the importance of addressing motivation when implementing cognitive remediation in the community.

A PILOT STUDY OF ILLNESS MANAGEMENT AND RECOVERY FOR PERSONS WITH PSYCHOTIC DISORDERS

P. Meyer,* D. Penn, K. Mueser, E. Waldheter
Cecil G. Sheps Center, University of North Carolina, Chapel Hill, NC, USA

Illness Management and Recovery (IMR) is a treatment program designed to promote recovery for persons who have experienced psychiatric symptoms. IMR focuses on teaching educational, motivational, and cognitive-behavioral strategies to help improve coping skills, reduce relapses, and work effectively with treatment professionals. As one of the evidence-based practices for mental health services, research has supported the four components of IMR: education, behavioral tailoring for medication, relapse prevention, and coping skills training, but no study has examined treatment outcomes when all the components are combined into one comprehensive treatment package. The purpose of this study was to examine the treatment outcomes from pilot feasibility data in a sample of persons with psychotic disorders. We compared outcomes (symptoms, social support, coping skills, knowledge about mental illness, rehabilitation, and recovery) using individual pre-post data from a small sample of individuals (N = 7). Using a 5-item version of a functional rehabilitation scale (range 1=less functional to 5=more functional independence and collaboration with treatment), participants reported improved functioning (Total Score pre M = 19.7, SD = 3.3; post M = 23.3, SD = 1.5), especially in the areas of knowledge of mental illness (pre M = 3.8, SD = 1.3; post M = 4.8, SD = 0.4) and self-reported hospitalizations (pre M = 4.0, SD = 1.4; post M = 4.5, SD = 0.6). In addition, there was a trend in the data that showed participants reported more effective coping for symptoms. No pre-post differences were found in symptom severity or perceived social support. This pilot study demonstrates the effectiveness of the strategies used in IMR to improve coping skills and impact rehabilitation outcomes. Future long-term studies need to be done to replicate these findings and determine more long-lasting effects on outcomes.

ADVANTAGES OF WORK-RELATED SOCIAL SKILLS TRAINING IN COMPARISON TO UNSPECIFIC SOCIAL SKILLS TRAINING IN VOCATIONAL REHABILITATION OF SCHIZOPHRENIA OUTPATIENTS: A RANDOMIZED CONTROLLED TRIAL

D. R. Mueller,* V. Roder, P. Zorn
University Hospital of Social and Community Psychiatry, University of Bern, Bern, Switzerland

Regaining the ability to work is widely viewed as an important goal in the treatment and rehabilitation of schizophrenia patients. Together with sheltered workshops and supported employment, social-skills training (SST) numbers among the interventions integrated in vocational rehabilitation. During the past few years, our research group developed a manualized cognitive social-skills training program for vocational functioning (WAF), which is applied in groups of 5-8 patients. The program consists of four stages: cognitive orientation, individual goal attainment, training of specific social skills, and coping with difficulties. WAF includes cognitive techniques in addition to behavioral exercises and specific stress inoculation training. The

goal of WAF is to activate and support patients in making use of rehabilitation offers in competitive employment. The aim of the present study was to compare WAF (experimental group, EG) with a conventional, unspecific SST program (control group, CG) in a randomized controlled trial. A total of 41 schizophrenia outpatients participated in the study (EG: n=21; CG: n=20). The aims of the study were to investigate effects in functional domains of schizophrenia, as well as in therapy motivation, relapse prevention, and employment rates within a catamnestic phase of two years. Results indicate a better outcome for EG patients in terms of psychopathology and social behavior compared to CG patients. In addition, patient therapy motivation is significantly improved during the course of treatment with WAF. Increased therapy motivation predicts a reduction of negative symptoms and improved social functioning at follow-up. Furthermore, EG patients obtain lower relapse rates in the two-year follow-up assessment. Finally, significantly more EG patients enter competitive employment during therapy and in the catamnestic phase compared to CG patients. In summary, the specific interventions of WAF including individual work-related topics that are particularly relevant for schizophrenia patients' daily lives seem to be superior to traditional SST in activating patients' therapy motivation and treatment compliance. These effects are associated with superior functional outcome of work-related SST compared to unspecific SST. Thereby, WAF could constitute an effective treatment within multimodal vocational rehabilitation.

DOES COGNITIVE REMEDIATION CONTRIBUTE TO COGNITIVE ENHANCEMENT IN SCHIZOPHRENIA

K. B. Murch,* M. Shepard, J. Eamma, J. Osuji, M. Cullum, A. S. Bellack, C. A. Tamminga
Psychiatry, University of Texas Southwestern Medical Center at Dallas, Dallas, TX, USA

Cognitive impairment is now considered to be a central feature of schizophrenia and a critical target for new treatment development. This observation has fostered an interest in the possibility of cognitive remediation. Recent studies involving cognitive remediation have indicated that several aspects of cognition that are impaired in schizophrenia can be improved through reinforcement and instructions. As such, we now know that cognitive change occurs in schizophrenia only after a significant amount of time and practice, which leads to the hypothesis that persons with schizophrenia are able to learn only under certain conditions. This current study aims to investigate improvements in cognition following one such remediation strategy (Bellack et al., 1990) Subjects are seen for screening and baseline visits before entering into the 8-week treatment phase of the study. Prior to beginning the 8-week treatment phase, participants are randomized to 1 of 2 groups: Cognitive remediation or Remediation control. Cognitive remediation utilizes educational software and an interactive coaching strategy, while remediation control exercises involve minimal coaching and computer games that are not likely to improve cognition. Cognitive remediation and remediation control sessions are held 3 times per week, each session lasting approximately 1 hour. All subjects are evaluated on a variety of measures including fMRI, a broad neuropsychological test battery, pre- and post-test remediation metrics, as well as several clinical instruments to assess social functioning, insight and symptoms. Preliminary results address pre- and post-test remediation metrics and neuropsychological findings. Three of the four volunteers received cognitive remediation. Data show that, overall, the participants in the remediation group improved in the performance of the remediation tasks. There is an average percent decrease in the time taken to complete a given level of 42.1%. Examination of neuropsychological scores revealed global improvement in one volunteer, mild improvement in a second volunteer, and stable overall scores in the two others. When improvement was seen, it most often occurred on the Continuous Performance Test, the Stroop Color-Word test, and the Texas Card Sorting Test, suggesting increased concentration/vigilance and executive functioning performances. Additional clinical data, addressing social functioning, insight and rCBF, will be further analyzed.

ADVANCES IN IMPROVING AND PREDICTING WORK OUTCOME IN RECENT-ONSET SCHIZOPHRENIA

K. H. Nuechterlein,* K. L. Subotnik, J. Ventura, M. J. Gitlin, M. F. Green, C. J. Wallace, D. R. Becker, R. P. Liberman, R. E. Drake, J. Mintz
Department of Psychiatry and Biobehavioral Sciences, UCLA, Los Angeles, CA, USA

Effective interventions shortly after onset of schizophrenia are critical for preventing chronic patterns of disability, particularly if they aid successful return to work or school. In a randomized, controlled trial with 51 recent-onset schizophrenia patients, the combination of Individual Placement and Support (IPS) and a Workplace Fundamental Module (WFM) was compared to traditional vocational rehabilitation. IPS is a form of supported employment/education that emphasizes integration of mental health and vocational services, rapid search for regular work and school positions, assertive community outreach, client preferences, and ongoing support. WFM is a social skills group approach that involves nine workplace skill areas and uses videotaped demonstrations, role-played practice, generation and evaluation of solutions, and homework assignments. The proportion of recent-onset schizophrenia patients who returned to paid work or regular school was strikingly increased by the IPS-WFM intervention. IPS-WFM led to 93% of patients returning to work or school within the initial 6 months, compared to 50% in the comparison group ($p < .001$). In the period of less intensive treatment (months 7-18), the proportion of IPS-WFM patients in paid work or school continued to be very high (93%) and substantially higher than in the comparison group (55%) ($p < .008$). IPS-WFM also led to better ability to maintain patients in treatment. Only 15% of IPS-WFM patients dropped out of treatment in 18 months, compared to 41% of patients provided traditional vocational rehabilitation ($p < .04$). This substantial advance in rate of return to work and school continues to leave room for improvement of quality of work. Baseline cognitive performance was found to be a powerful predictor of work performance. For the Work Behavior Inventory summary score, five cognitive factors predicted 42% of the variance ($R = .65$, $p < .02$). Early Perceptual Processing, Vigilance, and Problem Solving and Working Memory made the strongest contributions. Thus, an intervention combining supported employment/education and work-focused skills training was clearly effective in getting almost all of our recent-onset schizophrenia patients to return to some level of regular school or paid work. Cognitive deficits continue to be a major predictor of work performance levels and would benefit greatly from additional targeted intervention.

PSYCHOPHARMACOLOGICAL TREATMENT OF SCHIZOPHRENIA—HOW IS MEDICATION FAVOURED BY THE PATIENT?

F. G. Pajonk,* F. S. Schmitz, C. Birkenheier, W. Classen, D. Caspari
Dept. of Psychiatry and Psychotherapy, The Saarland University Hospitals, Homburg, Germany

Objective: Adherence is a major issue in the long-term therapy of schizophrenia for preventing relapse. Many patients do not take their medication as prescribed. Several factors influencing the adherence have been identified, however, the personal attitudes of patients towards a specific medication or the route of administration seems to be of particular importance as well as the subjective experience of therapeutic alliance with their psychiatrists. *Methods:* This is an interim analysis of a prospective longitudinal survey in five southwestern German psychiatric hospitals which is currently performed in patients with schizophrenia focussing on the attitude towards treatment in general and specific medication strategies in particular as well as the therapeutic alliance. Data on the current situation of life and the history of the illness was collected, and the patients were asked to fill out the Insight Scale (IS), the Drug Attitude Inventory (DAI) and a newly developed Questionnaire on Therapeutic Alliance (QTA). Further, patients gave information on experiences with specific medication and preferred route of administration. *Results:* 190 patients (male/female: 62%/38%; mean age: 39.0±12.0 years; mean age of onset of disease: 28.5±9.7 years; mean duration of antipsychotic treatment: 8.2±8.3 years) participated until now. 16% left the choice of medication to the psychiatrist, 47% preferred a shared decision making, 56% stated to ask for detailed information. 82% consented to require currently a pharmacological treatment, 72% to require a treatment for at least one year. The intake of tablets was assessed to be the route of administration of choice (64% preferred). A depot-injection was preferred by 25%, a surgical implantable long-term delivery system by 11%. The scores of the IS, DAI and QTA correlated positively. The attitude towards medication improved particularly when the therapeutic alliance was assessed to be good ($r=0.4$; $p<0.001$). Age, duration of illness and of antipsychotic treatment were not correlated to insight into illness, attitude towards medication or assessment of therapeutic alliance. *Conclusions:* A high proportion of patients agrees to require continuing medication. The attitude towards medication depends considerably on the insight into illness and the therapeutic alliance. Psychoeducation and a good relationship between patient and psychiatrist must be considered to be highly relevant for an improved adherence to medication.

THE OPUS TRIAL: A RANDOMISED MULTICENTRE TRIAL OF INTEGRATED VERSUS STANDARD TREATMENT FOR 547 FIRST-EPISODE PSYCHOTIC PATIENTS

L. Petersen,* M. Nordentoft, A. Thorup, J. Oehlenschlaeger, P. Jeppesen, T. Christensen, G. Krarup, P. Joergensen
Psychiatric Department E, Bispebjerg Hospital, Copenhagen, Denmark

Objective: Effective treatment in the early phases of schizophrenia and schizophrenia spectrum disorders need investigation in order to improve short-term and long-term outcome. Methods: We randomised 547 first-episode psychosis patients to integrated treatment or standard treatment. Patients were assessed after one and two year by independent investigators. Data from hospital records were available for 99% of the patients, and (77%) participated in one-year follow-up interviews and (67 %) in two-year follow-up interviews. The integrated treatment lasted for two years and consisted of assertive community treatment with programs for family-involvement and social skills training. Standard treatment offered contact with a community mental health centre. Results: At two-year follow-up, patients in integrated treatment had significantly better outcomes concerning psychotic and negative symptoms. Significantly fewer patients in the integrated treatment 17 % vs 21 % had a co-morbid diagnosis of alcohol or drug abuse and significantly more patients in integrated treatment adhered to and were satisfied with treatment. Patients in integrated treatment used 88 (mean) bed days during the two-year period, while patients in standard treatment used 111 (mean) bed days. No differences were found in social outcome data. Furthermore, results from analyses of quality of life and need for care are presented. Conclusion Integrated treatment was cost-effective, was superior to standard treatment and should be implemented in treatment of first-episode psychosis.

MEMEX: A MOBILE TELEPHONE AS A PROSTHETIC AID FOR COMPENSATING COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

M. Pijnenborg,* J. E. van der Velden, J. Evans, F. K. Withaar, R. J. van den Bosch, W. H. Brouwer
Department of Psychotic Disorders, GGZ Drenthe, Assen, Drenthe, Netherlands

The purpose of the MEMEX study is to investigate the efficacy of a new approach in the remediation of cognitive deficits in schizophrenia patients. In addition to impairments in speed of information processing and memory schizophrenia patients are particularly impaired in the domain of executive functions that involve planning and regulation in unstructured and socially demanding situations. Behavioral interventions aiming at the remediation of these deficits fail at one important point: the effects of training hardly generalize to other settings. Given this limitation, a different approach in cognitive remediation might be needed in addition to classical remediation. In the MEMEX (MEMory and EXecutive functioning) project a program was developed that sends SMS-messages to mobile phones on scheduled times, to remind patients of their appointments and daily obligations. The goals are chosen by the patients themselves and therefore highly individualized. Target behavior is monitored during the entire trial. The percentage of target behaviors achieved is compared in each subject, using an A-B-A design. Effects on indirect outcome measures, like psychiatric symptoms, self-esteem and social functioning will also be evaluated. A pilot study (n=7) with promising results was performed. Four patients improved on all target measures while one patient did not profit from MEMEX, although they were not able to establish a routine. Two other patients were withdrawn from the study because of a psychotic relapse. Currently, a larger evaluation of the intervention is carried out at the department of Psychotic Disorders, GGZ Noord Drenthe, Assen, The Netherlands. The results of this study (n=30) are promising, since about forty percent of the patients improve on at least one target measure. The preliminary results of the larger MEMEX study show that the use of a prosthetic is useful in the remediation of cognitive deficits in schizophrenia. Daily problems in schizophrenia can be ameliorated by prompting events with SMS messages. The patients who did not profit from MEMEX are more likely to suffer from a lack of initiation and/or negative symptoms. Results suggest that prolonged prompting is

indicated, because at follow up, performance dropped to baseline-level. This study is financially supported by ZonMw.

FINDING A WAY FORWARD FOR COGNITIVE REMEDIATION THERAPY (CRT): A NEW THEORY FOR THE RELATIONSHIP BETWEEN COGNITIVE FUNCTION AND OUTCOME

C. Reeder,* T. Wykes
Oxleas NHS Trust, London, United Kingdom

CRT research to date has assumed that (1) cognitive function can improve in people with schizophrenia, and (2) improved cognition will lead to better everyday functioning and symptoms. Although there is some evidence in support of both assumptions, there have been a number of anomalous findings which need to be explained in order to advance CRT research. For example, whilst there is clear evidence from meta-analytic studies that CRT can lead to improved cognition, response rates vary greatly within groups, between studies, and according to the particular cognitive functions under investigation. No consistent predictors of cognitive improvement have been identified. Furthermore, whilst a number of studies have shown an association between improved cognition and improved social functioning and symptoms, this is frequently apparent only for those who have received CRT. Thus, CRT seems to mediate the relationship between cogntiive function and outcome, suggesting that the link between the two is not direct. In this paper, two different approaches to explain these anomalies will be presented: an exploratory approach and a theoretical approach. The first assumption of CRT will be investigated using an exploratory approach. Data will be presented from a randomised controlled trial comparing CRT with treatment-as-usual for 85 people with schizophrenia. The results showed that whilst CRT led to improvements in cognitive function, there was a wide variation in response to treatment, which was accounted for primarily by age differences. Participants who were under 40 years showed consistent cognitive (verbal working memory, cognitive flexibility, long-term verbal and visuo-spatial memory) and functional improvements (negative symptoms and symptom severity), whilst those above 40 years showed much lower levels of improvement. These differential responses according to age could be accounted for differences in the ability to think flexibly in novel situations. A theoretical approach will be used to address the second assumption of CRT. A new model for CRT will be presented, which highlights the importance of metacognitive thinking in the ability to transfer existing cognitive skills and knowledge to new situations. This will provide a new framework with which to understand the relationship between cognitive function and outcome, allowing us to develop our understanding of the theoretical underpinnings of CRT and to refine our treatment programmes.

EMPIRICAL EVIDENCE FOR SOCIAL COGNITION THERAPY IN SCHIZOPHRENIA

V. Roder,* D. R. Mueller
University Hospital of Social and Community Psychiatry, University of Bern, Bern, Switzerland

During the past few years, a number of integrated models have tried to explain the association in schizophrenia between deficits in neurocognitive domains (NCOG) and functional outcome such as, for example, social competence (COMP). In addition, social cognition (SCOG) is considered to be a possible mediating factor between NCOG and COMP. Most of the cognitive-behavioral therapy approaches clinically applied today address only one of these treatment areas. One of the first comprehensive group therapy programs targeting deficits in all described functional areas is Integrated Psychological Therapy (IPT). IPT consists of five subprograms: the first subprogram focuses directly on NCOG, the second one addresses SCOG, and the last three subprograms target COMP. Against this background, the aims of the present study were to investigate 1) if schizophrenia patients improved additionally when treated with SCOG therapy in combination with NCOG compared to NCOG and/or standard care alone, and 2) if different IPT settings addressing NCOG and/or SCOG obtained vertical generalization effects on COMP. For this purpose, 22 independent evaluation studies of IPT with a sample of 998 schizophrenia patients diagnosed according to ICD or DSM criteria were included and evaluated. Results indicate that patients participating in IPT groups obtained additional effects in the described functional areas compared to control group patients. These effects were independent of treatment setting. Improvements in specific NCOG domains of schizophrenia (attention, memory, and executive functioning) could be identified. Furthermore, a combination of NCOG and SCOG therapies increased the effects in the targeted functional areas, and additionally in COMP variables. Patients being treated with the full course of IPT, including exercises in COMP, were most successful in terms of COMP outcome. Moreover, analyzing follow-up assessment patients who had participated in the full course of IPT revealed superior effects compared to analyses of patients treated with subprograms only. In summary, the results support the evidence for SCOG as an important mediating factor between NCOG and COMP. The efficient preceding treatment with SCOG therapy could represent a presupposition for successful rehabilitation in schizophrenia. Thereby, only the application of integrative therapy in all IPT subprograms achieves effects that are sustained after therapy.

DISSEMINATING FAMILY PSYCHOEDUCATION TO COMMUNITY CAREGIVERS AND RESIDENTS: A PILOT INVESTIGATION

I. S. Rosenfarb,* P. E. Smerud, M. A. Juan, R. S. Setpaul
California School of Professional Psychology, Alliant International University, San Diego, CA, USA

Psychoeducational family interventions have the greatest research base of any psychosocial treatment for schizophrenia, yet dissemination of this treatment has been hindered, in part, because many patients are disconnected from close family members. The purpose of the present pilot investigation was to develop and implement a 9-month family psychoeducational treatment program with community caregivers and residents. Falloon's Behavioral Family Management protocol was adapted and applied in a community board-and-care facility in San Diego. Five residents and a caregiver participated in the treatment. Preliminary results suggest that family psychoeducational interventions can be successfully implemented in a board-and-care facility and can lead to improvements in the family environment and residents' social functioning.

A RANDOMIZED TRIAL OF A TELEHEALTH INTERVENTION TO PROVIDE IN-HOME PSYCHOEDUCATION TO PERSONS WITH SCHIZOPHRENIA AND THEIR FAMILIES: INTERVENTION DESIGN AND PRELIMINARY FINDINGS

A. J. Rotondi,* G. Haas, C. Anderson, R. Ganguli, M. Keshavan, C. Newhill, J. Rosenstock, M. Spring
Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA, USA

The purpose of this study is to evaluate a telehealth psychoeducation intervention that provides on-line multi-family therapy and education to persons with schizophrenia, and to available families or other support persons. While family psychoeducation programs have been proven efficacious, translating and disseminating these programs successfully to the community faces many barriers. Online interventions have the ability to increase convenience and thus access to services for persons with schizophrenia and their families. Thirty-three persons with schizophrenia (including 24 family members/support persons) were randomized to the intervention or the usual care group. The web-based intervention has the following content: 1) three therapy groups (persons with schizophrenia only; family members and other support persons only; persons with schizophrenia and family members/other support persons); 2) a module that allows users to anonymously ask questions of experts associated with the project and receive a response; 3) a library of previously asked and answered questions, and; 4) educational reading materials on several topics (e.g., the medical and psychosocial aspects of schizophrenia, the warning signs are of getting sick again). Subjects remain in the study for nine months. Complete three-month data are available and have been analyzed using analysis of covariance. When compared to the control group, subjects with schizophrenia in the intervention group reported lower perceived stress (a = 0.044) and showed a trend for a higher perceived level of social support (a = 0.062). A primary goal of the project was to reduce perceived stress for persons with schizophrenia. These data indicate that persons with schizophrenia will use telehealth applications, including on-line therapy groups, and can benefit from their use. The findings have potentially important implications for telehealth-based delivery of care to persons with severe mental illness.

A BRIEF TRANSITIONAL COMMUNITY LINKAGE TREATMENT FOR INDIVIDUALS WITH A PERSISTENT MENTAL ILLNESS AND A CO-OCCURRING SUBSTANCE ABUSE DISORDER

D. A. Smelson,* M. Losonczy, K. Castles-Fonseca, B. D. Sussner, S. Rodriques, A. Kline, D. Ziedonis
Psychiatry, UMDNJ-Robert Wood Johnson Medical School/VA New Jersey, Lyons, NJ, USA

Objective: Individuals with co-occurring mental illness and substance abuse often fail to engage in outpatient treatment following discharge from inpatient psychiatric care and problems experienced during this transitional period often precipitate re-hospitalization. To improve outcomes during this vulnerable period, we developed an eight-week community linkage intervention. Method: Sixty-five dually diagnosed veterans participated in the study, 32 who received the new Transitional Case Management (TLC) service in addition to standard outpatient Mentally Ill Chemical Abuser treatment (MICA) and 33 who were discharged as usual to MICA services. Results: The veterans who received TLC had better attendance at the initial outpatient screening (p=.02), at the eight-week follow-up appointment (p<.01), and in outpatient MICA care during the eight week transitional period (p<.01). The TLC group also had a greater number of pharmacy prescription pick-ups (p=.11) and were less likely to be lost to contact at the eight-week follow-up period (p<.01). Furthermore, six-month post-study entry outcomes showed that the TLC group had a significant reduction in psychiatric re-hospitalization days (p=.05) and episodes (p=.01), and had higher Global Assessment of Functioning scale scores (p<.01) than the comparison group. Conclusion: TLC had robust treatment effects well beyond the eight weeks of treatment and appeared to decrease the recidivism common among this population. This work was supported by a grant from the Department of Veterans Affairs.

PARTICIPANT EVALUATION OF A CBT PROGRAM FOR ENHANCING WORK FUNCTION IN SCHIZOPHRENIA

A. M. Strasburger,* L. W. Davis, P. H. Lysaker
Roudebush VA Medical Center, Indianapolis, IN, USA

While much has been written about the benefits of Cognitive Behavior Therapy for persons with schizophrenia, little has been published to date exploring participant evaluations of these programs. This may be a result of difficulties inherent in the participant evaluation process such as reluctance to give negative feedback, lack of comparison groups, lack of standardized measures and sampling biases. We sought to address these difficulties while collecting participant evaluations during the feasibility study for a weekly group and individual CBT intervention we recently developed as an adjunct to work therapy in order to identify opportunities for improvement. Participants were 44 persons with a SCID confirmed diagnosis of schizophrenia or schizoaffective disorder who had completed a work therapy program that included a 6-month paid work placement and either a weekly support group (N=19) or weekly manualized CBT group and individual sessions (N=25). Participant satisfaction was assessed using the Client Satisfaction Questionnaire-8 (CSQ-8) and the Satisfaction Questionnaire (SQ) adapted as a structured interview. Comparison of the mean total of the CSQ-8 revealed significantly greater satisfaction for the CBT group (X=27.60, SD=2.6) vs. the control groups (X=26.44, SD=3.00; t=2.00, p<.05, one tailed). Groups differed significantly on two CSQ-8 items, with the CBT group reporting greater satisfaction with the overall quality of services (t=1.77 P < .05; one tailed) and a greater sense that the program had helped them to deal effectively with their concerns (t=2.54, p<.05). Results of the SQ structured interview revealed that participants were able to discuss what they did not like about the program and suggest changes, as well as identify what they liked, perhaps because individuals not strongly identified as treatment staff interviewed them. In the SQ interview CBT participants recommended changes in group time/length and topics, although they liked group interaction, support from program staff, and learning CBT principles and techniques. Results suggest the CBT intervention was associated with greater client satisfaction than support alone.

DEVELOPMENT AND VALIDATION OF THE NEW QOL SCALE OF PEOPLE WITH SCHIZOPHRENIA

T. Takamatsu,* T. Hashimoto, M. Taira, K. Maeda
Univ of Kobe, Kobe, Japan

Recently the importance of studying Quality Of Life (QOL) in patients with schizophrenia has been emphasized. We developed a brief (10-item) QOL scale of people with schizophrenia. This scale is based on a semi-structured interview designed to assess the level of recovery from schizophrenia. Emotional over involvements and sudden changes of environment might increase the risk for relapse into schizophrenia. We consider it important for people with schizophrenia to withdraw from social roles and social relationships on occasion. Therefore, we use this scale to assess the patient's ability to keep away from the crises. This ability is not evaluated by existing QOL scales. The subjects were 30 outpatients with a diagnosis of schizophrenia as defined by DSM-IV. This test was administered together with WHO-QOL26, Visual Analog Scale (VAS), and the Drug Attitude Inventory (DAI-10) to test the validity. Psychotic symptoms and extra pyramidal symptoms were also assessed using the Brief Psychiatric Rating Scale (BPRS) and the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS).

WORK-RELATED SOCIAL SKILLS TRAINING FOR VETERANS WITH SCHIZOPHRENIA: IMPACT ON WORK FUNCTION

W. N. Tenhula,* J. E. Strong Kinnaman, A. S. Bellack
Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA

The enormous economic, social and personal costs of schizophrenia (e.g. poor social and occupational functioning, poor quality of life) are generally not ameliorated by pharmacotherapy. Social skills training (SST) shows promise in teaching social skills to people with schizophrenia, but there is little evidence about whether patients actually use newly learned skills outside of the clinic. The primary goal of this project is to investigate whether patients with schizophrenia can apply work-related SST to their performance in work settings. Veterans with schizophrenia or schizoaffective disorder who are enrolled in vocational rehabilitation participated in a brief group SST intervention focused on social interactions at work. At the time of preliminary data analysis 27 participants were enrolled. Final data presented will include an N of approximately 60. Subjects were mostly male (93%) and were an average of 50 years old (SD = 6.1). Most were African American (67%), living in supervised housing (63%) and never married (67%). They had an average length of illness of 24 years (SD = 10.2) and 11.5 (SD = 9.5) psychiatric hospitalizations. Patients underwent a baseline assessment of cognitive, social, and work functioning and then served as their own "wait list control" during a one-month waiting period. Work functioning was re-assessed prior to participation in SST. Work function was again assessed following completion of SST and at 3- and 6-month follow-up. Assessments of the participants' work functioning were completed through a semi-structured interview with their work supervisor (Work Behavior Inventory; WBI). The WBI yields an overall rating of work behavior, and scores on Social Skills, Cooperation, Work Habits, Work Quality and Personal Presentation. Preliminary results demonstrate that ratings of participants' Social Skills ($F = 12.2$, $p < .001$), Personal Presentation ($F = 4.2$, $p < .05$), and Work Habits ($F = 6.9$, $p < .01$) improved from baseline to the post-treatment assessment. These data suggest that patients are able to learn the work-related social skills taught during SST and apply them to improve their social behavior in actual work settings. This is important in light of the research showing social interactions as a major factor in vocational function and job failures among persons with serious mental illness. Supported by a VA Merit Review Entry Program grant to Dr. Tenhula.

ASSERTIVE COMMUNITY TREATMENT VERSUS STANDARD PSYCHIATRIC TREATMENT FOR SEVERELY MENTALLY ILL PATIENTS IN DENMARK

M. H. Thoegersen,* M. Nordentoft
Bispebjerg Psychiatric Unit, Copenhagen University Hospital, Copenhagen, Denmark

Background: Assertive Community Treatment (ACT) is a well established service model in several countries for people with severe and enduring mental health problems who do not engage with psychiatric services. Community mental health teams based on the ACT model have only recently been introduced in Denmark. It is unclear how models of community care translate to a Danish culture and the degree of adaptation that may result. Method: This investigation assesses the effect of ACT in Denmark. The effect of ACT is compared with the effect of Standard Psychiatric Treatment (SPT) through a quasi-experimental design with matched control groups. 198 severely mentally ill patients have been allocated to two ACT teams (case-load 10-12 per case manager) and 200 severely mentally ill patients have been allocated to two matching SPT teams (case-load 30-35 per team manager). Social functioning, clinical symptoms, and contact with psychiatric services are measured at baseline, and 1 year. Outcome measures at 1 year also include quality of life (Lancashire Quality of Life Schedule (LQLS)), patient satisfaction (Patient Satisfaction Questionnaire (PSQ)) and perceived experience of Coercion (Coercion Latter(CL), and semi-structured qualitative interviews). Results: Preliminary results at baseline data and 1 year will be presented for the following measures; social functioning, contact with psychiatric services, LQLS, PSQ, CL and semi-structured interviews.

COGNITIVE REMEDIATION FOR ADOLESCENTS WITH EARLY ONSET PSYCHOSIS: A 1-YEAR FOLLOW-UP STUDY

T. Ueland,* B. R. Rund
Sogn Centre for Child and Adolescent Psychiatry, Oslo, Norway

The aim of the study was to investigate the long-term effects of a cognitive remediation program for adolescents with early onset psychosis. Twenty-five inpatients (mean age = 15.3, 13 male, 12 female) were randomly assigned to either cognitive remediation (n = 14) or control group (n = 11). All participants received a psychoeducational treatment program, while the experimental group received the addition of a 30-hour cognitive remediation program comprised of four modules; cognitive differentiation, attention, memory and social perception. Subjects were assessed on cognitive, clinical and psychosocial measures at baseline, at discharge after 6 months and one year after discharge. The current study presents results from the one year follow-up. Repeated measures

analyses of variance were conducted to investigate between-group effects over time. Although not significant, there was more than a 10-point difference in mean IQ between the groups, with the control group scoring higher. Analyses were therefore repeated using IQ as a covariate. The results showed an overall improvement over time for eight of the 10 cognitive variables as well as for psychiatric symptoms and psychosocial functioning. Prior to controlling for IQ no significant between-group differences were evident. After controlling for IQ the remediation group showed greater improvement in early visual information processing as measured by the SPAN of Apprehension Task ($p<0.05$). No other between-group differences were evident. No relationships were found between changes on cognitive measures and changes in measures of clinical symptoms and psychosocial functioning. Because of the small sample size and the risk for Type II error, we also conducted a more exploratory set of within-group analyses. The results showed that both groups improved on several measures over time, although the remediation group improved on more measures. In conclusion, the results indicate that early visual information processing can be improved through training and that this effect is evident more than 1 year after termination of the remediation program. Improved cognitive functioning in both groups may be caused by beneficial elements in the psychoeducational program. Because the sample size is small and the study may be underpowered, the results should be interpreted with caution.

PREDICTING ADHERENCE TO ORAL ATYPICAL ANTIPSYCHOTIC MEDICATIONS

D. I. Velligan,* D. A. Castillo, P. M. Diamond, M. Woolsey, D. C. Glahn, Y. W. Lam, L. Ereshefsky, A. L. Miller
Psychiatry, UTHSCSA, San Antonio, TX, USA

Medication adherence is poor for patients with schizophrenia. We examined predictors of adherence to oral atypical antipsychotic medications in a sample of 48 schizophrenia patients assessed upon hospital discharge and then followed prospectively for three months. The dependent variable was the percentage of pills taken as prescribed determined by randomly scheduled, in-home pill counts at 3 months. Independent variables included insight, cognitive functioning, therapeutic effect (side effect/benefit ratio), ability to take medication correctly as assessed from a performance-based test and drug attitude. The regression model accounted for 29% of the variance in adherence ($F(7,38)=3.59$ $p<.005$), however only two of the independent variables, cognitive function and insight, contributed significantly to the prediction. Patients with less insight and better cognitive functioning were less likely to take medication as prescribed. While cognition is positively related to the ability to take medication, it is negatively related to the amount of medication taken. Patients with significant cognitive deficits are more likely to get help with taking medication, which may account for them taking medication more regularly. Patients with better cognitive functioning are likely to have more independence and more chance for errors in self-medication. In addition, those with higher cognitive functioning may be more like the general population who have been found to adjust medication doses, and to decide which medications to take when. Environmental supports found to improve adherence may work by bypassing situational/environmental problems with attention/memory rather than cognitive ability per se, and/or by bypassing the decision-making process that leads to self-adjustment of medication.
Funded by R01 MH 62850-05.

ATTENTION SHAPING FOR CHRONIC SCHIZOPHRENIA

S. M. Wilkniss,* S. M. Silverstein, W. D. Spaulding, A. Menditto, A. Savitz, B. Essex, H. Starobin
Psychiatry, Univ. of Illinois at Chicago, Chicago, IL, USA

Many people with schizophrenia are characterized by attention deficits that preclude the ability to benefit from available psychosocial treatments (Green, 1996). Patients requiring the most structured levels of treatment have the most severe attentional deficits and the poorest outcomes in skills training (Spaulding & Sullivan,1992). Attention Shaping Procedures (ASP) are the only interventions that have demonstrated success in improving attentiveness in this group (Silverstein, Menditto, & Stuve, 2001). ASP is a behavioral technique that involves goal-setting, and the delivery of reinforcement for increasingly lengthy durations of attentiveness, with fading of reinforcement for earlier, lesser durations, until a target criterion is reached. The data presented are from two studies as part of a larger effort to develop a standardized version of the attention shaping intervention. The first study included random assignment of chronic schizophrenia inpatients to one of two treatment groups 1) experimental: integrated ASP and the UCLA Community Re-Entry (CREP) module or 2) control: UCLA CREP alone. The second, study compared integrated ASP and UCLA Basic Conversation Skills Module (BCS) with BCS alone (control) in chronic schizophrenia inpatients at three sites. In both studies, groups were matched for attention deficit and hours of treatment. The major finding from both studies was that there were large increases in attentiveness over time in the ASP conditions only. The slope of change of attentiveness over time in the control groups was effectively zero whereas for the ASP groups it indicated an over 25 degree change on average. In study two, the ASP group demonstrated approximately 150% improvement from pre- to post-group scores on the UCLA Module. Thus, Integrated ASP and UCLA skills training intervention is superior to skills training alone in improving attention and skill. Green, MF (1996). What are the functional consequences of cognitive deficits in schizophrenia? *American Journal of Psychiatry*, 153, 321-330. Spaulding, WD, & Sullivan, M (1992). From laboratory to clinic: Psychological methods and principles in psychiatric rehabilitation. In R. P. Liberman, (Ed.), *Handbook of psychiatric rehabilitation* (pp. 30-55). Boston: Allyn & Bacon. Silverstein, SM, Menditto, AA, & Stuve, P (2001). Shaping attention span: An operant conditioning procedure to improve cognition and functioning in schizophrenia. *Schizophrenia Bulletin*, 27, 247-257.

USE OF THE INDEPENDENT LIVING SCALES TO MEASURE COMMUNITY FUNCTIONING IN PATIENTS WITH SCHIZOPHRENIA

A. E. Wood,* A. Tapp, A. Kennedy, N. Kilzieh
VA Puget Sound Health Care System, Tacoma, WA, USA

Schizophrenia is associated with chronic impairments in community functioning and the activities of daily living. However, schizophrenia is a heterogeneous disorder and the level of functional abilities can range from needing institutionalized care to independent living. Thus, it is important to be able to measure the range of functional abilities seen in schizophrenia. The Independent Living Scales (ILS; Loeb, 1996) provides a standardized assessment of the instrumental activities of daily living. The instrument asks the subject to perform problem-solving skills, demonstrate knowledge, and demonstrate specific tasks. The ILS is comprised of five subscales designed

to measure important components of independent living: Memory/Orientation, Managing Home and Transportation, Health and Safety, and Social Adjustment. Additionally, two factors can be derived from different items on the subscales: Problem Solving and Performance/Information. The five subscales also combine to create an overall Full Scale Standard Score. Forty-eight subjects with schizophrenia or schizoaffective disorder were administered the ILS along with a questionnaire of activities of daily living (ADL), a battery of cognitive tests, and the Positive and Negative Syndrome Scale (PANSS) to measure psychiatric symptoms. The battery of tests was repeated at 12 weeks. Average age of the sample was 48.77 years and average level of education was 12.85 years. The ILS showed good test-retest reliability in this sample with the Full Scale Scores correlating strongly between administrations (r=.78, p<.01). The ILS also showed good content validity with significant correlations with the ADL at baseline (r=.68, p<.01) and 12 weeks (r=.64, p<.01). The ILS Full Scale Score was negatively correlated with the PANSS total score (r=-.56, p<.01), indicating that subjects with higher levels of psychiatric symptoms had lower levels of functional abilities as measured by the ILS. The ILS was also positively related to the measures of cognition, specifically measures of executive functioning, memory, and attention. Overall, the ILS demonstrated good validity and reliability with this sample of patients with schizophrenia and schizoaffective disorder. The ILS appears to have the sensitivity in measuring this population to detect relationships between functional outcome, psychiatric symptoms, and cognition.

ENVIRONMENTAL SUPPORTS IMPROVE TARGETED BEHAVIORS IN SCHIZOPHRENIA

M. Woolsey,* M. Wang, N. J. Maples, M. DiCocco, D. I. Velligan
Psychiatry, UTHSCSA, San Antonio, TX, USA

Cognitive Adaptation Training (CAT) is a psychosocial treatment using environmental supports such as signs, calendars, checklists, hygiene supplies, and electronic devices to cue and sequence adaptive behavior in the home environment. While previous studies have demonstrated the effectiveness of CAT relative to control conditions, results could not be specifically tied to the use of supports and may have been due to non-specific factors. In the present study, 63 patients with schizophrenia/schizoaffective disorder were assessed on measures of adaptive functioning and then randomized into one of three groups 1) CAT-customized environmental supports established and trained in the home environment 2) Generic Environmental Supports (GES)-a generic set of supports given to subjects at the time of a clinic visit and replaced at monthly intervals and 3) assessment only. Results of an analysis of covariance for scores on the Social and Occupational Functioning Scale (SOFAS) at 3 months with baseline SOFAS scores used as a covariate indicated a significant effect of group ($F_{(2,76)}$ =3.53; p<.035). Patients in CAT had better functional outcomes than those in standard treatment (t=2.57 (p<.012). In addition, there was a trend for those in GES to do better than those in standard treatment (t=1.80; p<.076). Rates of utilization over 3 months of treatment for the 43 patients assigned to CAT or GES averaged approximately 87% and 41%, respectively (t=43.28; p<.0001). Patients in CAT had utilization rates greater than 85% for all types of supports, while rates for those in GES varied from 21% to 48%. Patients with problems in specific areas of adaptive functioning (medication adherence, grooming and hygiene, and orientation) were classified as either high or low utilizers of supports in each area and as either improved or not-improved in that area on the basis of structured assessments. Results of a chi square analysis indicated that area-specific improvements were noted for those who used environmental supports targeted at specific deficits ($X^2_{(1)}$ =4.72 p<.03). This was true irrespective of treatment group. Environmental supports can improve functional behaviors for patients with schizophrenia and are more likely to be utilized if customized and set up in the home environment.

COGNITIVE REMEDIATION THERAPY: RCT RESULTS AND A MODEL FOR FUTURE THERAPY

T. Wykes,* C. Reeder, B. Everitt, M. Knapp, A. Patel
Psychology, Institute of Psychiatry, London, London, United Kingdom

Cognitive remediation therapy (CRT) is a novel method of improving cognition for people with schizophrenia. Several meta-analyses have shown cognitive improvements with CRT but so far it has not been possible to differentiate the therapeutic factors that provide the most consistent effects. A single blind randomised controlled trial was carried out with two groups, Cognitive Remediation Therapy (CRT) versus Treatment as Usual (TAU). The 85 participants had cognitive impairments and depended on psychiatric services for support. Overall the therapy was effective in changing memory but the effects on other thinking skills were variable. Medication had little effect on outcome and people improved if they were receiving either typical or atypical medications. Even when there were no group effects, the changes that were brought about within the CRT group seemed to have an effect on other functioning characteristics. Improvements in cognitive flexibility had an effect on symptoms (auditory hallucinations) and memory improvements had a knock on effect on social functioning. However, if thinking skills improved in the TAU group these did not have an effect on other areas of functioning. These results have fuelled a model of therapy that begins to explain the cognition to functioning association. The model defines the essential cognitive targets in terms of the types of behavioural and cognitive schemas that need to be in place, as well as the process of achieving "transfer" of cognitive improvements from within therapy to the real world. Metacognition is highlighted as an essential target for cognitive improvements to result in functioning improvements.

21. Health Economics & Services Research

EFFECTIVENESS OF AN EARLY PSYCHOSIS TREATMENT SERVICE

D. E. Addington,* J. M. Addington, S. Patten
Psychiatry, University of Calgary, Calgary, AB, Canada

Background: Systematic reviews of randomized studies for complex treatment systems such as early psychosis treatment services yield inconclusive recommendations. Effectiveness studies offer alternatives for addressing policy and clinical decisions. Relapse is a key performance measure that can be used to assess the effectives of an early psychosis treatment service. Methods: This was a two year, longitudinal cohort study of consecutive admissions to an early psychosis treatment service which served the entire population in a catchment area. The primary outcome measure was relapse. The results were compared with the published literature. Results: 120 consecutive consenting admissions were recruited, 92 (76%) of whom were followed to one year and 84 (70%) to two years. Relapse was assessed by clinicians using structured criteria, the reliability of which was assessed by independent chart review. The two year relapse rate among subjects with complete two-year follow-up was 33% (95% CI 23% to 44%). A Kaplan-Meier life table censoring subjects lost to follow-up yielded a comparable estimate: 29% (95% CI 22% to 40%). These estimates compare favourably with a published range of 60% to 70% in the literature. Conclusions: An early psychosis service which serves a geographic population and which is part of the routine mental health services of that population can achieve outcomes that compare favourably with the published literature.

PHYSICAL COMORBIDITY AND SCHIZOPHRENIA

J. Arena,* B. Singer, P. F. Buckley
Psychiatry, Medical College of Georgia, Augusta, GA, USA

It is well known that people with schizophrenia die prematurely. While suicide is a major cause, it is also apparent that various physical conditions are overrepresented in patients with schizophrenia and these contribute to the high mortality rates associated with this illness. These physical comorbidities have come into sharper relief recently with the emergent adverse effect profile of antipsychotic medications. Clinicians are focusing on the adverse effects of second generation antipsychotics, including weight gain, the emergence of diabetes mellitus, and cardiovascular risk associated with these conditions. The additive effects of current treatments combined with lifestyle factors frequently associated with persons with mental illness, such as smoking, addictive disorders, poor nutrition and lack of exercise, are of clinical significance. We evaluated the health status and prevalence of physical illness of 478 state hospitals inpatients admitted to the state hospital acute care facility in Cleveland, Ohio over a 5 month period. Health status data were categorized, where appropriate, into one of 12 categories and further classified as "previous" (pre-existing) and/or "current", based upon 12 categories of physical illness in previous studies (Patient Outcomes Research Team (PORT) Patient Survey, Phase II Primary Data Analysis, 1997). Information was also collected on the treatment of illness, including general hospital admissions and medical consultations. The results of these data will be presented at this meeting.

TYPE OF SYMPTOM REMISSION AND TREATMENT OUTCOMES IN THE LONG-TERM TREATMENT OF PATIENTS WITH SCHIZOPHRENIA

H. Ascher-Svanum,* B. Zhu, D. E. Faries, B. J. Kinon, J. M. Kane
Outcomes Research, Eli Lilly and Company, Indianapolis, IN, USA

Objective: This prospective study examined relationships between type of symptom remission and type of treatment outcomes during long-term treatment of patients with schizophrenia. Methods: We used data from a large 3-year multi-site naturalistic study of patients with schizophrenia in the United States in which participants were assessed at enrollment and at 6 or 12-month intervals thereafter. We identified four mutually exclusive groups of patients based on their type of symptom remission: (a) remission of psychotic symptoms (positive and negative), as defined by the Schizophrenia Working Group expert consensus criteria using the Positive and Negative Syndrome Scale, (b) remission of depressive symptoms, defined as a score of ?9 on the Montgomery-Asberg Depression Rating Scale, (c) remission of both psychotic and depressive symptoms, and (d) nonremitted status on both depressive and psychotic symptoms. A broad range of outcome domains was assessed with validated measures (e.g., occupational functioning, safety in the community, substance use, activities/relationships, mental health resource utilization, life satisfaction, quality of life). Effect sizes were calculated to assess the differential impact of each remission type relative to the nonremitted group on each outcome variable at enrollment, at the end of year 1, 2, and 3 of the study, and across the 3-year study. Results: Across the 3-year study, remission of both psychotic and depressive symptoms was accompanied by best treatment outcomes in many domains. Compared to remission of psychotic symptoms, remission of depressive symptoms was more related (greater effect sizes) to better mental health functioning, greater life satisfaction, better family relationships, greater medication adherence, lower likelihood of seeking emergency psychiatric services, fewer alcohol-related problems, and lower risk of being a safety concern in the community (suicidal thoughts, suicide attempts, violent behavior, being victimized). Remission of psychotic symptoms was more related to higher Global Assessment of Functioning (GAF) scores, better quality of life, and higher activity levels (social, daily, leisure, and productive activities). Conclusions: Remission of specific symptom domains appears to differentially contribute to distinct treatment outcomes. Treatments able to improve both psychotic and depressive symptoms are apt to provide greater therapeutic benefits and to impact more outcome domains.

RESEARCH INTO PRIMARY PREVENTION OF DIABETES IN SCHIZOPHRENIA: METHODOLOGICAL CONSIDERATIONS

A. G. Awad,* L. P. Voruganti
Humber Regional Hospital, Toronto, ON, Canada

Background: Primary prevention of diabetes (type 2) has been shown to be feasible in the general population. Adopting identical prevention strategies in schizophrenic population requires a critical review of the original research methodology. Objectives: This review will include i. A summary of the designs and methods employed in the major diabetes prevention trials in the general population, and ii. The scope to replicate similar intervention tri-

als in schizophrenic populations. Methods: Major diabetes prevention trials conducted in the general population are reviewed with regard to their sampling strategies, randomization procedures, choice and delivery of interventions, duration of follow up, range of outcome measures and interpretation of data. Comparable themes and variations from schizophrenia research are explored. Results: Evidence from previous long term studies in schizophrenic populations broadly supports the idea that research on primary prevention of diabetes in schizophrenia is feasible. There are significant variations, however, in terms of identifying the target population, screening procedures, delivery of interventions, choice of outcome measures and long term monitoring strategies. Health economic indicators should also be taken into consideration. Conclusion: Research on primary prevention of diabetes in schizophrenia is feasible and potentially rewarding, provided the unique aspects of schizophrenic population are taken into consideration while designing and executing the intervention trials.

THE RELATIONSHIP BETWEEN DIET AND ANTIPSYCHOTIC TREATMENT

M. P. Ball,* R. W. Buchanan
Maryland Psychiatric Research Center, University of Maryland Baltimore, Baltimore, MD, USA

In recent years, there has been considerable documentation of the risk of weight gain and other health risks associated primarily with new generation (atypical) antipsychotic medications. There is still, however, little known about the mechanism for the weight gain. There is much anecdotal evidence for changes in diet reported by patients taking these medications. In this study, we attempted to validate dietary differences among patients with a DSM-IV diagnosis of Schizophrenia or Schizoaffective Disorder taking new generation antipsychotic medications by administering the Block Food Frequency Questionnaire to three groups of patients: those taking olanzapine, those taking clozapine, and those taking other atypical antipsychotics. Forty-three patients have been recruited so far: 16 on olanzapine, 15 on clozapine, and 15 on other atypical medications. All had been on their current medications for at least 6 months. The Food Frequency Questionnaire, a standardized self-report instrument, which evaluates subjects' food choices over the last year, was completed by all subjects. It is analyzed by Block Dietary Data Systems and provides a description of respondents' dietary choices in terms of nutrient and food group estimates. Serum cholesterol, glucose, and triglycerides were analyzed for the three groups and no significant between group differences were found. Preliminary evaluation of the Food Frequency Quetionnaire reveals no significant differences in dietary choices among the three groups. While patients on olanzapine have reported snacking more, results from this study indicate no significant difference in their snacking behavior when compared to that of the other two groups. Since this study addressed only the current nutritional status of participants, it did not capture any changes in dietary habits or laboratory values of participants since initiation of treatment with atypical antipsychotic medication. That is difficult to do retrospectively, but would be a valuable area for further investigation. Twelve subjects in this sample had co-morbid medical conditions, primarily diabetes and hypertension. Seven of those were in the group on other atypical antipsychotics. Further analysis and discussion will address co-morbid medical conditions and weight changes in this sample.

ATTITUDE CHANGE IN THE GERMAN PUBLIC AFTER THREE YEARS OF INTERVENTIONS TO REDUCE THE STIGMA ATTACHED TO SCHIZOPHRENIA: 2001 AND 2004

A. Baumann,* H. Zaeske, W. Gaebel
Psychiatry and Psychotherapy, Heinrich Heine University, Duesseldorf, Germany

The stigma attached to schizophrenia is one of the main obstacles to successful treatment. A lack of knowledge about causes, symptoms and treatment options as well as contact to people affected from the disorder leads to prejudices, negative attitudes and consequently to social isolation and discrimination. In order to reduce the stigma attached to schizophrenia a variety of antistigma interventions has been conducted and evaluated within the research project "Reduction of Stigma and Discrimination because of Schizophrenia" in the framework of the German Research Network on Schizophrenia (GRNS) (Woelwer et al. 2003) from 2001 to 2004. Hereby, the global antistigma program "Open the doors" of the World Psychiatric Association has been implemented (WPA 1998). For evaluation of these interventions two representative attitude surveys have been conducted in the public in six cities in Germany before (Gaebel et al. 2002) and after the intervention phase with the same interviewees (Npre=7246, Npost=4624). Assessed were knowledge about schizophrenia, attitudes towards people affected from the disorder, awareness of social discrimination of people with schizophrenia and social distance towards them. The results of the surveys show a decrease of negative stereotypes and social distance in 2004. More of the interviewees who know at least one of the current antistigma initiatives in Germany could indicate sources for schizophrenia. Also, in 2004 less interviewees than in 2001 believed that people with schizophrenia are violent and a danger to the public. Interviewees with contact to mentally ill persons in 2001 and 2004 showed the lowest social distance, while those who had no contact, neither in 2001 nor 2004, have the highest social distance. The social distance decreases more in persons who know at least one of the antistigma initiatives, most significantly in the cities, where the program "Open the doors" has been conducted. Conclusion: Targeted antistigma interventions can be successful in changing negative stereotypes and reducing social distance towards people with schizophrenia. References Gaebel W, Baumann A, Witte M, Zaeske H (2002): *Eur Arch Psychiatry Clin Neurosci* 252: 278-287 Woelwer W, Buchkremer G, Haefner H, Klosterkoetter J, Maier W, Moeller HJ, Gaebel W (2003): *Eur Arch Psychiatry Clin Neurosci* 253: 321-329 World Psychiatric Association: WPA, New York 1998.

SCREENING AND TREATMENT OF OSTEOPOROSIS IN FEMALES WITH AND WITHOUT SCHIZOPHRENIA

J. R. Bishop,* B. Alexander, B. C. Lund, T. B. Klepser, V. L. Ellingrod
Clinical and Administrative Pharmacy, University of Iowa College of Pharmacy, Iowa City, IA, USA

Women with schizophrenia may be particularly at high risk for developing osteoporosis due to medications, poor nutrition, substance abuse, smoking, and possibly medications. The purpose of this study was to investigate whether osteoporosis screening, prevention management, and/or treatment medication (e.g., clinical services for osteoporosis) are consistently provided to females with and without schizophrenia in three Midwest Veterans Affairs medical centers and clinics. In addition, we conducted a preliminary analysis of docu-

mented fracture rates in our study population. Forty-six women >45 years of age with schizophrenia were frequency matched on age with 46 female medical controls. Twelve months of progress notes were reviewed for clinical services for osteoporosis (i.e. treatment or prevention medication, educational counseling, or DEXA scanning). In addition, smoking status, smoking cessation counseling, the use of ethanol, and fracture rates were compared between the two groups. Overall, significantly fewer patients with schizophrenia (61%) received a clinical service for osteoporosis compared to a medical control group (80%). This difference was primarily due to a significantly lower number of patients with schizophrenia (48%) receiving any osteoporosis medication compared to the control group (78%). Only 28% of patients with schizophrenia received hormone replacement therapy (HRT) compared to 54% of the control patients. The rate of total fractures in the patients with schizophrenia (12/46, 26%) was significantly greater than in the medical control group (1/46, 2%) (Fisher's exact test, $p = 0.001$). Only 6 DXA scans were performed in our patients with 5 in the control group and 1 in a patient with schizophrenia (Fisher's exact test, $p = 0.20$). In conclusion, females with schizophrenia in three Midwest Veterans Affairs Medical Centers did not receive the same level of osteoporosis care compared to age-matched medical control patients. This was primarily due to a lower utilization of osteoporosis medication, specifically HRT.

USE OF ATYPICAL ANTIPSYCHOTICS AMONG VA PATIENTS WITH SCHIZOPHRENIA: NATIONAL TRENDS

F. C. Blow,* J. F. McCarthy, M. Valenstein, D. A. Smelson, C. Reist

National Serious Mental Illness Treatment Research & Evaluation Center, Department of Veterans Affairs, Ann Arbor, MI, USA

With the rising cost of medications and increasing formulary expenditures, organized health systems have become more concerned with the appropriate use of second-generation antipsychotics. However, most organizations do not have "real time" information about treatment patterns within their organizations or the impact of treatments on clinical outcomes. As a result, many organizations have simply restricted access to these new, expensive medications. The information systems of the U.S. Department of Veterans Affairs offer unparalleled opportunities to study medication use patterns in a large national health care system. The VA's National Serious Mental Illness Treatment Research and Evaluation Center (SMITREC) has developed several patient registries, including a National Psychosis Registry (NPR) that allows timely tracking of treatment patterns and patient outcomes. Data from the NPR suggests that the patterns of antipsychotic use are consistent with the VA clinical practice guidelines for schizophrenia. For example, in fiscal year 2003 (FY03), of 94,395 patients diagnosed with schizophrenia, 78.7% received oral antipsychotic medications. Further, of the 74,329 patients receiving oral antipsychotic agents, 84.6% received some fills of a second-generation agent. The rapid increase in the use of second-generation agents has slowed in recent years; however, there have been substantial shifts in the market share of individual agents. Although in FY03 risperidone and olanzapine were still the most commonly prescribed second-generation agents, quetiapine use has been increasing rapidly, with increases of about 5% for each of the last four years. The increase in quetiapine use appeared to come primarily at the expense of olanzapine. Much quetiapine use appeared to be "off label", with an average dose of only 250 mg. This presentation will review trends in atypical use among VA patients with psychotic disorders, the usefulness of "real time" tracking in setting priorities, and the potential for linking evolving treatment patterns with patient outcomes. This study was funded by the VA SMITREC.

MENTAL STATE CHANGES DURING ACUTE PSYCHIATRIC HOSPITALISATION AND ASSOCIATIONS WITH INPATIENT AGGRESSION AND DIAGNOSIS

V. J. Carr,* T. J. Lewin, K. Sly, A. Conrad, P. Ward, S. Clark, T. Coombs

Centre for Mental Health Studies, University of Newcastle, Callaghan, NSW, Australia

The Acute Services Project was conducted in three health regions (Hunter, Illawarra and South Western Sydney) between 1999-2002. One of the aims of this project was to quantify patterns of aggression and to examine associated pathways to care. A series of clinical modules was developed, together with project specific logs. One of these measures, the Patient Daily Log (PDL), which was completed by nursing staff for each patient on each shift, recorded a range of clinical management and patient-related factors, including aggressive incidents and mental state. During the 12-month evaluation, approx. 54,000 PDLs were completed on day or afternoon shifts, 48.3% of which related to patients with a discharge diagnosis of schizophrenia, 17.3% to patients with bipolar disorder, and 34.4% to patients with other disorders. Overall, 19.9% of PDLs were for patients involved in at least one serious aggressive incident during their admission (ie, physical contact or a definite intention to inflict harm). A series of three-way ANCOVAs was conducted to examine mental state changes by diagnosis and aggression status. For all 5 Current Mental State scales, there were substantial reductions between admission and discharge (in order: emotional distress, psychosis, cognitive impairment, disinhibition, and withdrawal). Admissions during which an aggressive incident occurred were associated with higher levels of disinhibition, psychosis, emotional distress and cognitive impairment, but there were no differential changes over time or by diagnostic group (ie, no interactions involving aggression status). Emotional distress levels were comparable across diagnostic groups, withdrawal was lowest and disinhibition highest among those with bipolar disorder, while psychosis and cognitive impairment were lowest among those assigned to the other diagnosis group. Reductions in disinhibition, psychosis and cognitive impairment from admission to discharge were more marked for those with bipolar disorder, with intermediate level reductions among those with schizophrenia. While aggressive behaviour has been associated with a range of risk factors, including diagnostic group, observable mental state, both on admission and throughout the period of hospitalisation, is likely to be more disturbed among those who become involved in aggressive incidents. Clearly, we need to better identify the circumstances under which such incidents occur and to develop improved prevention and management strategies.

THE BURDEN OF DEPRESSIVE SYMPTOMS IN THE LONG TERM TREATMENT OF PATIENTS WITH SCHIZOPHRENIA

R. Conley,* H. Ascher-Svanum, B. Zhu, D. Faries, B. Kinon

Maryland Psychiatric Research Center, University of Maryland, Baltimore, MD, USA

Background: Depressive symptoms are an important symptom domain in schizophrenia, and are recognized as a prognostic indicator of recovery and quality of life. The aim of this prospective study

was to assess the relationships between depressive symptoms and a broad array of functional outcomes in the long-term treatment of people with schizophrenia in typical care settings. Methods: We used data of a large 3-year prospective naturalistic multi-site study of people with schizophrenia in the United States (US-SCAP), in which subjects were assessed at enrollment and at 6 and 12 months intervals thereafter. Subjects who were depressed at enrollment (defined as score at least 16 on the Montgomery-Asberg Depression Rating Scale) were compared to non-depressed subjects on several functional domains. Outcomes were measured by the SCAP-Health Questionnaire, a validated patient-reported measure, the Heinrichs-Carpenter Quality of Life scale, and medical records, which provided information about utilization of mental health services. Statistical analysis used univariate tests and multivariate regression adjusted for socio-demographics and clinical characteristics. Group comparisons were performed at enrollment, at each following year of the study, and across the 3-year study. Results: At enrollment, 40% of the subjects were found to be depressed. Compared to non-depressed subjects (N=1351), the depressed subjects (N=877) were significantly more likely to use relapse-related mental health services (psychiatric hospitalizations, emergency psychiatric services, sessions with psychiatrists), to be a greater safety concern in the community (violent behavior, victims of crime, suicidal thoughts, suicide attempts), to have poorer life satisfaction, lower quality of life, lower levels of mental health functioning, poorer family relationships, lower level of medication adherence, and greater substance-related problems. Similar results were found during each of the 3 years following enrollment and across the 3-year study. Conclusions: People with schizophrenia and concurrent depressive symptoms are prone to have poorer long-term functional outcomes compared to people who are not depressed. Because of their greater use of relapse-related mental health services and higher risk of involvement with law enforcement agencies, these people will require special treatment interventions to help improve their chance for effective recovery.

ADVERSE EVENTS DURING MEDICAL/SURGICAL HOSPITALIZATIONS FOR PERSONS WITH SCHIZOPHRENIA

G. L. Daumit,* P. J. Pronvost, C. B. Anthony, D. E. Ford, D. M. Steinwachs

Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Background: The Institute of Medicine report, "To Err is Human", focused national attention on adverse events. Persons with schizophrenia may be at even higher risk for patient safety concerns than the general population. Objectives: 1) To estimate the prevalence of adverse events in medical and surgical hospitalizations for persons with schizophrenia compared to those without; and 2) To examine the extent to which these adverse events may be associated with death. Methods: We performed a cross-sectional study using data from all acute care Maryland hospital admissions in 2001-2002. We applied the Agency for Health Care Research and Quality's Patient Safety Indicators (PSIs), developed to detect adverse events in hospital data. We compared PSIs for hospitalizations with a secondary diagnosis of schizophrenia to those without schizophrenia and performed logistic regression to determine the association between schizophrenia and each PSI adjusting for patient and hospital characteristics. For persons with schizophrenia, we then examined the association between each PSI and in-hospital death. Results: The table shows the prevalence of adverse events and the adjusted relative odds of having a PSI for persons with schizophrenia compared to those without. These adverse events also increased the odds of in-hospital death substantially with the following adjusted odds ratios for death: infections due to medical care=2.6; postoperative respiratory failure=9.5; postoperative venous thromboembolism=2.6; sepsis=7.5; aspiration pneumonia=8.7. Conclusions: Persons with schizophrenia are at substantially elevated risk of adverse events during medical/surgical hospitalizations. These adverse events are associated with an increased risk of in-hospital death. Improving patient safety on medical/surgical units could be an important way to decrease mortality for this population.

Adverse events in medical/surgical hospitalizations for persons with and without schizophrenia

***adjusted for age, race, gender, medical comorbidities, substance abuse, teaching hospital, trauma center, ER admission, medical/surgical primary diagnosis**

IS THE INTENSITY OF PSYCHOTIC SYMPTOMS OR PERCEIVED QUALITY OF LIFE RELATED TO PATTERNS OF NEED FOR CARE IN SCHIZOPHRENIA?

P. A. Delespaul,* J. J. van Os

Psychiatry & Neuropsychology, Maastricht University, Maastricht, Netherlands

Background. Distress is an important factor that is related to the difference between psychotic experiences and illness. Care seeking behavior is a response to distress. In the current study we explore the relation between psychotic symptoms and need for care. Methods. A cohort of 600 psychotic severely ill patients of the regional mental health services of Maastricht (The Netherlands) was assessed at least yearly using the Monitor for Needs of Care (MNC). The MNC assesses patient demographics, mental state (using the Brief Psychiatric Rating Scale) and needs for care (using a consensus Camberwell Assessment of Needs) as well as Quality of Life (using 7-point Likert scales validated against the Lancashire Quality of Life Profile) and Quality of Care. Analyses were done with Multi-Level Random Regression techniques to assess both between and within factors that influence the relations. Results. In this 'in care' population the relation between the intensity of psychotic symptoms and amount of problematic domains that need care was significant (Chi2(1)=123.75 p<.001). Solved (Chi2(1)=7.10 p<.01) and even more pronounced unsolved proportions (Chi2(1)=215.44 p<.001) were related to positive symptoms. Quality of life was related to unsolved (Chi2(1)= 92.98 p<.001) but not to solved problems (Chi2(1)= 0.72 n.s.). When combining psychotic symptoms with perceived quality of life both factors each contributed significantly to the prediction of unsolved (Chi2(2)= 282.77 p<.001), but not solved needs (Chi2(2)= 4.97 n.s.). Conclusion. The results provide some indication that success in alle-

viating distress related to psychotic symptoms is more related to aspects of failing intervention strategies (unsolved needs) than to therapeutic success (solved needs). Unsolved needs should actively be screened and managed in psychotic illness.

PSYCHIATRIC HOSPITALIZATIONS AND VIOLENT BEHAVIORS IN THE LONG-TERM NATURALISTIC TREATMENT OF SCHIZOPHRENIA PATIENTS WITH OLANZAPINE OR QUETIAPINE

D. Faries,* H. Ascher-Svanum, B. Zhu
Outcomes Research, Eli Lilly and Company, Indianapolis, IN, USA

Background/Objective: Previous meta-analytical research found atypical antipsychotics to differ on efficacy. Greater treatment efficacy may translate to better outcomes in community care, including a lower risk of hospitalization and of violent behaviors. This study prospectively assessed and compared the long-term risk of psychiatric hospitalizations and of violent behaviors among schizophrenia patients treated with olanzapine or quetiapine in usual care. Methods: Analyses included data of patients treated predominantly with olanzapine (n = 559) or quetiapine (n = 111) during the Schizophrenia Care and Assessment Program, a non-randomized, multi-site, prospective, naturalistic, 3-year study of schizophrenia, conducted in the United States between 7/1997 and 9/2003. Patients medical records provided information about the occurrence of a psychiatric hospitalization, the number of hospital admissions, and the total hospitalized duration. The occurrence of violent behaviors was based on patients self-reports on a validated questionnaire, which also assessed medication adherence. Outcome measures were assessed at enrollment and at 6-month intervals thereafter. Statistical analyses used Marginal Structural Models (MSMs), adjusting for patient characteristics and time dependent illness severity markers at the beginning of each 6-month assessment period. Results: Across the 3-year study, quetiapine-treated patients were twice as likely to be hospitalized (odds ratio 2.13, p = .002), and had approximately 50% more admissions per 6-month treatment period (17.6 versus 11.3, p=.001) compared to patients treated with olanzapine. The treatment groups did not significantly differ on total hospitalized duration among hospitalized patients (p=.644). In addition, the olanzapine treatment group had a reduced risk of violent behaviors (odds ratio 0.39, p = .011) and an greater likelihood of medication adherence than the quetiapine-treated patients (odds ratio 2.04, p= .028). Conclusions: In the long-term treatment of schizophrenia, olanzapine treatment was associated with a reduced risk of psychiatric hospitalization and a lower likelihood of violent behaviors as compared to quetiapine. These results may be due to the greater adherence observed during treatment with olanzapine treatment.

VETERANS' VIEWS ON SUSTAINING INVOLVEMENT IN CARE FOR SCHIZOPHRENIA

E. P. Fischer,* J. C. McSweeney, J. M. Pyne, T. Yates
Center for Mental Healthcare & Outcomes Research, Central Arkansas Veterans Healthcare System, Little Rock, AR, USA

As part of a mixed qualitative and quantitative methods study of predictors of long-term involvement in care for schizophrenia, we used qualitative ethnographic interviewing techniques to elicit personal beliefs about what helps and hinders sustained involvement in care (SI) for patients with schizophrenia in the VA healthcare system. The average age of our purposive sample of 16 veterans with a history of intermittent involvement in treatment was 50.4 years. Most were male. 50% were African-American; 50%, European American. Analysis based on content analysis and constant comparison techniques identified 4 major facilitators (provider relationships, personal motivation, program assistance, family/friend assistance) and 4 major barriers (provider relationships, personal characteristics, access, and program characteristics) to SI. Provider relationships were the predominant influence for 62% of veterans and were cited by 94%. Veterans reported that having an ongoing relationship with at least one provider, feeling listened to and respected by providers, and feeling involved in making treatment-related decisions, regardless of the outcome of those decisions, provided strong motivation to remain in care. Correspondingly, frequent turnover among providers and the perception that providers did not listen to them, respect their knowledge, or want to help them increased the likelihood that they would drop out of care. Interestingly, for the majority of the sample who had multiple providers (e.g., psychiatrist and case manager), a positive, long-term relationship with one of the providers was often sufficient to counteract the impact of frequent turnover or a negative relationship with the other. On the other hand, technologic advances like the VA's electronic medical record were associated with a perceived lack of provider interest and patient involvement as patients often felt that providers spent more time entering data than listening to them. Our findings of the primacy of interpersonal aspects of provider relationships among predictors of SI, if confirmed, should be welcome news for provider systems like the VA. Provider behavior is both modifiable and under system control or influence. Further, while efforts to reduce miscommunication and enhance patient involvement in decision-making are challenging, they do not require expensive investments in physical resources or system reorganization. This study was funded by VA HSR&D IIR01-116.

THE COST OF RELAPSE IN SCHIZOPHRENIA: A COMPREHENSIVE 2 YEAR RETROSPECTIVE AUDIT

P. B. Fitzgerald,* J. Kulkarni, D. Arya, A. de Castella, S. Meere, S. Crowley
The Alfred and Monash University Department of Psychological Medicine, Alfred Psychiatry Research Centre, Melbourne, VIC, Australia

Objective: To quantify the costs and resource utilisation associated with a relapse of schizophrenia or schizoaffective disorder. Methods: A retrospective audit of objective and subjective data from 200 patients diagnosed with schizophrenia or schizoaffective disorder was performed. These patients accessed both inpatient and community services from two mental health services in Australia between 1 June 2001 and 31 May 2002. Entry into the audit was determined by a hospitalisation due to relapse. Data was collected for the 12 months before and 12 months after the hospitalisation. Results: There was a significant increase in contacts per month, and associated costs, after the index admission and approximately 20 days of hospitalization associated with the relapse. Increase in service use persisted for the full 12 months (average number of contacts per month = 4.6 /-4.8 at 1 month post admission, 4.7 /-5.7 at 12 months post-admission) following the index relapse episode. Conclusion: Increased health care resource utilisation is associated with relapse episodes in patients with schizophrenia or schizoaffective disorder. Importantly, increases in service use are not transient and costs persist for a considerable time period after an episode of relapse.

PREDICTORS OF MEDICATION NONCOMPLIANCE: A FIVE-YEAR LONGITUDINAL STUDY OF FIRST-EPISODE SCHIZOPHRENIA

F. W. Fleming,* M. L. Sievers-Rients, N. C. Andreasen, B. C. Ho
Psychiatry, The University of Iowa, Iowa City, IA, USA

Background: Discontinuation of antipsychotic treatment is a frequent cause for symptom recurrence in schizophrenia. Although accurate assessment of medication compliance is difficult, non-adherence to medication treatment among schizophrenia patients is common, and is at least equivalent to patients with other chronic medical conditions. Few studies have examined factors assessed around the time of initial diagnosis of schizophrenia that may mediate future non-adherence to antipsychotic treatment. Methods: One hundred and forty-four schizophrenia patients were evaluated prospectively every 6 months in the Iowa Longitudinal Study of Recent-Onset Psychoses. Multiple sources of information were used to assess medication compliance during 5 years of follow-up. Sociodemographics, illness characteristics and neurocognition assessed around illness onset were entered in a stepwise regression analysis to examine for predictors of medication noncompliance. Results: Sixty subjects (42%) had at least one rating of *poor compliance* or *non-compliance* during the 5 years of follow-up. Mean medication compliance for the sample was rated as *good*, with a nonsignificant trend toward improvement during later years of follow-up. Male gender, greater severity of psychotic symptoms, poorer social support and poorer processing speed/attention were significantly associated with medication noncompliance. Together, these factors assessed at illness onset accounted for approximately 18% of the variance in subsequent antipsychotic treatment adherence. Conclusions: The causes of medication noncompliance among schizophrenia patients are multifactorial. Initial predictors for subsequent antipsychotic noncompliance can help identify subgroups of schizophrenia patients who may benefit most from targeted interventions to improve treatment compliance.

ASSESSMENT OF DIFFERENCES IN ANTIPSYCHOTIC-RELATED RISK OF DIABETES MELLITUS IN A MEDICAID PSYCHOSIS POPULATION: SENSITIVITY TO STUDY DESIGN

F. Gianfrancesco,* R. Wang, J. Pesa, H. A. Nasrallah
Pharmacoeconomics and Outcomes Research, HECON Associates, Inc., Montgomery Village, MD, USA

Retrospective studies using large patient databases have reported conflicting findings regarding diabetes risks associated with antipsychotics. Sensitivity of findings to study design was assessed within a Medicaid psychosis population. Administrative data were analyzed for >100,000 Ohio Medicaid patients with psychoses treated or untreated with antipsychotics. Odds ratios (ORs) for patients treated with atypical or conventional antipsychotics versus untreated patients were estimated, varying the following criteria: screening for preexisting diabetes, identification of diabetes with prescription claims only, and antipsychotic monotherapy. Logistic regression controlled for patient age, sex, type of psychosis, length of observation/treatment, antipsychotic dosage, preexisting excess weight or dyslipidemia, and use of other drugs with potential diabetogenic effects. Selection bias was also assessed for risperidone, olanzapine, and quetiapine. Under the weakest study design (no prescreening, use of medical or prescription claims, and no monotherapy requirement), all antipsychotics were associated with statistically significant ($P<0.05$) higher ORs relative to untreated patients. Estimated ORs were clozapine 1.468 (95% confidence interval [CI]: 1.333–1.617), olanzapine 1.108 (1.050–1.170), quetiapine 1.270 (1.197–1.348), risperidone 1.232 (1.169–1.299), ziprasidone 1.226 (1.100–1.367), and conventionals 1.159 (1.098–1.224). Under the strongest study design (screening for diabetes 8 months before observation, use of prescription claims only, antipsychotic monotherapy), ORs relative to patients untreated with antipsychotics were significant for clozapine (1.484, 95% CI: 1.138–1.934) and olanzapine (1.149, 1.001–1.319) but nonsignificant for quetiapine (0.998, 0.834–1.195), risperidone (1.124, 0.983–1.284), ziprasidone (0.717, 0.415–1.239), and conventionals (1.025, 0.885–1.187). Selection bias favored olanzapine but not risperidone or quetiapine. Estimated risks of diabetes among antipsychotics are affected by study design. Employment of a more rigorous study design indicates that the risk of diabetes among the atypical antipsychotics was significantly greater with clozapine and olanzapine than in untreated patients with psychosis. These findings were made despite evidence indicating selection bias favoring olanzapine and disfavoring risperidone and quetiapine.

CHANGES IN SUBSTANCE USE IN PATIENTS WITH DUAL DIAGNOSIS: LINKS TO USE SEVERITY, SERVICE UTILIZATION, AND PROCESSES OF CHANGE

S. Gjonbalaj,* M. E. Bennett, A. S. Bellack
Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA

People with severe mental illness (SMI) have high rates of substance use disorders (SUDs). While treatment for SUDs is critically important, much is unknown about how use changes over time and the factors that impact change. Variables such as diagnosis, use severity, service utilization, and processes of change have not been examined together to determine their influence on change. We will examine factors that influence change in substance use in patients with SMI. We will use data from a 5-year study examining changes in substance use among patients with major depression or schizophrenia who met DSM-IV criteria for current cocaine dependence with or without a comorbid alcohol use disorder. Patients completed assessments of substance use, service utilization, processes of change, and reasons for change five times over their year in the study. Diagnoses and severity were measured with the Structured Clinical Interview for DSM-IV, substance use and service utilization were measured with the Substance Use Event Scale for Schizophrenia, and processes of change were assessed with the Processes of Change Scale and the Decisional Balance Scale. Our analyses address three questions. First, we examine the relationship between changes in use and severity of SUD by comparing substance use in patients with current cocaine dependence alone to those with both current cocaine dependence and current alcohol dependence. This will allow us to examine how alcohol disorders impact changes in drug use/abuse over time. Second, we investigate the relationships among changes in use, service utilization, and processes of change in our patient groups. This will provide a look at how clinically relevant variables such as treatment use and change strategies are related to actual change. Finally, we will look at the reasons given by patients to explain the changes in their substance use. This will give us some understanding of how

patients think about the factors that influence change. The implications of the findings for identifying treatment needs and designing and implementing interventions to decrease substance abuse in this patient population will be provided.

AGREEMENT BETWEEN CLINICALLY ASSESSED AND SELF-RATED MEDICATION ADHERENCE WITH SCHIZOPHRENIA IN HONG KONG

C. L. Hui,* E. Chen, C. Chiu, C. Law, K. Yip, C. Kan
Department of Psychiatry, The University of Hong Kong, Hong Kong, China

Adherence to antipsychotic treatment is an important aspect of long term management of schizophrenia and other related psychotic disorders. Since medication non-adherence is related to relapse, the correct identification of patients who are at risk of non-adherence problems is important. This study evaluates the sensitivity and specificity of the clinicians screening evaluations and explores factors that are related to non-adherence. Clinicians' rated questionnaires and matching patients' self rated questionnaires were administered to 511 consecutive outpatients (mean age 37.8 years and mean duration of illness 11.1 years) and their clinicians in four hospital clinic sites in Hong Kong. Items in the questionnaires addressed adherence behaviors and attitudes towards medication. In addition, clinicians also estimated the presence of adverse factors such as substance abuse, cognitive impairments etc. Patients' self report and clinicians' estimation suggested similar proportion (about 20%) of patients to have non-adherence behaviors (i.e. forgot to take the medication and decided to stop medication on their own). Clinicians' detection of non-adherence behaviors achieved relatively high specificity (0.84) but low sensitivity (0.33). A logistic regression analysis on patients' decision to stop medication revealed that significant predictors include clinicians' perception of patients' unawareness of illness, patients' reported lack of perception from the benefits of medication, patients' reported negative feelings associated with regular medication and younger age. Non-adherence is a widespread phenomenon affecting a significant proportion of outpatients under treatment. Clinicians are relatively more accurate in judging patients without non-adherence problems but are less effective in identifying patients with non-adherence problems. Non-adherence behavior is predicted by younger age, patients' negative attitudes towards medication, patients' lack of perceived medication benefit and poor illness awareness. We acknowledge partial support for this study from an unrestricted education grant from Janssen Pharmaceuticals.

THE SCOTTISH SCHIZOPHRENIA OUTCOMES STUDY: PHASE 1 OUTCOMES

R. Hunter,* R. Cameron, J. Norrie
Department of Psychological Medicine Gartnavel Royal Hospital, University of Glasgow, Glasgow, Scotland, United Kingdom

Background National Standards for Schizophrenia were introduced in Scotland in 2001 to establish a research-informed framework of care for schizophrenia to improve clinical outcomes. Useful outcome measures require reliability, validity, change-sensitivity, relevance to patients needs, and utility in practice. Outcome measures should encompass the perspective of both clinician and patient. This study was commissioned to assess the outcomes of a representative 10% sample of schizophrenic patients living in Scotland during and after the introduction of the Dept of Health Standards. We report data for Phase 1: sample characteristics & patient outcomes with reference to recommended Standards. Methods A 4 year naturalistic, observational, longitudinal cohort study. Clinicians from all NHS provider organizations in Scotland participated and trained in the use of outcome measures. Participants aged 18-65 with an ICD10 F20 diagnosis were recruited. Data on socio-economics, interventions (treatments, services, medication), and outcomes (pragmatic, HoNOS & AVON) were collected at intervals throughout the study. Results A representative sample of 1015 patients met entry criteria and were recruited in Phase 1 (Baseline). Participants were recruited in a 2:1 ratio of community to in-patient settings. Characteristics of the group are presented together with services and interventions received. This was compared with an audit of how well NHS provider organisations are meeting the prescribed Standards. Comment The results from Phase 1 of this observational study describe the interventions received, type of outcome & quality of care in a large sample of people with schizophrenia. Research-informed standards have emphasized modern approaches including community-based care, second generation anti-psychotics, & psycho-social interventions. Yet few if any of these treatments have been evaluated for effectiveness in naturalistic settings. These results show that outcomes are still poor for most patients with schizophrenia, even in developed services where considerable effort is made to attain high standards of care with modern interventions.

EFFECT OF ZIPRASIDONE INITIAL DOSING ON DISCONTINUATION IN SCHIZOPHRENIA

A. T. Joyce,* D. J. Harrison, D. A. Ollendorf
PharMetrics Inc., Watertown, MA, USA

We conducted this study to examine the effects of initial ziprasidone dose on discontinuation rates, using the PharMetrics integrated medical and pharmacy claims data. Patients ≥18 years with a diagnosis of schizophrenia and a ziprasidone claim between March 2001 and February 2003 continuously enrolled for ≥6 months before and ≥3 months after initiation of ziprasidone were stratified by initial daily dose (≥40 mg and <80 mg [Low] versus ≥80 mg and <120 mg [Medium] versus 120-160 mg [High]). The 6-month risk of discontinuation was examined using Cox proportional hazards models controlling for gender, psychiatric comorbidities, and pre-ziprasidone utilization of antipsychotics (atypical, conventional, none). Mean age of the sample (N=1058) was 38 years; 42% were male. The 6-month risk of discontinuation was significantly greater in patients with a Low versus a High initial dose (HR 1.357; 95% CI 1.070-1.721; P=0.012) and trended towards significance when comparing a Medium versus a High initial dose (HR 1.163; 95% CI 0.905-1.494; P=0.237). The largest difference in discontinuation rates between dose groups occurred after the first prescription. In conclusion, patients initiating ziprasidone therapy with an initial dose of at least 120 mg/d had better medication adherence compared with those initiating at lower doses. This finding may reflect improved efficacy at daily doses ≥120 mg.

OLANZAPINE VERSUS RISPERIDONE IN NEWLY ADMITTED ACUTELY ILL PSYCHOTIC PATIENTS

J. E. Kraus,* B. B. Sheitman, A. Cook, R. Reviere, J. A. Lieberman
Psychiatry, University of North Carolina Hospitals, Chapel Hill, NC, USA

Objective: Risperidone and olanzapine are the two most widely prescribed second-generation antipsychotics. The purpose of this study

was to compare the efficacy of risperidone and olanzapine using duration of hospitalization as the primary outcome measure. This outcome was selected as it is an indirect measure of how well patients are responding to the medication and represents a "real world" endpoint relevant to practicing hospital psychiatrists. Method: The study was done at a large state psychiatric hospital in North Carolina from 2001 to 2003. Subjects were eligible for inclusion if they required treatment with an antipsychotic (e.g., positive symptoms) and were able to provide informed consent. 85 patients entered the study and were randomly assigned to risperidone (n = 40) or olanzapine (n = 45). Treatment was naturalistic, and dosing was based on the discretion of the treating physician. Results: There were no significant differences in the demographics of either treatment group or in the use of PRN/concomitant medications. Eighty percent of each group remained on the study medication at discharge. There was no difference in the mean duration of hospitalization for the risperidone group (7.9 days) as compared to the olanzapine group (8.1 days). Conclusions: Risperidone and olanzapine were equally efficacious, suggesting that measures other than "efficacy" (e.g., side effects, cost) should be considered when determining overall "effectiveness" of treatment. This study was supported by a grant from the Stanley Medical Research Institute.

PATTERNS OF COMBINATION ANTIPSYCHOTIC TREATMENT FOR VETERANS WITH SCHIZOPHRENIA

J. Kreyenbuhl,* M. Valenstein, J. F. McCarthy, D. Ganoczy, F. C. Blow
Psychiatry, University of Maryland, Baltimore, Baltimore, MD, USA

Background: Although clinical guidelines consider antipsychotic monotherapy the standard of care for the treatment of schizophrenia, results of prescription surveys suggest that use of antipsychotic combinations (or 'polypharmacy') is a relatively common practice. Empirical support for the safety and efficacy of antipsychotic combinations is lacking, while evidence for risks to patients is accumulating. The objective of this study is to describe the patterns of combination antipsychotic treatment in a national sample of VA patients with schizophrenia. Methods: The source of data for this study is the VA National Psychosis Registry, which contains administrative encounter records of all health services and prescriptions dispensed to patients with psychotic disorders in VA facilities across the U.S. We identified all VA patients with a diagnosis of schizophrenia or schizoaffective disorder in 2000 and report the prevalence and patterns of use of persistent combination antipsychotic treatment, defined as prescription of 2 or more different antipsychotic medications that overlapped for 90 or more consecutive days. Results: A total of 60,942 VA patients met diagnostic criteria, received antipsychotic medication, and could be observed for at least 90 days during the study period. During 2000, 9.5% (n=5,871) of the sample received combination antipsychotic treatment for at least 90 days. Almost three-quarters of patients received combinations of one first- and one second-generation agent, 18.2% received combinations of two second-generation agents, and 6.3% received two first-generation agents concurrently. The mean dosages of olanzapine, quetiapine, and risperidone were significantly higher when used in combination versus monotherapy, whereas doses for clozapine were similar between the groups. Comparable proportions of patients prescribed polypharmacy (11.8%) and monotherapy (10.9%) received concurrent antiparkinson medications (p=0.05).A smaller proportion of patients prescribed polypharmacy received concurrent antidepressants (15.2 vs. 19%; p<0.0001), whereas a larger proportion received concurrent anti-anxiety agents (24.5 vs. 22.5%; p<0.0001) and mood stabilizers (36.8 vs. 27%; p<0.0001) relative to patients prescribed monotherapy. Conclusions: Many veterans with schizophrenia are prescribed long-term combination antipsychotic therapy. More research is required to understand the impact of this practice on symptoms, side effects, service use, and costs.

THE USE OF DEPOT ANTIPSYCHOTICS IN CROSS CUTLURAL SETTINGS: RELATIONSHIP TO POLYANTIPSYCHOTIC AND POLYPSYCHOTROPIC PRESCRIBING

T. J. Lambert,* T. Callaly, A. Wheeler, C. Ng, P. Udomratn, N. Jan, B. Singh
University of Melbourne, Parkville, VIC, Australia

Objective: While trends of depot prescribing among patients with a psychotic disorder have been well documented in the literature comparatively few have examined cross-cultural differences. The aim of this study was to contrast differences in depot prescribing among outpatients with a psychotic disorder in Australia, New Zealand, Malaysia and Thailand. A secondary aim was to examine the hypothesis that the rate of polyantipsychotic therapy and general psychotropic polypharmacy will be determined in part by country, depot-use rate, service delivery model, and SGA use rate. Method: The Service Evaluation and Economic Research unit (SEER) has undertaken audits of psychotropic prescribing in outpatient, community, and inpatient settings in Australia and New Zealand since 1998. In recent years, these audits have been extended to include Asian countries and the US. In this study, the variables examined were: a) types of depot medication prescribed, b) examination of single and polyneuroleptic patterns of prescribing, and c) assessment of any adjunctive psychotropics prescribed. Data were utilized from Australia, NZ, Thailand, and Malaysia in outpatient / community settings. Results: While depot prescribing has decreased in Australian clinics over the years, it is still more commonly observed than in the comparator countries. Malaysia and Thailand had very low prescribing of depot monotherapy, although depot and oral combinations were prescribed to one half of patients in Malaysia. Rates of polyantipsychotic and polypsychotropic prescribing were linked to the sophistication of the service model, background rate of clozapine use, and country, although NZ data were not classifiable with a simple multivariate model. Discussion: The implications of prescribing differences between countries, as well as rates of polypharmacy with depots will be discussed.

INDIVIDUAL PLACEMENT AND SUPPORT TO HELP PEOPLE WITH SEVERE MENTAL ILLNESS FIND AND MAINTAIN COMPETITIVE EMPLOYMENT: PRELIMINARY RESULTS OF THE FIRST CANADIAN RANDOMIZED TRIAL

E. A. Latimer,* T. Lecomte, D. R. Becker, R. E. Drake, I. Duclos, M. Piat, N. Lahaie, M. S. St-Pierre, C. Therrien
Douglas Hospital Research Centre, Verdun, QC, Canada

Background: Most people with severe mental illness (2-3% of the population) want competitive employment, but most remain unemployed. Traditional approaches emphasize sheltered settings. A rel-

atively new U.S. specification of supported employment for people with severe mental illness, Individual Placement and Support (IPS), places people quickly into individually matched competitive settings. Several U.S. trials indicate that IPS is singularly effective at helping people find and maintain competitive employment. The purpose of this study, a first in Canada, was to investigate the effectiveness of IPS in a Canadian setting. Differences in welfare regulations, legislation pertaining to hiring of people with disabilities, alternative vocational programs, and other factors, were thought likely a priori to affect outcomes. Setting: The Douglas hospital is a psychiatric facility in Montreal that serves a geographic sector of about 260,000 people. Methods. 149 adults with a diagnosis of severe mental illness who were not previously employed and who expressed a desire to work in a competitive setting were randomly assigned to receive either IPS services (n=75) or traditional vocational services at the Douglas hospital(n=74). They were interviewed at baseline and successive 2-month intervals for one year. Employment outcomes (hours, wages, type of work) were tracked, as well as several non-vocational domains including symptoms (BPRS), self-esteem, social network and quality of life. Results: Over the first 12 months of the study, 16 IPS clients and 8 control clients were lost to follow-up ($p<0,08$). Intent-to-treat analyses indicate that over the 12 months of follow-up, 46% of clients in the IPS group obtained at least some competitive employment, vs. 22% of the control group ($p<0.002$). IPS clients worked on average 10.5 hours per month in competitive employment and earned $78.01 from such employment, compared to 6.0 hours ($p<0.01$) and $42.81 ($p<0.01$) in usual services. Consistent with previous studies, we did not find that group assignment affected non-vocational outcomes. Conclusions: IPS appears more effective than usual services at helping people with severe mental illness find regular employment in Quebec also. Results might have been even better were the Quebec government to modify regulations that currently provide economic disincentives to competitive employment for the disabled.

A QUALITATIVE INQUIRY INTO FACTORS INFLUENCING THE ACCESS TO SOMATIC HEALTH CARE AMONG PEOPLE WITH SCHIZOPHRENIA AND OTHER SERIOUS MENTAL ILLNESSES

A. Lucksted,* R. Goldberg
Psychiatry, Univ of Maryland, Baltimore, Baltimore, MD, USA

This study explored the situations and experiences that may form facilitating and/or obstructing factors for people with SMI receiving quality somatic healthcare, from the consumer point of view. This inquiry used semi-structured qualitative in-person interviews with volunteers after full informed consent. Potential participants were recruited as they waited for mental health appointments at two diverse local outpatient mental health clinics. Interviews were audiotaped and transcribed with identifying details removed. A data-driven, grounded theory approach was used to extract and organize the various types and roles of facilitators and barriers. Results indicate that participants experience many of the same difficulties and preferences regarding somatic health care as reported by the general population: insufficient funds and insurance coverage to pay for needed care, bureaucratic frustration, harried and hurried providers. Additionally, some discussed barriers more specific to having schizophrenia or other SMIs: difficulties in self-care and health promotion behaviors, experiencing stigma while accessing health care, particular poverty and transportation barriers due to being unable to work. Regarding facilitating factors, participants expressed many positive experiences and preferences that are common in the general population, including being more comfortable, engaged, and confident of receiving quality care when they perceive providers as compassionate, caring, patient, friendly, listening, and well informed about medicine. Participants also discussed aspects of coordination between mental and somatic health care, with one particularly strong theme that mental health programs and practitioners seem to inquire about a clients somatic health and needs much more often and with much more active follow-through (referrals, assistance) than somatic providers do about the clients mental health or needs. Many also expressed high initiative in obtaining needed care, and high desire to understand their own health issues better. We conclude that the somatic health of people with schizophrenia and other SMIs could be enhanced if somatic health care providers were able to engage with patients in more humanistic, considerate, patient, and empowering ways. We also conclude that the health related motivation shown by participants could be an important mechanism for helping SMI clients help themselves, by providing desired patient education and advice.

ADHERENCE TO TMAP GUIDELINES FOR TREATMENT OF SCHIZOPHRENIA

A. Miller,* M. A. DiCocco, T. M. Kashner, M. L. Crismon, J. A. Chiles, A. J. Rush
Psychiatry, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

In the Texas Medication Algorithm Project (TMAP) participants were trained on and supported in implementing specific medication management parameters. Clinical coordinators worked with physicians to follow the guidelines and TMAP investigators had conference calls and on-site visits with each of the four public mental health clinic sites implementing the schizophrenia algorithm with 168 patients over 1-2 years. The procedures manual contained recommendations with regard to: antipsychotic dosing, titration of new antipsychotics, duration of therapeutic trials, frequency of visits, symptom assessments at each visit, decision to switch to new antipsychotic, and use of combination antipsychotics. Antipsychotic doses were within recommended ranges at 76% of visits. For antipsychotic trials lasting at least three weeks, titration to minimum therapeutic dose within three weeks occurred 72% of the time. In 85% of new antipsychotic trials a therapeutic dose was achieved, and 90% of the time once a therapeutic dose was reached it continued in the therapeutic range for at least four weeks. Frequency of patient visits increased after initiation of new antipsychotics. About 75% of the time the next visit was scheduled within two weeks. Recommended symptom measures were obtained by the clinical coordinators at 99% of visits. Although positive symptoms were the most common reason for changes in antipsychotic medications, persistent positive symptoms often did not lead to a medication change in patients with two or more prior medication failures. In 59 such episodes a new medication was begun within 12 weeks in 3% of instances and at any time prior to end of study in 25% of instances. Clozapine was underutilized. Combination antipsychotics were recommended only after failure or refusal of clozapine and trials on multiple antipsychotic monotherapies. Only 26% of 19 instances of long term use of combination antipsychotics met these criteria. In contrast to the findings

of the Patient Outcomes Research Team (PORT) study of medication use in public mental health clinics, dosing and medication management conformed well with expert recommendations among TMAP participants. This difference is likely due to TMAP's implementation support and ongoing guidance. The lowest provider adherence to recommendations was with the sickest, most persistently ill patients, particularly in terms of underutilization of clozapine.

VA HEALTH SYSTEM TREATMENT RETENTION AMONG PATIENTS WITH PSYCHOSES: A NATIONAL ASSESSMENT

J. F. McCarthy,* K. L. Barry, F. C. Blow, E. P. Fischer, T. J. Hudson, R. V. Ignacio, R. R. Owen, M. Valenstein
National Serious Mental Illness Treatment Research & Evaluation Center, Department of Veterans Affairs, Ann Arbor, MI, USA

Objectives: Treatment retention and continuity are essential components of quality care for patients with schizophrenia and bipolar disorder. Psychosis treatment guidelines recommend at least three outpatient contacts per year. To target interventions, this study seeks to identify characteristics of patients at increased risk for loss to care. Methods: Using the VA's National Psychosis Registry, we identified 162,830 patients with diagnoses of schizophrenia or bipolar disorder during fiscal year 1998 (FY98) who were alive at the start of FY99. We assessed time to first 12-month gap in VA utilization during FY99-FY01. Using multivariate survival analysis, we evaluated the influence of patient and health system factors. Patient measures included age, gender, race/ethnicity, marital status, miles to nearest VA medical center (VAMC), psychiatric diagnosis, Charlson comorbidity score and setting of last utilization in FY98. Facility measures included academic affiliation, region, and an index of mental health services delivery. We controlled for days since last VA contact, at the start of FY99. Robust variance estimates adjusted for the nested nature of the data. Results: Over three years, 10,099 patients had a 12-month gap in care (6.2%). By comparison, 8.0% died before a gap was observed. Patients were at increased risk ($p<0.001$, unless otherwise noted) of a gap if they were younger; male; black, Hispanic, or Native American; had bipolar disorder; or lived farther from VAMCs ($p<0.05$). Patients with greater medical morbidity were less likely to have a gap ($p<0.01$). However, those whose final treatment of FY98 occurred in an inpatient psychiatric setting had greater risk than those treated in ambulatory or non-psychiatric ($p<0.05$) institutional settings. Patients at facilities in the West, with greater academic affiliation, or that provided more mental health services were more likely to experience gaps in care ($p<0.05$). Implications: Sustainable retention requires specifying patient subpopulations at highest risk. Among patients with psychotic disorders, those with the greatest need for psychiatric treatment may be most likely to fall out of care. The VA should consider targeting its efforts to improve retention of high-risk patients, particularly after psychiatric discharges.

CONFORMANCE TO QUALITY STANDARDS IN SCHIZOPHRENIA SERVICES

E. McKenzie,* H. Chuang, H. Smith, Z. Ismail, S. Boucher, D. Addington
Psychiatry, University of Calgary, Calgary, AB, Canada

The purpose of this study is to compare conformance rates to standards of care provided in schizophrenia treatment services in Calgary, Canada with published conformance rates in the United States. Conformance is defined as the percentage of cases in which the care delivered matches a previously defined standard of care provided to individuals with schizophrenia. The Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations (1998) were used as the standards in our study. We randomly selected 223 patients from three services providing outpatient care to individuals with schizophrenia. The main outcome measures were conformance to PORT treatment recommendations, which were evaluated using medical records and clinician interviews. Twenty six percent of patients receiving antidepressants either did not have a chart diagnosis of depression or depressive symptomatology noted in their medical records. Eligible patients for family treatments reported ongoing contact with their family. Vocational rehabilitation conformance rate referred to eligible patients only. Conformance to standards for care was generally modest and similar to rates published in the United States. This suggests the need to improve the quality of care delivered to individuals with schizophrenia. Not unexpectedly, medical records data was often lacking in detail and necessitated concluding non-conformance to specific treatment recommendations.

Conformance Rates to PORT Treatment Recommendations (Cdn % vs. United States %)

(1) Lehman et al.(1998). Patterns of usual care for schizophrenia: Initial results from the schizophrenia patient outcomes research team (PORT) client survey. *Schizophrenia Bulletin*, 24, 11-20.
(2)Dickey et al. (2003) Guideline recommendations for treatment of schizophrenia. *Archives of General Psychiatry*, 60, 340-348.
(3)Young et al. (1998) Measuring the quality of outpatient treatment for schizophrenia. *Archives of General Psychiatry*, 55, 611-617.

PREDICTORS OF HEMOGLOBIN A1C LEVELS OVER TIME IN PERSONS WITH DIABETES AND SERIOUS MENTAL ILLNESS

D. R. Medoff,* J. Kreyenbuhl, F. Dickerson, C. Brown, K. Wohlheiter, R. Goldberg, L. Dixon
Psychiatry, University of Maryland, Baltimore, MD, USA

Epidemiological evidence suggests an increased prevalence of impaired glucose tolerance and Type 2 diabetes in people with serious mental illness (SMI). Medications side effects, adherence with treatment and health behaviors are important factors in health outcomes of both SMI and diabetes. Glycosylated hemoglobin (HbA1c) is a direct biochemical marker of diabetes control over the preceding 2-4 months. In the general population, HbA1c levels correlate with advancing age, minority status, obesity, lack of exercise, non-adherence with diabetes medications and diet. The object of this study was to compare HbA1c levels of patients with Type 2 diabetes and schizophrenia to patients with Type 2 diabetes and major mood disorders and Type 2 dia-

betes and no severe mental illness and to assess correlates of HbA1c values between groups and over time. We used an 18 month longitudinal study of 300 patients with Type 2 diabetes:100 with a schizophrenia diagnosis (SZ), 101 with a major mood disorder diagnosis (MA), and 99 had no identified severe mental illness (NSMI). Subjects were interviewed at baseline and at an 18 month follow up. Thirty percent of subjects were lost to follow up at 18 months. At baseline and at the 18 month follow up, all three groups of subjects had mean HbA1c values that exceeded recommended levels. No group showed a significant change in HbA1c over time. Significant bivariate correlates of change in HbA1c over time include the baseline values of receipt of diabetes education, high blood pressure, the number of cigarettes smoked (in the subgroup that smoke), and treatment with olanzapine (in the subgroup that receives antipsychotic drug treatment). Receiving more emergency room or inpatient health services at baseline correlates with a worsening of glycemic control and the receipt of more outpatient services correlates with an improvement in glycemic control. Clinicians should be aware that glycemic control may be influenced by modifiable factors such as medication choice, blood pressure, smoking and frequency of outpatient visits.

Glycosylated Hemoglobin (HbA1c)

IMPLEMENTING EVIDENCE BASED PSYCHOSOCIAL PRACTICES: LESSONS LEARNED FROM STATEWIDE IMPLEMENTATION OF TWO PRACTICES

L. L. Moser,* N. L. DeLuca, A. L. Rollins, G. R. Bond
Psychology, Indiana University Purdue University at Indianapolis, Indianapolis, IN, USA

As part of the National Evidence-Based Practices Project, we examined barriers and strategies to implementation of two evidence-based practices (EBPs) in Indiana. Over a 15-month period we observed 8 assertive community treatment (ACT) programs and 6 integrated dual disorders treatment (IDDT) programs and noted pertinent actions taken by the state mental health agency influencing implementation. We created a database containing summaries of monthly visits to each program and interviews with key leaders. Using this database and clinical impressions, we rated barriers and strategies at each site on 7 factors: Attitudes, Mastery, Leadership, Staffing, Policies, Workflow, and Program Monitoring. At the site level, the most frequently observed barriers were in the areas of leadership, staffing and policies for ACT, and mastery and leadership for IDDT. Overall, barriers were more evident for IDDT than for ACT. Strategies were less frequently noted but generally paralleled the areas noted for barriers. However, our central finding was that ACT was generally more successfully implemented than IDDT throughout the state, and that this difference could be traced in large part to state-level factors relating to historical preparation for the practice, establishment of standards, formation of a technical assistance center, and funding.

Definitions of Specific Factors Differentially Impacting Individual Agencies

TRI-ETHNIC DIFFERENCES IN SYMPTOM REMISSION DURING THE LONG-TERM TREATMENT OF PATIENTS WITH SCHIZOPHRENIA

R. A. Munoz,* B. Zhu, H. Ascher-Svanum, D. Faries, C. Barrio, R. Hough, A. Yamada
San Diego State University of Social Work, San Diego, CA, USA

Background/Objective: Achieving symptomatic remission is an important goal in the treatment of schizophrenia, which may be influenced by ethnic differences in illness phenomenology. This study assessed differences between three ethnic group, Euro-Americans, African Americans, and Latinos, in remission of depressive symptoms, remission of psychotic symptoms, or remission of both depressive and psychotic symptoms. Method: Data were drawn from a large (N=2327) multi-center naturalistic 3-year prospective study of patients with schizophrenia. Four types of symptom remission were identified at enrollment and at 12-month intervals thereafter: remission of psychotic symptoms (using the Remission in Schizophrenia Working Group expert consensus criteria), remission of depressive symptoms (score of at least 9 on the Montgomery-Asberg Depression Rating Scale), remission of both psychotic and depressive symptoms, and non-remitted status. Using Generalized Estimating Equation (GEE) model, adjusted for clinical and socio-demographic characteristics, the ethnic groups were compared on the proportion of patients achieving each type of remission across the 3-year study. Results: Latinos (N=222) were more likely to experience remission of psychotic and depressive symptoms than Euro-American (N=1099) or African-American (N=817) patients ($p<.01$). African-American patients were least likely to experience remission of psychotic symptoms ($p<.001$). Latino patients were more likely to experience remission of depressive symptoms compared to Euro-American ($p=.03$), with no other significant group differences.

RELIGIOSITY AMONG RELATIVES OF PATIENTS WITH SCHIZOPHRENIA AND SMI: IMPLICATIONS FOR CAREGIVING AND PSYCHOSOCIAL ADJUSTMENT

A. Murray-Swank,* L. Dixon, A. Lucksted, B. Stewart, Y. Yang, K. Wohlheiter
VISN 5 MIRECC, Maryland VA Healthcare System, Baltimore, MD, USA

When family members become ill, people frequently turn to religion and spirituality as a means of coping. Religiosity has been linked to better adjustment among family caregivers of patients with a variety of illnesses (e.g., Alzheimers disease, Cancer, childhood disabilities). This study focused on religious coping among family members of persons with schizophrenia and other SMI, with the following aims:(1) to examine the frequency of religious coping; and (2) to test hypotheses that dimensions of religiosity would be associated with better psychosocial adjustment for family members. Participants in a family education program (N=78) completed interviews at baseline and six months follow-up. Family members were assessed regarding receipt of spiritual support, use of religious coping, three dimensions of religiosity (i.e., attendance, importance, relation to God), and psychosocial adjustment in the following areas: depression, self-esteem, mastery and worry and displeasure concerning their ill relative. This sample of family members was deeply involved in caregiving for relatives with schizophrenia and other SMI (92% were very or somewhat involved). At each time point, 38% of family members reported receiving religious or spiritual support related to their relative′s illness during the previous three months. The most common types of religious coping included: prayer and meditation, reading religious scriptures, and seeking support from clergy and congregation members. Demographic variables (age, income, race, level of education) were not related to receipt of spiritual support. Greater religiosity was consistently linked to higher ratings of self-esteem (rs = .29 - .45) and mastery (rs = .24 - .38). Dimensions of religiosity were unrelated to family members level of depression and the amount of worry and displeasure they felt about their ill relative. Results indicate that family members of persons with SMI often turn to spirituality as a method of coping, and that religiosity may offer benefits as a coping resource via links to self-esteem and mastery. Further research is needed to better understand the consequences of religious and spiritual coping among caregivers, and the implications this has for service delivery. Studies are also needed to better understand the role of religion and spirituality in the lives of patients with schizophrenia and other serious mental illnesses. Supported grant from the RWJ Foundation to LBD.

THE VALIDITY OF THE GLOBAL ASSESSMENT OF FUNCTIONING (GAF) IN THE LONG-TERM TREATMENT OF SCHIZOPHRENIA

D. L. Noordsy,* H. Ascher-Svanum, D. E. Faries, B. Zhu, B. J. Kinon
Dartmouth-Hitchcock Medical Center, New Hampshire-Dartmouth Pyschiatric Research Center, Lebanon, NH, USA

Objective: This study assessed the convergent, discriminant, and predictive validity of the Global Assessment of Functioning (GAF) in the long-term treatment of patients with schizophrenia. Methods: We used data of the Schizophrenia Care and Assessment Program, a large (N=2327) multi-site naturalistic 3-year prospective study of patients treated for schizophrenia in the United States, conducted between 7/1997 and 9/2003. Patients were assessed at enrollment and at 12-month intervals thereafter with the GAF and various outcome measures, including clinician-rated scales and a patient self-report questionnaire. Psychiatric resource utilization was abstracted from medical records. Outcomes were measured in 7 primary domains: productivity, activities/relationships, safety in the community, health-related quality of life (HRQOL), resource utilization, substance use, and symptom severity. We assessed the relationships between the GAF and outcome variables that theoretically should be associated with the GAF (convergent validity), and variables that theoretically should not (discriminant validity). Predictive validity assessed the relationships between GAF at enrollment and outcomes assessed one year later. Statistical analyses included multivariate analyses adjusted and unadjusted for patient clinical characteristics such as symptom severity on the PANSS. Most analyses were repeated for each year of the study, and across the 3-year study. Results: The GAF was found to have good convergent, discriminant, and predictive validity, even after controlling for symptom severity. Across the 3-year study, higher GAF scores were significantly associated with greater productivity (e.g., employment, occupational accomplishments), higher level of activities/ better relationships (e.g., social activity, family relationships), greater safety in the community (less: violent behaviors, arrests, suicidal thoughts, suicide attempts), better HRQOL (e.g., quality of life, medication adherence), less resource utilization (psychiatric hospitalization, days hospitalized, emergency services), less severe substance-use problems, and less severe symptomatology (e.g., psychotic symptoms, depressive symptoms). Conclusions: The GAF was found to have sound convergent, discriminant, and predictive validity, and appears to reliably measure psychological, occupational, social, and service use outcomes during the long-term treatment of patients with schizophrenia.

AN INTERVENTION TO IMPLEMENT MEDICATION MANAGEMENT RECOMMENDATIONS OF SCHIZOPHRENIA GUIDELINES

R. R. Owen,* T. J. Hudson, C. R. Thrush, D. K. Williams, T. L. Armitage, P. Thapa
Center for Mental Healthcare & Outcomes Research, Central Arkansas Veterans Healthcare System, North Little Rock, AR, USA

Purpose: An “enhanced” strategy for implementing medication management recommendations of VA schizophrenia guidelines was tested in comparison to a basic educational strategy. Methods: 6 VA medical centers — 2 sites in each of 3 VA networks — participated. One site in each network was randomly selected to receive an “enhanced” implementation strategy, in which a trained nurse prompted provider guideline adherence and patient adherence. Patients with acute exacerbation of schizophrenia were enrolled and interviewed at baseline and 6 months using the Positive and Negative Syndrome Scale (PANSS). Medical records were reviewed. Logistic regression models were developed for two recommended practices, (a) switching patients from conventional antipsychotics to newer agents and (b) guideline-concordant antipsychotic dose, as a function of intervention assignment and patient case-mix characteristics. Multivariate multiple regression models were developed for PANSS Positive, Negative, and General Symptom subscales as a function of intervention, controlling for patient characteristics and network. Results: Of 291 subjects included in the analysis, 94% were male, 63% African American, 29% Caucasian, and 8% Hispanic. Mean age was 46 years (SD=7.9). Patients at enhanced sites who were receiving

conventional antipsychotics were more likely to be switched to a newer agent or have a new agent added (58%) than were patients at basic sites (30%, Chi-square = 6.9, $p < 0.01$, adjusted OR = 4.6, 95% CI 1.5-14.2). Guideline-concordant antipsychotic dosing showed no evidence of intervention effect. The effect of the intervention on PANSS subscales varied across sites, with a pattern of greater decreases in PANSS total and subscale scores at the enhanced sites as compared to basic sites. In the multivariate model, there were significant effects for two higher order interactions: network x intervention x age (p=0.0021), and network x intervention x baseline medication adherence (p=0.0089). Conclusion: The multi-component intervention significantly increased guideline-consistent switching of patients from conventional antipsychotics to newer agents, but did not affect use of recommended antipsychotic doses and effect on symptom outcomes was mixed. Further research should ascertain which intervention components were most effective and examine barriers to implementation. The work was supported by VA Health Services Research & Development (CPG 97-027).

RISPERIDONE LONG-ACTING INJECTION: PREDICTORS FOR CLINICAL IMPROVEMENT AT SIX MONTHS

M. X. Patel,* C. Young, D. M. Taylor
Psychological Medicine, Institute of Psychiatry, London, United Kingdom

To date, few studies have examined the utilisation of risperidone long-acting injection (RLAI) in the everyday clinical setting. This 6 month follow-up observational study aimed to investigate prognostic indicators for clinical improvement for patients commenced on RLAI. Consecutive sampling was conducted for all patients commenced on RLAI in the South London and Maudsley NHS Trust where policy dictates that RLAI is dispensed only for patients entered into an audit study (therefore 100% identification of eligible patients was feasible). There were no exclusion criteria. Prescription and clinical data were collected prospectively. The main outcome measure was clinical improvement six months after RLAI commencement, as measured by a one or more CGI point decrease (Clinical Global Impression scale). Logistic regression multivariate analyses were conducted for potential predictors including sociodemographic factors, illness characteristics and drug history. 140/250 patients clinically improved over 6 months although 132/250 discontinued RLAI prematurely. The best fit model for predicting clinical improvement included prior negative history of clozapine use and continuation of treatment with an interaction with clinical indication for RLAI commencement (non-adherence versus other). In comparison with clozapine naive patients, patients with a history of prior clozapine were less likely to have clinical improvement (12/39 vs 128/211; adjusted OR 0.27, 95%CI: 0.12-0.57, p=0.001), adjusting for continuation and clinical indication. In continuers, those with a clinical indication for RLAI commencement of non-adherence were more than four times as likely to have a clinical improvement than those with other clinical indications (53/65 vs 26/53), whilst adjusting for history of prior clozapine (adjusted OR 4.54, 95%CI: 1.94-10.61, p<0.001). The effect of clinical indication on clinical improvement was not statistically significant in discontinuers. Sociodemographics, illness characteristics, prior antipsychotic (depot versus other) and maximum dose did not enhance the model and thus were not included. Therefore in conclusion, a negative history of clozapine is a positive prognostic indicator for clinical improvement with RLAI. Additionally, clinical indication for RLAI commencement of non-adherence is a strong prognostic indictor in patients continuing on RLAI for 26 weeks (but not in those discontinuing before 26 weeks), whilst controlling history of prior clozapine.

TREATMENT COMPLIANCE AND PERSISTENCE AMONG SCHIZOPHRENIA PATIENTS: ATYPICAL VERSUS TYPICAL ANTIPSYCHOTICS

K. Rajagopalan,* F. Gianfrancesco
AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA

While atypical antipsychotics are increasingly used over typical antipsychotics due to fewer extrapyramidal symptoms and other advantages, treatment adherence continues to be a concern. In this study of schizophrenia patients, the atypicals were compared with typicals and with one another with respect to treatment compliance and continuation. A large claims database (1999–2003) representing several US commercial health plans was used. A total of 7216 antipsychotic monotherapy treatment episodes for patients with schizophrenia were identified. Adherence measures included: treatment compliance, captured with the "medication possession ratio;" and treatment continuation, measured by duration of treatment episodes. Antipsychotics included atypicals (risperidone, olanzapine, quetiapine, and ziprasidone) and the leading typicals (haloperidol, perphenazine, thioridazine, and thiothixine). Treatment-related factors associated with poorer medication compliance and shorter treatment continuation also were investigated. Multiple regression techniques adjusted for differing patient characteristics between groups. All atypicals had significantly greater compliance than the typicals. Quetiapine had the highest compliance, which was significantly ($P<0.05$) greater than that of risperidone (6% greater) and olanzapine (4% greater). Olanzapine also had significantly greater compliance than risperidone (2% greater). Olanzapine and the typicals showed significant negative associations between compliance and dosage levels, suggesting dose-related adverse events. Additionally, none of the atypicals had significantly longer treatment continuation than the typicals, but risperidone and olanzapine had longer continuation than quetiapine (7% and 10% longer, respectively). Cessation of all psychotropic therapy or switching to other psychotropics followed treatment termination. While switching significantly predicted shorter treatment continuation, ziprasidone alone showed a significantly greater likelihood of switching. Although all atypicals showed better compliance than typical antipsychotics, among atypicals, compliance with quetiapine was significantly better than with olanzapine or with risperidone. On the other hand, quetiapine had shorter treatment continuation than risperidone and olanzapine. However, this was not associated with a greater likelihood of switching to other psychotropic medications.

RATES AND PREDICTION OF RELAPSE IN AN INNER-CITY CLINICAL SAMPLE

A. Rollins,* S. J. O'Neill, K. E. Davis, T. S. Devitt
Research Department, Thresholds, Chicago, IL, USA

Overwhelming evidence from 26 controlled trials now establishes integrated mental health and substance abuse treatment as an evidence-based practice for consumers with severe mental illness and co-occurring substance use disorders. We also have excellent models for engaging and motivating consumers who are in early stages of treatment for substance use disorders. Unfortunately, less information is available on relapse prevention strategies for consumers in

this population who have moved to later stages of treatment and achieved remission from substance use disorders. This study documented rates of substance use relapse and explored predictors of sustained remission for consumers with severe mental illness at Thresholds, a large mental health agency in Chicago. Consumers with severe mental illness and a history of substance use disorder who had achieved remission and had at least two subsequent follow-up points (12 months after remission) were assessed using existing clinical records. Substance use information was recorded using standardized scales rated by clinicians over a four year period. Consumers who relapsed within 12 months after remission were compared to those who sustained their remission on a number of characteristics, including demographics, diagnoses, functional indicators, and living arrangements. Of the 133 consumers in full remission, 91 (68.4%) sustained remission at six months follow-up, and 69 (51.9%) sustained remission at 12 months follow-up. The strongest predictor of sustained remission at 12-month follow-up was residential status, with consumers living in Thresholds residential programs having lower rates of relapse. Multivariate analysis showed that consumers who were older, held jobs, and lived in Thresholds residential programs at initial remission had a higher likelihood of sustaining remission at 12 months. Therapeutic housing and employment appear to help consumers to maintain remission from substance use disorders.

USE AND COST OF POLYPHARMACY IN SCHIZOPHRENIA: DATA FROM A RANDOMIZED, DOUBLE-BLIND STUDY OF RISPERIDONE AND QUETIAPINE

M. F. Rupnow,* S. Stahl, A. Greenspan, C. Kosik-Gonzalez, G. Gharabawi
CNS Outcomes Research, Janssen Medical Affairs, L.L.C., Titusville, NJ, USA

Purpose: The use of concomitant antipsychotics and other psychotropic medications, symptom improvement, and the costs of polypharmacy in patients randomized to risperidone or quetiapine were examined in a double-blind, 2-phase trial. Methods: Patients with an acute exacerbation of schizophrenia or schizoaffective disorder received risperidone, quetiapine, or placebo in a 14-day monotherapy phase. This was followed by a 28-day additive-therapy phase during which clinicians were allowed to add antipsychotics or other psychotropic medications. Doses of risperidone and quetiapine were fixed in the additive-therapy phase. Results: Mean (± SD) doses at phase-1 endpoint were 4.7±0.9 mg/day of risperidone and 579.5±128.9 mg/day of quetiapine. Primary efficacy and safety data have been presented elsewhere. During the additive-therapy phase, additional psychotropics in total were received by 40% of 133 patients in the risperidone group and 57% of 122 in the quetiapine group ($P<0.005$ risperidone vs quetiapine); 62% of 53 placebo patients received psychotropics. Specifically, antipsychotics were received by 33%, 53%, and 57% of risperidone, quetiapine, and placebo, respectively ($P<0.005$ between risperidone and quetiapine). The relative risks (quetiapine vs risperidone) were 1.90 (95% CI 1.29–2.80) for antipsychotic polypharmacy and 1.68 (95% CI 1.16–2.42) for psychotropic polypharmacy. During both phases, reductions in PANSS total scores were greatest among risperidone-treated subjects (data presented elsewhere). The mean costs per patient of psychotropic polypharmacy during the additive phase were $62.34 in the risperidone group and $105.05 in the quetiapine group ($P=0.013$). The costs of polypharmacy per 1,000 patient-months of treatment were $63,322 in the risperidone group and $108,428 in the quetiapine group. Total drug costs (including the primary medications) per 1,000 patient-months of treatment were $360,364 in the risperidone group and $528,300 in the quetiapine group. Conclusions: The results confirm earlier observations from naturalistic/retrospective studies of higher rates of polypharmacy with quetiapine than with risperidone. These findings suggest that differential costs associated with polypharmacy can be substantial. Supported by Janssen Medical Affairs, L.L.C.

AN ITEM RESPONSE ANALYSIS OF THE POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS)

D. Santor,* H. Ascher-Svanum, R. Obenchain, J. Lindenmayer
Dept of Psychology and Psychiatry, Dalhouise University, Halifax, NS, Canada

Background/Objectives: The Positive and Negative Syndrome Scale (PANSS) is the most widely used measure of symptom severity in schizophrenia. Although extensively researched, it is unclear how each individual item differs in its usefulness in assessing the severity of schizophrenia. Item Response Theory was used to examine the degree of usefulness of each PANSS item in assessing overall severity of schizophrenia. Method: Data included baseline PANSS item scores of 9205 schizophrenia patients enrolled in an observational study or in one of 12 randomized clinical trials of antipsychotics. Using a nonparametric item response model, option characteristic curves were produced to examine how the probability of endorsing a particular option changes with increasing overall severity of illness, as measured by the PANSS total score. Illness severity was defined as the total score on the entire PANSS and on subscale (Positive, Negative, and General Psychopathology). Results: Option characteristic curves identified 9 PANSS items that performed very well (e.g., delusions, suspiciousness), 7 items that were good (e.g., grandiosity) and 14 items that performed less well (e.g., somatic concerns, depression). The Positive and the Negative subscales were more discriminating than the General Psychopathology subscale or the PANSS total score. Conclusions: Most of the PANSS items appear to be very good or good at assessing the overall severity illness. Results did show where a number of items and options might be improved and suggest that the Positive and the Negative subscales may be more sensitive to change than the general psychopathology subscale or the PANSS total score.

PATIENT COMPLIANCE IN SCHIZOPHRENIA: IMPROVING THE RATING OF MEDICATION INFLUENCES SCALE

C. Sapin,* P. Auquier, C. Francois
Health Economics & Epidemiology, H. Lundbeck A/S, Paris, France

Compliance with treatment frequently complicates successful management of schizophrenia. Few studies have been conducted concerning patient attitudes towards antipsychotic medications, most with contradictory results. This may be explained by a lack of consensus among professionals in evaluating compliance. The objective of this study was to develop an easy-to-interpret compliance criterion based on the Rating Of Medication Influences (ROMI) scale. Data came from the European Schizophrenia Cohort (EuroSC) of 1,208 patients from Great Britain, France and Germany. Patient follow-up

was every 6 months for 2 years. Clinical, compliance, quality of life and economic assessment scales were administered at each visit. The ROMI is a compliance instrument with 24 items whose response formats range from 1 to 3. Eight scores can be calculated to evaluate patient's reasons for compliance or non-compliance with treatment regimens. Logistic regressions were performed in order to select the most relevant questions among the 24 items, using backward, forward and stepwise selection methods. Then, a priori literature-based hypotheses were tested using Chi-square tests or t-tests when appropriate. Among the 1,208 patients included, 999 (82.7%) filled-in the ROMI at baseline. Whatever the selection method used, 10 out the 24 ROMI items were identified as the most relevant. Each dimension was composed of either one or two items. A binary criterion was then created in order to compare the compliant and the non-compliant patients. Significant differences were found when comparing ROMI dimension scores per compliance status ($p<0.001$), indicating that the binary criterion aptly summarised the information derived from the eight dimensions. As previously stated in the literature, severity of the disease assessed by the Positive and Negative Symptoms Scale was significantly linked to compliance, as well as quality of life and social functioning. Using adequate methodology, it seems relevant to assess compliance using a binary criterion based on the ROMI items. These preliminary results need to be confirmed, but this easy-to-interpret criterion can help decision-makers in comparing different therapeutic strategies and patient attitudes towards treatments.

THE INTERNATIONAL GP STUDY ON EARLY PSYCHOSIS (IGPS)

A. E. Simon,* D. Umbricht
Department of Psychiatry, Psychiatric Outpatient Services, Bruderholz, Switzerland

General practitioners (GPs) play a pivotal role on the pathways to care of patients in early phases of psychosis. In the first comprehensive survey on diagnostic and therapeutic knowledge among GPs, a nationwide survey among 1089 Swiss GPs was conducted in 2001 which showed that GPs not only wished specialized, low-threshold referral and assessment services, but also that GPs often underidentified insidious features of the prepsychotic and psychotic phases (Simon & Umbricht 2004). In 2003, the Swiss study was internationally replicated in 12 sites (New York, Toronto, Ottawa, Quebec, Melbourne, Sydney, Southern New Zealand, Ireland, United Kingdom, Stavanger/Norway, Austria, Prague). The overall response rate was 27% with a sample size of 2544. Independent of geographic region and health systems, GPs' underidentification of insidious features of the disease as well as their need for specialized, low-threshold referral and assessment services was reconfirmed. Our results give strong support for the establishment of such specialized facilities in order to improve appropriate recognition and intervention at the earliest possible stage for patients with beginning psychosis.

LINKS BETWEEN VIOLENCE, ADDICTION, AND PERSONALITY TRAITS IN FIRST EPISODES: MYTH OR REALITY?

A. Spidel,* T. Lecomte, J. C. Yuille
University of British Columbia, Vancouver, BC, Canada

Although there is evidence that individuals with severe mental illness are at higher risk for violent behaviour, few studies have looked at this relationship in a first episode of psychosis sample. This relationship might be an artefact of other mediating factors or only be present in those living with a mental illness for many years. For one, the diagnoses of personality disorder and substance abuse have been found to be strongly related to violence among criminal and psychiatric populations (Hodgins, 1993). There is also a considerable amount of comorbidity among major mental disorders, personality disorders, and substance abuse disorders (Rice & Harris, 1997). The current investigation aimed at: 1) assessing the prevalence of violence and substance abuse in a sample of first episode clients; and 2) comparing those with a history of violence to those without on addiction, personality traits, and symptoms. Method: Subjects: 53 clients have been recruited for the study to date. Inclusion criteria were: aged between 15 and 35; primary diagnosis in the psychosis spectrum, first break of psychosis within the last two years; and, consent to the study. Measures: Violence was measured with the MOAS (Kay et al, 1988) which assesses physical, verbal aggression and property aggression. Substance abuse was assessed using the ASI (Zanis et al, 1997) and symptoms were assessed with the BPRS (Ventura et al, 1993). The NEO-PI-R (Costa & McCrae, 1992) was used to assess personality traits. Results: Preliminary results show fairly high frequencies of violent acts (49%) within our sample, of which verbal aggression was the most frequently reported (53%). When comparing participants with a history of violence to those without, substance abuse and overall symptomatology were not significantly different for both groups. Physical violence was correlated with the BPRS total score ($r=.29$, $p<.05$). Verbal violence was significantly correlated with addiction severity scores for several drug types (hallucinogens: $r=.28$, $p<.05$; cocaine: $r=.30$, $p<.05$; and heroin: $r=.337$, $p<.02$). No significant differences were found for the NEO-PI-R subscales except for the agreeableness subscore, which differentiated individuals with a history of physical violence from those without ($t(50) = 8.696$, $p = .005$). Results from a bigger sample size will be presented and discussed.

TIME TO ALL-CAUSE DISCONTINUATION OF ATYPICAL VERSUS TYPICAL ANTIPSYCHOTICS IN THE NATURALISTIC TREATMENT OF SCHIZOPHRENIA

M. Swartz,* B. Zhu, H. Ascher-Svanum, D. Faries, S. Tunis, R. Landbloom, J. Swanson
Department of Psychiatry & Behaviorial Sciences, Duke University Medical Center, Durham, NC, USA

Background/Objective: This study compared atypical and typical antipsychotics on time to all-cause medication discontinuation, an important effectiveness measure in the usual care of patients with schizophrenia. Methods: Data were drawn from a large 3-year naturalistic prospective multi-site study of schizophrenia treatment in the United States, conducted between 7/1997 and 9/2003. Patients who were initiated on oral atypical antipsychotics (clozapine, olanzapine, risperidone, quetiapine, or ziprasidone) or oral typical antipsychotics (low, medium, or high-potency) were compared on treatment effectiveness, defined as time to all-cause medication discontinuation during the 1-year following medication initiation, and measured by the number of days of continuous treatment up to first medication gap of >30 days. Group comparisons used Kaplan-Meier and Cox proportional hazard model, controlling for patient demographic and clinical characteristics. Results: Patients treated with atypical antipsychotics (N=1166) had a significantly longer time to all-cause medication discontinuation compared to patients receiving any typical antipsychotics (N=537, $p<.001$). Atypical agents significantly differed from high-potency (N=320, $p<.001$), medium-potency (N=141, $p=.001$), and low-potency typical antipsychotics (N=76,

p=.035). Among the atypical antipsychotics, only clozapine and olanzapine-treated patients had a significantly longer time to all-cause medication discontinuation compared to patients treated with low, medium, or high-potency typical agents. Further, when compared to patients treated with perphenazine, a medium-potency typical antipsychotic medication, only clozapine and olanzapine-treated patients had a significantly longer time to medication discontinuation (p<.001, p=.015, respectively). Analysis was repeated using a medication gap >14 days, and again with more vigorous control for group differences at initiation. Results remained essentially unchanged. Conclusion: In the naturalistic treatment of schizophrenia patients, atypical antipsychotics were found to be superior to typical antipsychotics on time to all-cause medication discontinuation. Findings appear, however, to be primarily driven by olanzapine and clozapine, and to a lesser extent by treatment with risperidone.

PERCEIVED EXTENT OF RECOVERY AND RISK OF RELAPSE FOLLOWING FIRST-EPISODE PSYCHOSIS

D. Tam,* E. Chen, C. Law, C. Chiu, J. Wong
Psychiatry, The University of Hong Kong, Hong Kong, China

Patient's perception of recovery from first-episode psychosis is a less well covered area in existing assessment and research. The Psychosis Recovery Inventory (PRI) is a self-administered questionnaire developed to address key issues in the recovery stage. This study applied the PRI to survey perceived extent of recovery and the risk of relapse in a sample of patients recovering from first episode psychosis. The PRI was administrated to 51 patients in the recovery period following a first psychotic episode. The PRI required patients to rate their perceived levels of recovery and risk of relapse with a visual analog scale. In addition, respondents indicated their attitudes towards 32 items covering different aspects of recovery with a 6-point Likert scale. We explored how these attitudes are related to the perceptions of recovery and relapse. More than 33.3% of patients perceived a low risk of relapse (10% or lower), but only 7.9% of them recognized a high relapse risk (90% or higher). 11.8% of the patients considered they had a full recovery, while on the other hand, 21.6% of the patients perceive they had recovered less than 50%. Perception of non recovery is related to the presence of cognitive problems and impairment in occupational functioning. In addition, the need to continue on medication is rating as an important recovery for the perception of non-recovery. We successfully applied a tailor-made questionnaire to explore attitudes and perceptions of relapse and recovery in a sample of patients recovering from a first psychotic episode. Despite comprehensive psychoeducation, patients still tended to underestimate their risks of relapse. The need for continuing medication is a major contributor to the sense of non-recovery in first episode patient. These issues have potential therapeutic implications.

A SYSTEMATIC REVIEW OF PHARMACOEPIDEMIOLOGICAL STUDIES IN SCHIZOPHRENIA

L. D. Tennakoon,* J. Regan, M. Dell'Olio, A. Yung, P. D. McGorry
Department of Psychiatry, University of Melbourne, ORYGEN Research Centre, Melbourne, VIC, Australia

Background: Pharmacoepidemiology can be defined as the study of the use of and the effects of drugs in large groups of people (Strom BL, 1994). The emergence of large population based prescription databases is a new development in pharmacoepidemiology. Objectives: The aim of the review is to highlight the importance of pharmacoepidemiological studies in schizophrenia and to provide comprehensive literature review of the existing publications. Method: A literature search was carried out using MEDLINE, pubmed and OVID databases. All papers, that investigated the pharmacoepidemiology of schizophrenia, were included. We discussed published studies under three main categories; treatment, adverse events and prescription pattern. Results: Eleven studies were identified and some of the significant findings were: - a cohort study (n=1500) based on a drug exposure database found that clozapine related neutropenia caused very low morbidity and zero mortality. In another study (n=103) reported that patients received high doses of neuroleptics despite a persistent lack of response to treatment. A survey (n=2395) related to drug utilization found that haloperidol was the most commonly prescribed neuroleptic in schizophrenia. A prospective study (n=2322) reported that olanzapine treated patients were less likely to experience extrapyramidal symptoms compared with risperidone and haloperidol treated patients. Another drug utilization survey (n=2322) reported that 75% were prescribed antipsychotic drugs, 50% received benzodiazepines and 33% received antidepressants. Conclusions: There have been only 11 studies done so far on this important field and there is a need for future pharmacoepidemiological studies to evaluate the treatment strategise in schizophrenia. The pharmacoepidemiological approach would facilitate a more comprehensive assessment of prescribing practices and strategies in routine clinical care. One of the methodological problems of pharmacoepidemiology is the possibility of confounding by indication Reference: Strom BL. What is pharmacoepidemiology? In Strom BL (ed): *Pharmacoepidemiology*, 2nd edn. Chichester: John Wiley & Sons, 1994: p 3.

GRIEF: THE PSYCHOLOGICAL CONSEQUENCE OF THE CAREGIVING DYNAMIC ON FAMILY CAREGIVERS OF PERSONS WITH SEVERE MENTAL ILLNESS

H. Thorning
Social Work, New York State Psychiatric Institute, New York, NY, USA

An important but overlooked aspect of the family care givers (FCG) reaction to the onset of SMI in a family member is a profound sense of grief. The overall aim of this study was to identify and understand unique predictors of grief among FCG as a psychological consequence of SMI. The study examined the interaction between cognitive, psychological and relational dimensions of the caregiving relationship to document variation in the family caregiving experience of grief. Structured interviews with Family care givers (N=180) from a study conducted in 1995 by Dr. Struening at New York State Psychiatric Institute and Columbia University were used. The data set reflected characteristics common to FCG of adults persons with severe mental illness (PSMI). Multiple regression analyses were used to test specific and unique stressors related to illness related factors, family related stressors and mediating factors that predict FCG grief. Findings indicated that greater FCG grief is predicted by characteristics of PSMI such as severity of illness ($p < .05$), fewer years of illness (p<. 05), and of FCG self-evaluation such as negative attitude towards the PSMI (p<. 001), self-blame (p<. 001), feeling stigmatized (p<. 001), avoiding others (p<. 01), and using substances (p<. 01). Decreased grief was also found in Afro-American (p<. 001) compared to White and Hispanic FCGs. The overall model explained 65 % of the variance. Grief, as a mental health risks factor for family caregivers of the mentally ill is an important area to study. It is essential information for mental health professionals when design-

ing prevention-based interventions for all touched by severe and persistent mental illness. This study contributes to an understanding of caregiver grief and informs models for clinical interventions.

THE SCHIZOPHRENIA TREATMENT ACCEPTANCE RESPONSE TRIAL: EVALUATION OF A NOVEL PSYCHOSOCIAL APPROACH TO SUPPORTING PATIENT ACCEPTANCE OF A LONG-ACTING, INJECTABLE ANTIPSYCHOTIC

R. Urioste,* R. A. Lasser, G. M. Gharabawi, N. R. Schooler, J. P. Docherty
Janssen Medical Affairs, LLC, Titusville, NJ, USA

In light of mounting evidence of a strong relationship between treatment acceptance, ongoing adherence, and resultant treatment outcome in psychiatric illness, we evaluated a novel approach to supporting treatment that is based on motivational enhancement therapy. GAIN is a structured clinical discussion tool developed to address patient ambivalence to treatment; it comprises 4 sequential steps to promote long-term goal setting (G=goal setting), developing a treatment action plan (A=action), initiating treatment (I=initiation), and continual nurturing of goal-oriented behaviors (N=nurturing motivation). The Schizophrenia Treatment Acceptance Response Trial, (START), compared GAIN with approach as usual (AAU) and assessed treatment acceptance and adherence to long-acting risperidone in patients with schizophrenia. The study a was conducted in community mental health centers in the US, randomly assigned to GAIN or AAU. The primary measure of effectiveness was the percentage of patients accepting long-acting risperidone therapy at sites randomized to GAIN vs to AAU. As a secondary effectiveness measure, we compared the percentage of patients adhering to treatment (measured by discontinuation rate). We also measured healthcare provider satisfaction with GAIN or AAU through self-report questionnaires. A total of 650 patients entered into the study (386 GAIN, 264 AAU) across 268 sites. Preliminary analysis of the data indicates high treatment acceptance in both groups. Further, patients treated at GAIN sites had lower discontinuation rates compared with AAU sites. Preliminary data indicate high levels of healthcare provider satisfaction with the ease of implementation and effectiveness of GAIN. Final data analyses will be available in December 2004. Preliminary results suggest that GAIN can be implemented with relative ease by schizophrenia treatment teams in routine clinical settings. Final data analyses will test the hypothesis that GAIN provides a more effective method of engaging clinicians and patients into collaborating on supporting acceptance and adherence to treatment with a long-acting, injectable antipsychotic. Furthermore, the innovative study design of combining both pharmacologic and psychosocial interventions to enhance treatment adherence may encourage others to implement future studies of this type.

DIFFUSION OF A NEW ANTIPSYCHOTIC IN A LARGE HEALTH SYSTEM: PATIENT AND FACILITY FACTORS

M. Valenstein,* J. F. McCarthy, R. V. Ignacio, G. W. Dalack, T. Stavenger, F. C. Blow
HSR&D/SMITREC, Department of Veterans Affairs Ann Arbor Health Sytem, Ann Arbor, MI, USA

Background/Objectives: When new medications are introduced, a period of diffusion, evaluation, and adoption follows. This study evaluates the influence of patient and facility characteristics on the dissemination of a new antipsychotic, ziprasidone, in the 33 months following FDA approval among VA patients with schizophrenia. Methods: Data on demographics, diagnoses, and outpatient pharmacy fills were obtained from the VA National Psychosis Registry (NPR). We used multivariate analyses to assess the impact of patient and facility-level factors on ziprasidone use during Fiscal Years (FYs) 2001, 2002, and 2003. Supplemental exploratory analyses examined patient and facility characteristics associated with changing to ziprasidone after periods of stable antipsychotic monotherapy. Results: In FY 2001, 1.2% of VA patients with schizophrenia on antipsychotics, received ziprasidone. Ziprasidone use tripled by FY02, with 4.0% of these veterans receiving ziprasidone during the year, and more than quadrupled by FY03, with 5.9 % receiving ziprasidone. In each year, patients were more likely to receive ziprasidone if they were white, younger, or female. Patients with previous psychiatric hospitalizations or with diabetes were also more likely to receive ziprasidone. Differences by race diminished over time, while differences by age persisted. Facility academic affiliation and geographic region were minimally associated with ziprasidone use. Conclusions: Ziprasidone use increased rapidly in the VA Health System following FDA approval, suggesting a pool of patients and physicians eager to try a new agent. In the initial diffusion period, patients were more likely to receive ziprasidone if they were white, younger, or or had more severe psychiatric disorders. Disparities in the use of new psychotropic medications is a repeated finding, but the mechanisms underlying these early disparities and the implications for affected patient subgroups are unclear. This research was supported by Department of Veterans Affairs, Health Services Research and Development Service, RCD 98-350, by the Serious Mental Illness Treatment, Research, and Evaluation Center, Ann Arbor, MI, and by an unrestricted grant from Pfizer, Inc.

PREVENTION OF DIABETES IN SCHIZOPHRENIA: A REVIEW OF THE SCOPE AND LIMITATIONS

L. P. Voruganti,* S. Strong, H. C. Gerstein
Psychiatry & Behavioral Neurosciences, McMaster University, Hamilton, ON, Canada

Background: Diabetes mellitus (type 2) is 2-5 times more prevalent among people treated for schizophrenia; and its potential contribution to increased mortality, morbidity and health care costs is staggering. There is an urgent need to explore the scope for primary prevention of diabetes, and examine strategies for implementing the diabetes prevention guidelines in schizophrenic population. Objectives: The presentation will review the literature on i. Cumulative research evidence on the primary prevention of type 2 diabetes in general population, and ii. Explore the feasibility of implementing the diabetes prevention guidelines in schizophrenic population. Methods: Major prospective trials on the effectiveness of pharmacological and life style interventions in reducing the risk of developing diabetes in general population are reviewed. Studies relevant to the prevention of diabetes in schizophrenia are screened to identify the scope and potential barriers to implement the life style modifications and pharmacological interventions. Results: There is unequivocal evidence from the general population studies that diabetes is preventable through life style modifications and pharmacological measures. However, the scope for primary prevention of diabetes in schizophrenia remains unexplored. Currently there is limited information available on the schizophrenia-diabetes comorbidity, especially on the issues of screening, accessibility, availability and

quality of care, treatment-adherence and clinical outcomes. Conclusion: Prevention of diabetes in schizophrenia is a priority. However the diabetes prevention guidelines developed for general population may not work as effectively in the schizophrenic population. There is a need to develop novel diabetes prevention strategies based on the principles of cognitive, behavioral and psychosocial interventions with proven effectiveness in this population.

ENGAGING PEOPLE WITH SCHIZOPHRENIA IN HEALTH PROMOTION IN THE UK: A CHALLENGE FOR HEALTHCARE PROFESSIONALS

L. Walker,* G. Doody, T. Arthur, M. Abbott
Research and Development, Nottinghamshire Healthcare NHS Trust, Nottingham, United Kingdom

In the UK the mortality and morbidity from circulatory disease amongst people with severe and enduring mental health problems is two and a half times that of the general population. People with schizophrenia are frequently prevented from adopting healthier lifestyles due to both personal factors and barriers in accessing services designed to promote physical health . This study tested the feasibility of conducting a randomised controlled trial offering a complex intervention of coronary heart disease (CHD) prevention versus standard care to people with schizophrenia living in the community, in an urban city. Baseline measures were taken for risk factors for CHD and the 10 year predictive risk calculated. All subjects were followed up at nine months post randomisation and baseline measures were repeated. 36 eligible people were identified, 25 consented to contact and finally 12 consented to randomisation. 123 home visits were made by the researcher to recruit 12 subjects pre randomisation. The nature of the complex intervention varied dependent upon participant priorities, all smoked but none chose to address this.Most people chose to focus on healthy eating and exercise.A focus group after the study was open to all participants, only three attended. The greatest challenge in this pilot study was recruitment, this acted as an intervention in itself. Subjects were reluctant to agree to randomisation for fear that they might lose contact with the researcher, if allocated to the standard care group. We sought to breakdown some of the barriers preventing people with schizophrenia from engaging in activities promoting a healthier lifestyle. However, we underestimated the degree to which mental illness may eclipse concern about the future prevention of CHD in this vulnerable group of people. Researchers must now think creatively about how best to deliver interventions to improve physical health for people with schizophrenia.

RECOVERY FROM SCHIZOPHRENIA IN THE TWENTIETH CENTURY

R. Warner
Mental Health Center of Boulder County, Boulder, CO, USA

A meta-analysis of studies of outcome from schizophrenia in Europe and North America throughout the twentieth century reveals that there has always been a substantial social and complete recovery rate from the illness, but that that there has been no improvement in these recovery rates since the immediate postwar years. The advent of antipsychotic drug treatment does not appear to have led to an improvement in long-term outcome from schizophrenia. During the last two decades of the twentieth century outcome from the illness deteriorated in Britain, but not in the US. Potential explanations for these findings, including economic forces, will be presented.

GUIDELINE ADHERENCE IN INPATIENT SCHIZOPHRENIA CARE

S. Weinmann,* B. Janssen, W. Gaebel
District Hospital, Guenzburg, Germany

German Guidelines for Schizophrenia Care have been developed since 1996. However, there are few incentives for guideline implementation and practical use. Within the multicenter German Research Network in Schizophrenia (GRNS), seven psychiatric hospitals participated in a quality management study with the aim to improve schizophrenia treatment outcome by implementing guidelines and quality circles, and benchmarking relevant processes and outcomes. Baseline data point to significant differences in patient case-mix and treatment processes between the seven hospitals. Mental state at admission, particularly thought disturbance, and a chronic disease course were the best predictors for mental state outcome at discharge. Guideline adherence among hospitals was moderate. To correlate guideline adherence with outcome, case-mix adjustment models had to be used controlling for mental state, duration of disease, age, comorbidity, and occupational and residential situation. Overall low guideline adherence concerning a variety of treatment domains was associated with poorer outcomes. However, results differed when mental state or social functioning were used as primary outcome parameters. In conclusion, guideline adherence among hospitals was moderate even though it correlated with a better outcome in routine psychiatric care. Grant support: Germany Federal Ministry of Education and Research, Bonn, Germany (grant 01 GI 9932/7) Reference: Woelwer W, Buchkremer G, Haefner H, Klosterkoetter J, Maier W., Moeller HJ, Gaebel W: German research network on schizophrenia. Bridging the gap between research and care. *Eur Arch Psychiatry Clin Neurosci* 2003;253: 321-329.

UNSAFE PRACTICE: SURVEY RESULTS OF MENTAL HEALTH AND CRIMINAL JUSTICE PROFESSIONALS ASSISTING INDIVIDUALS WITH SCHIZOPHRENIA

R. L. Weisman,* C. Cerulli, P. Sheffield
Psychiatry, University of Rochester Medical Center, Rochester, NY, USA

This study surveyed mental health and legal professionals on their experiences as victims of aggressive behavior committed by their clients with schizophrenia and their perceptions of skills required for safe practice. Audience members at a recent mental health and criminal justice conference were surveyed on their experience with client related violence. Of those respondents who reported backgrounds in either profession (n = 129), 63% were female and 37% male. Overall, 56% (n=72) of respondents reported a client being physically aggressive toward them with a mean (SD) of 3.9 (4.6) times. Independent t-tests indicate statistically significant differences for age ($p<.05$) and years of experience ($p<.01$) for those respondents who reported being the recipient of client aggression as compared to those who were not. A statistically significant correlation ($p<.01$) between the years of experience worked and the reported number of physical incidents was found. Univariate analyses showed that women and mental health staff respectively were more likely to be victims of aggression ($p<.05$). Multivariate analyses utilizing logistic regres-

sion controlling for gender, age, years of experience and background revealed only years of experience (p<.05) and background (p<.01) as significantly associated with assault. Seventy-four percent (n=95) of the respondents reported being threatened and controlling for gender, age, professional background and years of experience, logistic regression results provide that only a professional background in mental health was significant (p<.05) in predicting the likelihood of being threatened. Mental health professionals also reported a greater need for safety training as a priority in professional development. Challenges exist towards integrating legal and mental health care systems for the welfare of individuals with schizophrenia involved with the criminal justice system. The concern over safe and effective mental health and legal practice with this population has led to programs targeting the training in assessment and management of violence within this population (1). Further research is needed to evaluate such efforts and inform policy towards violence prevention training for professionals working with high-risk individuals with schizophrenia. 1 Weisman, R L, Lamberti JS. Violence Prevention and Safety Training for Case Management Services. *Community Mental Health Journal*. 38(4):339-348, August, 2002.

DIABETES KNOWLEDGE AMONG PERSONS WITH SERIOUS MENTAL ILLNESS AND TYPE 2 DIABETES

K. Wohlheiter,* F. B. Dickerson, R. W. Goldberg, C. H. Brown, J. A. Kreyenbuhl, L. Fang, D. Medoff, L. B. Dixon
Psychiatry, University of Maryland, Baltimore, Baltimore, MD, USA

Objective: To assess disease-specific diabetes knowledge among persons with severe mental illness and co-occurring type 2 diabetes. This study explored the association between diabetes knowledge and psychiatric and diabetes-related variables. Methods: We recruited psychiatric outpatients who met the following inclusion criteria: 18-65 years old, diagnosis of type 2 diabetes and diagnosis of schizophrenia or major mood disorder. Diabetes knowledge was assessed with the Diabetes Knowledge Test. We also measured perceived benefits and barriers of diabetes care, diabetes history, psychiatric symptoms, and cognitive functioning. Results: The sample consisted of 201 persons with major mental illness, 100 persons with schizophrenia and 101 with a major mood disorder. The mean age was 51.1 years and the mean education was at the level of high school graduate. The mean percentage correct on the Diabetes Knowledge Test was 53.6 (s.d. = 18, range 14-100%). Score on the Diabetes Knowledge Test was significantly associated with psychiatric diagnosis; the mean score was lower among participants with schizophrenia (48.6%, s.d. 17.3) than those with a mood disorder (58.6%, s.d. 17.5) (F=16.6, p<.0001). In a multivariate analysis, diabetes knowledge was significantly associated with educational level, score on the RBANS cognitive test, and receipt of diabetes education.. Diabetes knowledge also predicted lower levels of perceived barriers of diabetes care. Diabetes knowledge score was not significantly associated with age, gender, psychiatric symptom severity, age of diabetes onset, duration of diabetes, or current receipt of insulin (all p>.05). Discussion: Our findings raise several important concerns about diabetes knowledge in persons with severe mental illness. The mean score on the diabetes knowledge test was 53.6%, suggesting considerable gaps in illness specific knowledge in this population. It is important for providers to recognize these deficits when providing or developing education to this population. We also found a significant and inverse association between knowledge and perceived barriers to diabetes care. Ours is the first study of which we are aware that characterizes a cohort of persons with severe mental illness and co-occurring diabetes with information about their diabetes knowledge as well as their psychiatric status and their diabetes condition.

ARE ATYPICAL ANTIPSYCHOTICS BETTER THAN CONVENTIONAL ANTIPSYCHOTICS? TAIWAN EXPERIENCES

L. Yeh,* T. J. Hwang, H. G. Hwu
Graduate Institute of Long-Term Care, Taichung Healthcare and Management Uinversity, Taichung, Taiwan

Numerous literatures reveal atypical antipsychotics are better than conventional antipsychotics in terms of varied outcome definitions. According to results of clinical trial studies, atypical antipsychotics are now considered first line treatments for schizophrenia. Nevertheless, clinical experiences show that a certain amount of patients taking conventional antipsychotics still could maintain clinically stable. In order to answer the question that how many patients can still benefit from traditional antipsychotics, this research aimed to search all patients with schizophrenia in Taiwan and analyze the differences on disease outcomes between those who taking only one atypical antipsychotic and those who taking only one conventional antipsychotic. All study subjects were recruited began from January 2001 to December 2001, and were observed for exactly one-year ended before December 2002. This study used the claim data of Bureau of National Health Insurance, which embodies all patients seeking for care in Taiwan. The inclusion criteria were as follows: (1) with a primary diagnosis of ICD9 295 (2) must have been taking only one antipsychotic continuously for twelve months. The outcome variables include readmission rate, emergency services, length of stay in hospital, and costs (psychiatry and non-psychiatry) during the same one-year period. The results showed that, among a total of 83824 schizophrenia patients, 19295 fulfilled the inclusion criteria. The group used conventional antipsychotics (CG) had 16383 subjects (19.5% of all patients), while the group used atypical antipsychotics (AG) had 2912 subjects (3.5%). The mean readmission rate was 5.3% in the CG and 6.2% in the AG (p>0.05). The mean rate of emergency services was 5.0% (CG) and 5.6% (AG)(p>0.05). The mean length of stay in hospital was 70.2 days (CG) and 74.9 days (AG)(p>0.05). The costs related to psychiatric service and non-psychiatric service were 42188 NTD and 17132 NTD in the CG, and 81075 NTD and 17146 NTD in the AG. The naturalistic study showed that 19.5% of schizophrenic patients with one conventional antipsychotic have performed similarly to their counterpart in terms of readmission rate, length of hospitalization, and emergency service utilization, but with lower costs. Although outcomes longer than one year were not assessed in this study, the results suggested that a significant proportion of schizophrenia patients could still benefit from conventional antipsychotics.

THE EFFECT OF A MEDICATION COPAYMENT INCREASE ON VETERANS WITH SCHIZOPHRENIA

J. E. Zeber,* K. L. Grazier, F. C. Blow, M. Valenstein, P. M. Lantz
Veterans Affairs HSRD, VERDICT, San Antonio, TX, USA

Introduction: With the VA facing $3 billion per year in outpatient pharmacy costs, Congress implemented the Veterans Health Care

Act (Millennium Bill) in 2002. This policy raised medication copayments from $2 to $7 for low priority veterans: the goal to slow the 19% annual rise in pharmacy costs. Veterans with schizophrenia constitute a complex, chronically ill group; 40% are already medication non-adherent, substantially increasing the risk of hospitalization andrelapse. We used the Health Belief Model and the Donabedian concept of benefits equity to examine potential ramifications of higher copayments on medication and health utilization in these vulnerable patients. Methods: With National Psychosis Registry data, longitudinal models (20-months Pre-Post copayment increase, adjusted for patient characteristics) observed changes in number of prescriptions, health utilization and pharmacy costs between veterans with copayments (N=40,654) and a control group of exempt patients (N=39,983). Results: Compared to steady growth among exempt patients, overall prescriptions were constrained in the Copayment group following the copayment increase. More conspicuously, psychotropic refills dropped substantially, nearly 25%. Though outpatient visits did not differ between groups, the risk for psychiatric admission and total inpatient days rose slightly for Copayment patients (5-10%), particularly 10-20 months post-policy. Factoring in additional copayment revenue, the VA would realize a revenue increase of over $13 million annually from this sub-population alone. Discussion: The policy appears to have successfully reduced pharmacy fills and costs as intended. However, the marked decrease in psychiatric drug utilization and small increase in hospitalization for this seriously mentally ill population is troubling. Research studies investigating the longer-term clinical consequences of medication cost increases are required. Conclusion: When balancing budgetary concerns with quality care provision, benefit changes for veterans with debilitating conditions should be implemented cautiously and outcomes carefully followed. This is particularly true with a system responsible for providing care to a aging population during ongoing Medicare prescription debates.

A PROSPECTIVE STUDY OF RISK FACTORS FOR NONADHERENCE WITH ANTIPSYCHOTIC MEDICATION IN PATIENTS WITH SCHIZOPHRENIA

B. Zhu,* H. Ascher-Svanum, D. Faries, J. Lacro, C. Dolder
Health Outcomes Research, Eli Lilly and Company, Indianapolis, IN, USA

Background/Objective: Nonadherence with antipsychotic medication is associated with poor and costly treatment outcomes. This study examined numerous potential risk factors to identify the best single predictor, and the best set of predictors of risk for nonadherence with antipsychotic medication in the treatment of patients with schizophrenia. Method: We used data of 1579 participants in a 3-year prospective naturalistic study of schizophrenia patients in the USA. Adherence with any oral antipsychotic medication was assessed using medical record prescription information and patient-reported medication adherence. Patients who reported being nonadherent at enrollment and had during the 1-year after enrollment a Medication Possession Ratio of at least 80% (MPR, percent days with any oral antipsychotic), were defined as nonadherent (N=296, 18.8%). Thirty-nine previously reported potential risk factors of nonadherence with antipsychotic medication were assessed at enrollment with valid and reliable measures. Risk factors represented major domains, including illness profile, functional level, adverse events, socio-demographics, and prior healthcare utilization patterns. Statistical analysis used stepwise logistic regression models. Results: The best single predictor of future nonadherence was nonadherence during the 6 months prior to enrollment (Odds Ratio 4.1, 95% Confidence Interval 3.1-5.6, p<.0001). The best set of predictors of nonadherence, ordered by strength of association, included: prior nonadherence, current drug use, current alcohol use, not receiving antidepressants, and greater medication-related cognitive impairment per patients self-report. Conclusions: Nonadherence with antipsychotic medication is associated with a well-defined set of risk factors that can be used to identify patients most likely to benefit from adherence intervention.

A PROSPECTIVE STUDY OF THE COSTS OF CARE FOR PATIENTS WITH SCHIZOPHRENIA

A. R. de Castella,* P. B. Fitzgerald, K. Filia, W. Montgomery, J. Kulkarni
Alfred Psychiatry Research Centre, The Alfred Hospital, Melbourne, VIC, Australia

Background: the treatment of patients with schizophrenia in Australia consumes a considerable proportion of health service budgets. Despite this, there have been few attempts to prospectively analyze the costs of care and the relationship of these to clinical outcomes measures such as quality of life and occupational functioning. Methods: Direct care costs and clinical outcomes were prospectively studied in a cohort of 348 patients in Dandenong, Australia over three years. Data was collected at six month intervals directly from subjects and continuously from National and State based healthcare databases. Results: There was a progressive significant improvement in symptoms (PANSS, MADRS, GAF) and Quality of Life (QLS) over the course of the 3 years. Service utilisation data showed that the majority of services were provided to patients via outpatient services through the public hospital system. There was a progressive shift from the prescription of typical to atypical antipsychotic medications. Costs of care (per patient per 6 months) decreased from $8685 at the start of the study to $6923 in the last study phase. The majority of costs (76%) were driven by inpatient hospitalisations. There were a small proportion of subjects who had disproportionately high levels of costs and use of services. Conclusions: Considerable resources are required for the provision of treatment for patients with schizophrenia. However, this expenditure is accompanied by an improvement in clinical outcomes and reported quality of life.

22. Drug Side Effects & Tardive Dyskinesia

SIDE EFFECTS OF ANTIPSYCHOTIC TREATMENT IN CHILDREN

H. Adami,* I. Verovsky, D. Carmichael, I. Wonodi, G. Thaker
Maryland Psychiatric Research Center, Catonsville, MD, USA

Objective: Children with emotional problems are difficult to diagnose and treat. In recent years the use of antipsychotic medications to treat psychiatric symptoms in children and adolescents has increased dramatically. These drugs are often prescribed for pediatric patients without knowing about the long-term side effects. The purpose of our study is to compile data collected as part of standard clinical exams for antipsychotic medication side effects. Methods: We established satellite clinics in children's (ages 5-18) inpatient and residential treatment facilities for the purpose of evaluating side effects of antipsychotic medication. Clinical information included ECG values, height and weight measurements, laboratory values, ratings for involuntary muscle movements, and history of acute dystonic reaction. Children were also asked about acute side effects such as somnolence, appetite changes, nausea and rhinitis. Preliminary Results: We have examined more than 391 children (mean age=11), for medication side effects. Children were taking an average of 5.5 psychiatric medications at time of evaluation (antidepressants, anti-anxiety, antipsychotic, mood stabilizers). 56% of children are taking antipsychotic medications although only 12% had some history of psychotic symptoms. Other diagnoses for the children show that 83% have a mood disorder, 57% are diagnosed with ADHD, 33% with oppositional or conduct disorders and 12% with current or past psychotic disorder. 23 children (5.9 %) had a history of an acute dystonic reaction. Additional data analysis focused on a subgroup of patients on antipsychotic medications (AP+, n=135), who were matched to antipsychotic naive patients (AP-, n=28) on age, sex, ethnicity, clinical diagnoses, and concurrent medications. Body mass index (BMI) was significantly higher in AP+ (23 + 6) compared with AP- children (20 + 5; $p < 0.01$, Cohens d effect size = 0.55). There were no significant differences on metabolic and blood pressure measures however AP + children had values indicating poor health (complete data were not available in all subjects). Cholesterol levels were similar in the two groups, but LDL levels were higher and HDL lower in AP+ group (effect sizes, 0.29 and 0.47, respectively). Systolic blood pressure was higher in the AP+ group (118 + 14) compared with the AP- group (111 + 16; effect size 0.47). Results from the complete data analysis regarding side effects will be provided in a larger cohort.

CIRCADIAN PATTERN HEART RATE AND HEART RATE VARIABILITY IN PATIENTS TAKING CLOZAPINE

S. R. Addis,* D. P. Sherwood, H. G. Stampfer
Alma Street Centre, Fremantle Hospital, Fremantle, WA, Australia

There is an increased awareness of the potential for adverse cardiac side effects associated with neuroleptic medications. While Clozapine has a profound effect on the autonomic nervous system, its effect on heart rate variability has emerged as a concern. This study reports on the effect of Clozapine on the circadian pulse rate and pulse rate variability (PRV). Ten patients who met DSM for schizophrenia were recruited in a prospective fashion for the study (6 male and 4 female, aged between 23 and 49 years old with a mean age = 34.1). Subjects where excluded when known to be abusing illicit substances or known history of cardiac disease or acute medical illness. Ranges of concomitant neuroleptic medications were in use and did not exclude the subjects from the study. All participants provided written informed consent. Pulse rate was monitored for 24 hours on participants before starting Clozapine and after Clozapine had commenced. The subjects wore a pulse monitor for 24 hours. The pulse monitor recorded the pulse rate and body movement for each minute of the 24-hour period (1440 minutes). Medications taken in the 24 hours of monitoring were recorded. Pulse rate monitoring occurred from six days up to 604 days from the start of Clozapine. Clozapine was associated with a significant rise in 24 hour pulse rate and decrease in PRV compared to pre treatment values (Wilcoxon Rank Test, Z=-2.80, p=.005). Simple linear regression confirmed that the above changes observed were dose related for the 24 hour PRV, AM PRV and PM PRV post Clozapine. Age was not a significant factor in the regression models. In this study patients on Clozapine were found to have a significant dose related attenuation of PRV over a 24-hour period. Clinicians should be aware that this may expose their patients to an increased risk of sudden cardiac death.

A RETROSPECTIVE STUDY OF OBESITY RELATED OUTCOMES ASSOCIATED WITH ANTIPSYCHOTIC USE AMONG THE US VETERANS

A. Adityanjee,* S. Sheikh, P. Thuras, S. Johnson, L. Suvalsky, S. Aoun
Minneapolis VA Medical Center, Minneapolis, MN, USA

Electronic medical records were reviewed retrospectively at the Minneapolis VAMC for period starting from October 1998 to September 2001 as part of a larger multi-site VA study that looked at obesity related outcomes in association with antipsychotics. For inclusion in the study, the patients had to have a diagnosis of schizophrenia, be on an antipsychotic agent, and have linkable data in all three relevant VA databases (PBM, Austin and BIRLS). Patients taking weight loss drugs were excluded. A chart review worksheet was designed and relevant data was extracted from charts into these worksheets. Data were collected on the following parameters: psychiatric diagnosis, co-morbid medical diagnosis, weight gain, BMI, vital signs, total cholesterol, LDL, HDL, Triglycerides, HbA1C, Gluocse, and antipsychotic medications. A total of 190 charts were reviewed locally at the Minneapolis VAMC from a list of previously identified patients as part of the larger multi-site study. Study was approved by the Minneapolis VAMC IRB. Data were collected 12 months apart for each patient while on a particular antipsychotic agent. 59 out of 190 pateints were on olanzapine, 30 on risperidone, 10 on quetiapine and 5 on clozapine and 49 were on various conventional antipsychotics. 36 patients were on more than one antipsychotics and hence were excluded from analysis. There were no signficant differences when exposure to conventional vesus atypical antipsychotics was analysed on any of the parameters except for LDL. The patients on conventionals had elevated LDL levels after 12 months exposure as compared to the patients on atypical antispychotics (p=0.03). The project had several limitations of a retrospective chart review of existing data. Relevant information on a number of variable was missing, incomplete or inconsistently recorded. The sample size for this dataset is very small. The veterans are not representative of the general US population and are predominantly males. Therefore, the results are not generalizable to other groups.

The results of the larger multi-site VA study would be more meaningful.

SOCIODEMOGRAPHIC VARIABLES AS MODERATORS BETWEEN PSYCHOTIC SYMPTOMS AND TARDIVE DYSKINESIA: A COMPARISON OF SCHIZOPHRENIA AND SCHIZOAFFECTIVE PATIENTS

C. L. Adkins,* R. R. Lewine
Department of Psychological and Brain Sciences, University of Louisville, Louisville, KY, USA

This study explored the relationship between tardive dyskinesia (TD) and the clinical expression of schizoaffective disorder compared to schizophrenia. Adkins and Lewine (2004) previously reported that sociodemographic variables such as race and sex moderated the relationship between TD severity and symptoms in schizophrenia. We repeat that analysis with schizoaffective patients. Of an original sample of 423 inpatients and outpatients with schizophrenia-related disorders, we selected those with a DSM-IIIR diagnosis of schizoaffective disorder between the ages of 18 and 65 (n = 72). The following variables were entered in to a backward stepwise linear regression to predict TD severity: age, sex, illness duration, NRS total score, and positive and negative symptom scores. The primary dependent variable was the total AIMS score. The variables used in the regression analysis were originally proposed by the Yuen et al (1996) study and repeated by Adkins and Lewine to predict TD severity. Thirty-four percent of the patients in our sample with schizoaffective disorder met Schooler and Kane (1982) criteria for presence of TD, as compared to 19% of patients with schizophrenia. This finding is consistent with current literature that suggests patients with affective disorders on antipsychotics are more likely to exhibit symptoms of TD. In addition, we found that sex moderates the relationship between psychotic symptoms and TD severity among the schizoaffective sample. Specifically, the best model predicting TD severity among females consists of greater tremor, older age, fewer positive symptoms and fewer negative symptoms while the best model among males consists of greater tremor, older age, and fewer positive symptoms. Clinical implications of the findings are discussed.

Regression Models Predicting TD Severity among Schizophrenia and Schizoaffective Patients

*** p<.05**
****p<.01**

THE EFFECT OF HEPATOPROTECTORS ON INCREASED SERUM TRANSAMINASE INDUCED BY ATYPICAL ANTIPSYCHOTICS

W. Bahk,* W. Kim, J. H. Chae, C. H. Kim, D. J. Yoon, T. Y. Jun, K. S. Kim
Psychiatry, The Catholic University of Korea, Seoul, South Korea

Objectives: Atypical antipsychotics are reported to induce serum transaminase increase frequently in Korea, although most cases are benign. So some hepatoprotectors are commonly prescribed to manage transaminase increase rapidly in patients with schizophrenia. We performed retrospective chart review to investigate the effect of two hepatoprotectors, biphenyl dimethyl dicarboxylate+garlic oil combination(BDD), and silymarin+silybin combination(SMR) on transaminase (AST/ALT) increase induced by atypical antipsychotics. Methods: The records of 53 schizophrenic patients who experience serum AST/ALT increase after treatment with atypical antipsychotics were reviewed. Patients with preexisting liver disease or increased AST/ALT above in-house normal limitation at admission were excluded. We obtain the level of serum AST/ALT at the time of hepatoprotectors administration, 1 weeks, 2 weeks, 3 weeks, 4 weeks after administration. Repeated Analyses of variance were conducted to identify sequential change of serum AST/ALT level, and Fishers exact test were conducted to detect the impact of two hepatoprotectors on number of patients whose serum AST/ALT levels were normalized below in-house upper normal limitation. Results: Among all patients, 36 patients were treated with BDD and 17 patients were treated with SMR. Mean age of all patients was 35.32(10.59), 34 was male and 19 was female. After administration of hapatoprotectors, both serum AST and ALT level were significantly reduced during 4 weeks($F=8.27$, $p=0.002$; $F=6.46$, $p=0.005$). We could see that both AST and ALT level were significantly reduced in only one week ($t=2.44$, $p=0.029$; $t=3.28$; $p=0.005$). BDD was superior to SMR in number of patients whose ALT level was reduced below in-house upper limitation after 4 weeks(83.3%, 52.9%, $p=0.042$), but there was no difference between BDD and SMR in aspect to AST level. Conclusions: Both hepatoprotectors, BDD and SMR were effective in reducing serum AST/ALT level increased by atypical antipsychotics, especially within only one week. Increased liver enzyme were normalized in most patients within 4 weeks. BDD was superior to SMR in normalizing serum ALT level.

GLABELLAR TAP SHOULD BE REMOVED FROM THE SIMPSON-ANGUS SCALE!

N. Bark
Psychiatry, Albert Einstein College of Medicine, Bronx, NY, USA

This presentation argues that the glabellar tap, a primitive reflex, correlates with soft neurological signs (SNS) in schizophrenia, is not usually a sign of parkinsonism and distorts the total score on the Simpson-Angus drug-induced parkinsonism Scale (SAS) of which it is one item. In the original article on the SAS, published in 1970, the glabellar tap separates out as the only item in a distinct factor. In some textbooks describing Parkinson's disease it is reported to occur in 50% of those with severe disease; in others it is not even mentioned; and it occurs in other neurological disorders. Most of the studies of new antipsychotics show that 10 to 20 percent of subjects on placebo have some parkinsonism according to the SAS. It is usually assumed that this is because of persistent parkinsonism from previously taken antipsychotics or that similar symptoms are part of schizophrenia. However it could be that the glabellar tap (and hypersalivation) are contributing disproportionately to this score, and these

items may not indicate parkinsonism at all. In a study of Soft Neurological Signs (SNS) 30 patients with chronic schizophrenia were also examined with the SAS (and AIMS, Barnes, PANSS and various cognitive tests). Pearson product moment correlations between the soft signs and other tests were undertaken. The glabellar tap correlated significantly with left and right and total SNS scores and the left sequencing SNS subscale. The total SAS only correlated with the abnormal movements SNS subscale which includes tremor. The SNS total also correlated with the PANSS cognitive factor, IQ, CVLT and WCST. The right SNS correlated with the PANSS total and Excitement factor and WCST. The left SNS correlated with the PANSS cognitive factor and perseverative errors on the WCST. Thus the glabellar tap is more akin to soft neurological signs than parkinsonism, and parkinsonism does not correlate with SNS except abnormal movements. Furthermore in the author's experience glabellar tap scores either 0 or 4 more often than 1-3. Especially when, with the newer antipsychotics, parkinsonism is less frequent the glabellar tap distorts the evaluation of parkinsonism and should be removed from this scale. (I think the same applies to salivation which may be increased by for example clozapine.) The SAS data from the large scale studies of the new antipsychotics should be analyzed with and without the glabellar tap (and salivation) items to confirm this.

WEIGHT EFFECTS, GLYCEMIC CONTROL AND PLASMA LIPID LEVELS IN LONG-TERM ARIPIPRAZOLE TREATMENT

R. Berman,* R. McQuade, E. G. Stock, A. Torbeyns, W. H. Carson, A. R. Saha, S. Kaplita
Bristol-Myers Squibb, Wallingford, CT, USA

Two studies examined the effects of long-term treatment with aripiprazole on weight, glucose, lipids, and glycosylated hemoglobin levels in patients with schizophrenia. Metabolic parameters were studied in a 26-week trial of aripiprazole treatment for the prevention of relapse in patients with chronic stable schizophrenia. 310 patients were randomized to aripiprazole 15 mg or placebo. Fasted blood samples were collected during the study and analyzed for glucose, plasma lipids, and glycosylated hemoglobin (A1C) levels. Body weight and plasma lipids were studied in a 26-week trial randomizing 317 patients with acute relapse of schizophrenia to aripiprazole (15–30 mg/day) or olanzapine (10–20 mg/day). Patients in both aripiprazole and placebo groups showed minimal changes in mean fasting plasma glucose levels from baseline to endpoint (0.1 mg/dL and 2.1 mg/dL, respectively). Decreases in A1C levels were similar in the aripiprazole (–0.11%) and placebo (–0.17%) groups. Both treatment groups showed small decreases in fasting total and LDL cholesterol levels and slight increases in fasting HDL cholesterol levels. Fasting plasma triglyceride levels showed a median decrease from baseline to endpoint of 12 mg/dL with aripiprazole treatment and 4 mg/dL with placebo. In the comparative study with olanzapine, significantly more olanzapine-treated than aripiprazole-treated patients experienced a weight increase of ≥7% from baseline. Mean changes in body weight showed significant differences between the groups; at week 26 there was a mean weight gain with olanzapine treatment of 3.35 kg compared with a mean weight loss with aripiprazole treatment of 0.86 kg ($p<0.001$ [LOCF data]). In the olanzapine group, there were mean increases in fasting values for total cholesterol (+9.18 mg/dL), LDL cholesterol (+5.04 mg/dL), and triglycerides (+17.07 mg/dL) from baseline at endpoint. Mean decreases in these parameters were observed with aripiprazole (total cholesterol, –3.47 mg/dL; LDL cholesterol, –1.43 mg/dL; triglycerides, –20.20 mg/dL [LOCF data]). Long-term aripiprazole therapy in patients with schizophrenia was not associated with adverse metabolic changes during treatment. Effects on plasma lipid profile and glycemic control seen with aripiprazole were similar to those observed with placebo. Aripiprazole treatment was associated with a significantly lower incidence of weight gain and dyslipidemias than olanzapine therapy.

SPANISH SERIOUS CASES OF INTENTIONAL ZIPRASIDONE OVERDOSE

M. Bernardo,* T. de Flores, J. R. Gutierrez, R. Gandia, T. Diez, L. Ramos
Hospital Clinico, Barcelona, Spain

Objective: to review the safety of all cases of ziprasidone overdose spontaneously reported to Pfizer Spain alert database. Ziprasidone is a new atypical antipsychotic with a unique pharmacological profile which has been shown in placebo and active comparator controlled clinical studies to be effective in treating the positive, negative and affective symptoms of schizophrenia, with a low risk of metabolic side effects. Ziprasidone was first marketed in Sweeden in 1999 and in Spain in 2003, therefore the current information in overdose is scanty. We have reviewed all spontaneous cases reported of an intentional ziprasidone overdose included in the Pfizer Pharmacovigilance Spanish database since ziprasidone was marketed in Spain, Jan03, until 15Sep04. A total of four cases of overdose have been reported. Three of them were male and one a female. The overdose of ziprasidone reached in two cases more than 4000 mg. The highest overdose of ziprasidone was 37 times over the therapeutic recommended dose. The four patients were treated at emergency room and none of them required hospitalization in an intensive care unit, although subsequently were admitted in the Psychiatric Service. All remained conscious and stable clinically. Both the blood test and EKG performed were normal in all the four cases. Neither of the cases showed cardiac adverse effects nor a clinical relevant QTC interval prolongation. There was not any relevant neurologic clinic except a mild to moderate somnolence. The analysis of these four cases confirmed the potential safety of ziprasidone in common situations in psychiatric patients with overdose due to suicide attempts.

LONG-TERM WEIGHT CHANGE WITH QUETIAPINE TREATMENT IN SCHIZOPHRENIA: A COMPREHENSIVE DATA REVIEW

M. Brecher,* R. Leong, L. Osterling-Koskinen, M. Jones
AstraZeneca, Wilmington, DE, USA

To determine the magnitude and pattern of weight change in patients with schizophrenia treated with long-term (≥26 weeks) quetiapine ('Seroquel') monotherapy. A retrospective analysis of data from quetiapine-treated patients with schizophrenia was conducted. Data from all patients in the AstraZeneca clinical trials program who received quetiapine monotherapy for ≥26 weeks, had baseline weight and height measurements, and weight and dose information from a visit at Week 26 or later were analyzed. Descriptive statistics are presented for change in weight (kg) from baseline to final observation, stratified by baseline body mass index (BMI; kg/m^2) category and modal dose of quetiapine. Confidence intervals (95% CI) were calculated for the mean change in weight from baseline to last observation. This analysis includes a total of 661 patients (69% male, 31% female) with diagnoses of schizophrenia who had been treated with quetiapine monotherapy for ≥26 weeks. The mean duration of quetiapine treatment was 17.8 months and the mean modal dose was 467 mg/day. Mean weight change in these patients was +2.3 kg (95% CI

1.6, 3.0) and the median weight change was +1.5 kg. Analysis of mean weight change stratified by baseline BMI category showed that the greatest weight gain (+4.0 kg; 95% CI 1.4, 6.7) occurred in patients who were underweight at baseline (BMI ⟨18.5; n=26). Patients with a normal baseline BMI in the range 18.5 to ⟨25 (n=325) had a mean weight change of +3.3 kg (95% CI 2.4, 4.2) and those in the BMI 25 to ⟨30 group (n=189) had a mean change of +1.6 kg (95% CI 0.4, 2.9). In contrast, in patients with a baseline BMI ≥30 (n=121), the mean weight gain of +0.4 kg was not statistically significant (95% CI −1.6, 2.4). Weight change was also analyzed according to patients' modal daily dose of quetiapine. This analysis showed no relationship between quetiapine dose and weight change: at doses ≤300 mg/day (n=218), mean weight gain was 2.1 kg (95% CI 1.1, 3.2); at ⟩300 to 500 mg/day (n=172), it was 2.7 kg (95% CI 1.4, 4.1); and at ⟩500 mg/day (n=271), it was 2.2 kg (95% CI 1.0, 3.3). Mean weight change during long-term (≥26 weeks) quetiapine treatment of patients with schizophrenia was +2.3 kg. There was no apparent association between weight change and dose of quetiapine. This research was supported by AstraZeneca Pharmaceuticals LP.

CONSIDERATIONS IN THE USE OF ATYPICAL ANTIPSYCHOTICS IN WOMEN

M. Compton
Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA

Schizophrenia manifests itself differently in women than it does in men (later onset, less-severe symptoms), perhaps in part because of a protective effect of estrogen. Atypical antipsychotics likewise affect female patients uniquely, and certain common side effects are of particular significance to women. Based on a review of published literature and recent research, treatment considerations relevant to women with schizophrenia will be discussed. Atypical antipsychotics can cause hormone-related side effects, including impaired sexual function, hyperprolactinemia, and weight gain, which can compromise treatment adherence, diminish quality of life, and increase health risk. Hyperprolactinemia, which can cause serious short- and long-term problems, results from blockade of dopamine-2 (D2) receptors in the tuberoinfundibular pathway. Risperidone has high affinity for D2 receptors and a corresponding higher risk of hyperprolactinemia than other atypicals. Switching to a prolactin-sparing antipsychotic (such as quetiapine or clozapine) can reverse hyperprolactinemia. Weight gain varies among atypical antipsychotics; olanzapine and clozapine cause the greatest increases in weight. Women with schizophrenia have special treatment needs. Choosing an atypical antipsychotic with a favorable safety profile, especially with regard to prolactin and weight, is an important treatment consideration.

PROSPECTIVE STUDY OF SECOND-GENERATION ANTIPSYCHOTIC-INDUCED INSULIN RESISTANCE IN ANTIPSYCHOTIC-NAIVE CHILDREN AND ADOLESCENTS

C. U. Correll,* V. Olshanskiy, T. Mughal, U. H. Parikh, J. M. Kane, A. K. Malhotra
Psychiatry Research, The Zucker Hillside Hospital, Glen Oaks, NY, USA

Objective: Second-generation antipsychotics (SGAs) have been associated with a risk for diabetes. This study aimed to assess the effect of SGAs on glucose metabolism and insulin resistance in youth independent of the confound of previous antipsychotic treatment. Methods: 12-week, prospective, open-label study in antipsychotic-naive subjects, age 5-18 years with psychotic, mood and/or disruptive behavior-spectrum disorders, treated with riperidone, olanzapine or quetiapine. Comedication were not restricted. At baseline, 4 and 12 weeks, height, weight, fat mass and percentage (via impedantiometry), waist circumference, fasting glucose, insulin, prolactin, leptin and SGA levels (ensuring compliance) were measured. Insulin resistance was calculated using the homeostatic model (HOMA-IR: insulin umol x glucose mmol/22.5). Results: In 93 antipsychotic-naive youngsters (mean age: 14.1+/-3.4 years, 54.8% male, 46.2% Caucasian), treated with risperidone (n=51), olanzapine (n=30) or quetiapine (n=12) for 8-13 (mean: 11.6+/-1.7) weeks, fasting glucose (p=.004), insulin (p=.01) and insulin resistance (p=.004) increased significantly. while increases in insulin and HOMA-IR remained significant only for olanzapine (p=.02, respectively). One premorbidly obese youngster (1.1%) developed diabetes on quetiapine. Medications did not differ in their effect on glucose (p=.95) and insulin (p=.29), or on absolute and relative HOMA-IR changes (olanzapine: 0.81+/-1.6, 62.2%; quetiapine: 0.95+/-/-2.4, 19.1%; risperidone: 0.30+/-1.5, 32.0%, p=.31 and p=.25, respectively). However, regarding individual SGAs, increases in glucose reached significance only for risperidone (p=.01), while changes in insulin and HOMA-IR were only significant for olanzapine (p=.02, respectively). In a logistic regression model, glucose increase was correlated with low baseline glucose levels and male gender (R2=0.48, p<.0001). Increase in HOMA-IR (R2=0.21, p<.0001) was correlated with weight gain and a diagnosis of disruptive behavior disorders. Conclusions: Increased insulin resistance in youths after three months of treatment with olanzapine, risperidone and quetiapine, a risk state for the future development of type II diabetes, is of considerable concern. Careful selection of appropriate patients for SGA treatment and routine monitoring of weight and glucose metabolism are strongly recommended in this vulnerable population.

RAPID DIABETES ONSET AND ITS REVERSAL AMONG PATIENTS TREATED WITH SECOND GENERATION ANTIPSYCHOTICS

M. A. De Hert,* D. Van Eyck, M. Wampers, L. Hanssens, A. Scheen, J. Peuskens
Psychosis Units, UC St Jozef, Kortenberg, Vlaams Brabant, Belgium

Epidemiological studies have demonstrated relevant increased risk of diabetes in schizophrenic patients treated with second generation antipsychotics (SGA). This prospective study sought to identify the potential effects of different SGAs on the glucose metabolism. Extensive metabolic data are being collected in a large naturalistic study of treated schizophrenic patients, who will be followed prospectively for 1 year. A subset of patients in this study (n=50) are either receiving a SGA for the first time, or are switched to another SGA. All patients underwent a full metabolic screening at baseline, which includes an oral glucose tolerance test (OGTT, 75 gram glucose load, and assessment of both glucose and insulin). Patients received a control OGTT and a full lipid profile at week 6 and week 12. OGTT data at baseline, 6 weeks and 12 weeks have been analyzed on 50 patients. Six percent (n=3) of patients developed diabetes within the 3 months follow-up. Another 12% (n=6) developed impaired glucose tolerance (IGT). All had a normal OGTT at baseline. Diabetes was remitted in two of the three patients after switching them to another SGA. The third patient was treated with oral antidiabetic medication. Our data suggest that diabetes can occur early after starting SGA. If detected early via full metabolic screening, diabetes onset can be reversed by

switching patients to an SGA with a better metabolic safety profile. This is the first such study which suggests a reversal of rapid onset diabetes by switching agents. It also highlights the relevant predictive value of comprehensive metabolic screening throughout the early course of SGA treatment.

SECONDARY EFFECTS OF ANTIPSYCHOTICS IN CHILDREN AND ADOLESCENTS: PRELIMINARY RESULTS OF A LONGITUDINAL STUDY

A. Doll,* C. Arango, P. Laita
Psychiatry, Hospital General Gregorio Maranon, Madrid, Spain

BACKGROUND: The prescription of second generation antipsychotics has increased largely in recent years. This applies not only to adult population, but also to children and adolescents, a group in which their safety and tolerability have scarcely been assessed. Moreover, none of these drugs are approved for the treatment of children and adolescents. We hypothesized that side effects in this group of patients will be more pronounced than those seen in adults. METHODS: We are conducting a one year longitudinal naturalistic study of 125 children and adolescents treated with antipsychotics, regardless of the diagnosis. The study is being conducted in inpatient and outpatient units. The information gathered at each visit (baseline, 6 months and 1 year) includes electrocardiogram, blood test, height and weight, and extrapyramidal side effects(EPS), which are evaluated with the Involuntary Movements Scale (IMS). RESULTS: At present, we have evaluated 110 children, 18 of whom were drug-naive at baseline. 46 have completed the six-months follow-up. The mean age in our sample is 15.17years(SD =1.96). 57.3%(n=63) of our patients are male. 34.5% have a psychotic disorder, 13.63% have an eating disorder, 8% non specific conduct disorders, and 13.63% affective disorders. At baseline, 44.9% of our patients have been on first generation antipsychotics, 84.4% on second generation antipsychotics; and 9.1% have taken both. The mean number of antipsychotics is 1.81(SD = 1.21). 8.8%(7) had previous history of dystonic reactions. In the drug-naive group we have found prevalence rates of 11.8% for light dyskinetic movements, and 5.6% for light parkinsonian signs at baseline. Among patients that were already taking antipsychotics(n= 92), 30.9% showed light dyskinetic movements, and 16.3% light parkinsonian signs. Differences between these two groups were statistically significant ($p<0.01$). We have not found significant changes in blood tests, except for hyperprolactinaemia in 81.8% of patients at baseline. Comparing baseline and six-months follow-up results, there is a significant increase in global dyskinesia ratings ($p<0.05$), but not in parkinsonism or akathisia. There is a significant increase in weight ($p<0.01$), and a significant decrease of prolactin levels($p<0.03$). CONCLUSIONS: Side-effects of antipsychotic drugs should be carefully monitored in children and adolescents. Further investigation in this area is required.

TISSUE-SPECIFIC CHANGES IN INSULIN SENSITIVITY DURING ATYPICAL ANTIPSYCHOTIC TREATMENT OF SCHIZOPHRENIA

K. Flavin,* D. Haupt, J. A. Schweiger, A. Luber, M. Hessler, J. Maeda, P. Fahnestock, J. Newcomer
Psychiatry, Washington Univeristy School of Medicine, St. Louis, MO, USA

Increased adiposity can disturb glucose and lipid metabolism, and schizophrenia patients experience a higher prevalence of overweight and obesity, diabetes mellitus and the metabolic syndrome in comparison to the general population. Increases in fat mass, plasma glucose and certain lipid fractions are known risk factors for cardiovascular disease (CV), and schizophrenia patients experience higher rates of CV. Recent interest has focused on the contribution of certain antipsychotic medications to metabolic abnormalities. Reports in this area have spanned uncontrolled observations, retrospective database analyses using surrogate indicators, and a limited number of controlled studies with rare randomized clinical trials using sensitive measures. Treatment effects on metabolic variables can be measured using sensitive techniques in the setting of randomized assignment to selected antipsychotic medications. Adiposity can be directly measured using whole body dual energy x-ray absorptiometry (DEXA) and abdominal magnetic resonance imaging (MRI). Both adiposity measures can be analyzed in relation to whole-body glucose and lipid kinetics, with stable isotope tracer methodology during hyperinsulinemic-euglycemic clamp conditions. These methods can be used to calculate tissue-specific changes in insulin sensitivity that might occur independent or dependent on fat mass. In this ongoing study, schizophrenia patients undergo prospective randomized assignment to 12 weeks of treatment with olanzapine, quetiapine, risperidone, or ziprasidone, with no other medication changes allowed. Covarying baseline DEXA total fat mass (to control for baseline differences in fat), significant time X treatment group interactions for glycerol rate of appearance (Ra) ($F[1,3]=194$, $p=0.005$) are observed. Exemplifying changes in relation to changing fat mass, ziprasidone treated subjects experienced predicted changes in glucose Ra ($p=.03$), rate of disappearance ($p=.04$) and glycerol Ra ($p=.01$). These results indicate treatment-induced changes in insulin sensitivity in liver, skeletal muscle, and adipose tissue, respectively. These sensitive measures can be used to evaluate medication-induced changes in glucose and lipid metabolism, relevant to the risk of diabetes and cardiovascular disease. Support Contributed By: NIMH, R01 63985; NIH, (USPHS #M01RR00036): GCRC.

PREVENTION OF WEIGHT GAIN, BY BEHAVIORAL INTERVENTIONS, IN PATIENTS STARTING NOVEL ANTIPSYCHOTICS

R. Ganguli,* J. S. Brar
Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

Weight gain and its associated morbidities like diabetes are of increasing concern for patients taking novel antipsychotics. Given that efforts to reduce weight have low probability of success, prevention of weight gain assumes greater importance. This is a randomized controlled clinical trial of a behavioral intervention to prevent weight gain in patients after they started on novel antipsychotics. Forty nine pattients with a diagnosis of schizophrenia or schizoaffective disorder were randomly assigned to a stepped behavioral intervention aimed at preventing weight gain or to usual care, within 30 days of being started on a novel antipsychotic (clozapine, risperidone, olanzapine, quetiapine, ziprasidone). The active intervention was provided in 4 steps of increasing intensity, triggered by weight increase, if any. Patients in the behavioral intervention were weighed weekly and the behavioral treatment intensified, only if weight gain was detected. Control patients were weighed monthly and allowed to be treated as usual. Follow up lasted for 16 weeks after randomization Of the 27 patients in the active intervention, 17 gained no weight, as compared to 5 of 23 in the control group ($p=.009$). Weight gain of 1kg or 2kg was also present in statistically significantly smaller proportions of patients in active treatment as compared to the control patients (table). There was a trend for

patients on clozapine and olanzapine to gain more weight that patients on other antipsychotics, but there was insufficient power to compare the efficacy of the intervention in patients on different antipsychotics. We conclude that behavioral interventions, in patients monitored for weight gain, can prevent this complication in a significant proportion of these patients. Additional larger studies might clarify the relative efficacy of this approach with respect to different antipsychotics. Supported by an investigator-initiated grant from Eli Lilly.

PROPORTION (%) GAINING WEIGHT

TOLERANCE TO SOMNOLENCE: PRECLINICAL MECHANISMS AND CLINICAL EVIDENCE WITH QUETIAPINE

J. M. Goldstein,* K. Zhong
AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA

Somnolence is a common side effect in patients receiving atypical antipsychotic drugs, a possible result of the affinity of this class of drugs for the histamine (H_1) receptor. As a consequence of the binding profile of quetiapine, the H_1 receptor is completely blocked at very low doses, and rapid tolerance to somnolence may develop after continued dosing. The objective of this analysis was to determine whether tolerance to somnolence occurs with quetiapine use by analyzing the incidence, severity, and duration of somnolence in patients treated with quetiapine. A retrospective analysis of the quetiapine safety database consisting of data from 77 clinical studies (8 placebo-controlled) was conducted (N=7894). A subanalysis of the double-blind placebo-controlled studies in the database was also performed (N=1291 quetiapine, N=612 placebo). Descriptive statistics are presented for all reports of somnolence as an adverse event, including data on time of first onset, severity, and resultant withdrawals. Of the 7894 patients who received quetiapine, 2013 (25.5%) reported somnolence at least once. In the subanalysis of placebo-controlled trials, 330/1291 (25.6%) quetiapine-treated patients reported somnolence compared with 57/612 (9.3%) placebo-treated patients. Somnolence was of mild intensity in the majority of patients receiving quetiapine (71.2%) and placebo (80.7%) and was most common in the first week of treatment, with <1% of patients reporting somnolence after week 4. The median duration of somnolence was 8 days for all quetiapine-treated patients and 5 days and 4 days for quetiapine- and placebo-treated patients, respectively, in the subanalysis. Sixty-two percent of patients who reported somnolence experienced resolution by treatment end. Of the patients who reported somnolence while taking quetiapine, only 38% reported somnolence on the last treatment day. Only 1.3% of patients withdrew because of somnolence. Somnolence was not dose related. Analysis of the quetiapine database has shown that somnolence events were generally mild, occurred early in treatment, and subsequently disappeared with prolonged treatment. These effects most likely can be attributed to the rapid development of tolerance resulting from the complete blockade of the H_1 receptor at low doses of quetiapine.

CAN MEASUREMENT OF GLYCOSILATED HAEMOGLOBIN (HBA1C) BE USED TO SCREEN FOR DIABETES IN SCHIZOPHRENIC PATIENTS?

L. Hanssens,* M. De Hert, M. Wampers, D. Van Eyck, G. L'Italien, A. Scheen, J. Peuskens
Service of Epidemiology and Public Health, University Liege, Liege, Belgium

Schizophrenic patients treated with atypical antipsychotics show an increased risk of diabetes irrespective of concomitant weight gain. This epidemiological observation has revealed a clear need for adequate screening methods to detect undiagnosed diabetes in this population. Generally, assessment of fasting glucose is recommended as screening and monitoring for diabetes (ADA/APA consensus) although an Oral Glucose Tolerance Test (OGTT) remains the gold standard (Expert committee on the diagnosis and classification of diabetes mellitus). HbA1c is accepted as a useful index of mean blood glucose levels in the treatment of patients with diabetes but was not selected by the expert committee as a means for screening. Since HbA1c testing can be performed at any time of day without special patient preparation it could be a more convenient screening method for both patients and caregivers. A recent consensus on the management of diabetes risk in schizophrenia of British psychiatrists suggests that assessment of HbA1c can be used for screening. We therefore aim to evaluate the use of HbA1c in screening for diabetes in a schizophrenic population. A large scale prospective naturalistic study on metabolic disturbances in schizophrenic patients, including an OGTT is currently ongoing. At this moment 350 patients have entered the study, they will be followed prospectively for 1 year. We analyzed data on 632 OGTTs in combination with an assessment of HbA1c. To diagnose glucose abnormalities the criteria of the American Diabetic Association are used. According to these criteria 7.9% of OGTT meet criteria for diabetes. Impaired glucose tolerance (IGT) is present in 9.5% and impaired fasting glucose (IFG) in 11.9% of OGTT. In the overall study population mean HbA1c-values differed significantly between 3 patient groups: patients suffering from diabetes, patients diagnosed with glucose abnormalities (IFG or IGT) and patients without any glucose abnormalities. HbA1c showed a high sensitivity and specificity for detecting diabetes. Large inter-individual differences in HbA1c-values were however observed in each patient group rendering it impossible to correctly categorize individual patients based on HbA1c alone.

ZIPRASIDONE VS OLANZAPINE: CONTRASTS IN CHD RISK

D. J. Harrison,* A. Cheli, A. Loebel, S. Murray
Pfizer Inc, New York City, NY, USA

This analysis was conducted to examine differences in coronary heart disease (CHD) risk arising from short-term treatment with ziprasidone and olanzapine. Hospitalized schizophrenic adults underwent 6 weeks' randomized, double-blind treatment with ziprasidone or olanzapine, with data collected at baseline and endpoint for fasting lipids and weekly for blood pressure. A Framingham algorithm was used to calculate percentage CHD risk over 10 years in subjects ≥30 years (per algorithm). Baseline-to-endpoint mean changes in age-adjusted risk by sex were compared using ANCOVA (baseline adjusted). In men ≥30 years, there was a significant difference in mean changes in total cholesterol for olanzapine versus ziprasidone (+18.5 mg/dL [n=53] and -8.5 mg/dL [n=44], respectively; P=0.0006). A

significant difference was also seen in mean changes in low-density lipoprotein cholesterol for olanzapine versus ziprasidone (+13.0 mg/dL [n=45] and -7.2 mg/dL [n=40], respectively; P=0.004). Mean CHD risk in men increased by 0.6% (baseline 8.1%) with olanzapine (n=53) and decreased by 1.1% (baseline 9.6%) with ziprasidone (n=42). In women ≥30 years, between-group differences were trending toward significance for lipid changes and CHD risk. Neither treatment had significant effects on blood pressure. In conclusion, our findings indicate that in short-term treatment of men, olanzapine was associated with significant changes in lipid profile versus ziprasidone, with a consequent increase in CHD risk versus ziprasidone. These findings, coupled with those of significant weight gain with olanzapine versus ziprasidone, warrant investigation in longer-term trials.

EFFECTS OF DIVALPROEX/ANTIPSYCHOTIC POLYPHARMACY OF SCHIZOPHRENIA ON ADIPOSITY AND FASTING LIPIDS

D. Haupt,* K. S. Flavin, M. J. Hessler, J. A. Schweiger, A. Luber, P. A. Fahnestock, J. Maeda, J. W. Newcomer
Psychiatry, Washington University School of Medicine, Saint Louis, MO, USA

Schizophrenia patients are commonly exposed to polypharmacy, but few studies have described the effect of commonly used polypharmacy on lipid metabolism. It has been reported that combination therapy involving antipsychotic medications and divalproex may be associated with decreases in total plasma cholesterol levels, but these conclusions have been based on limited data, with few studies evaluating fasting rather than commonly-reported random lipid profiles. This ongoing study measures changes in sensitive measures of adiposity and lipid metabolism during combination therapy with divalproex and antipsychotics. Nondiabetic schizophrenia patients (n=23) underwent a 6-week baseline control period with a pre- and post-baseline assessment of metabolic endpoints to confirm stability of metabolic endpoints prior to the experimental treatment intervention. Subjects whose baseline condition was antipsychotic monotherapy subsequently initiated adjunctive divalproex treatment, while subjects who began the study already receiving combination treatment were withdrawn from divalproex and continued on antipsychotic treatment alone. Repeat metabolic assessments were conducted after 12 weeks following the second baseline measurements. Metabolic assessments relevant to this analysis included dual energy x-ray abpsorptiometry (DEXA), quantifying total body fat, fasting plasma measurements, and Brief Psychiatric Rating Scale (BPRS) measures of clinical status. For subjects starting adjunctive divalproex, a main effect of time (averaged baseline versus 12-week endpoint) was detected for DEXA total fat (F[1,15]=10.56, p=.005) and fasting triglycerides (F[1,17]=4.54, p=.048), indicating significant increases in associated with initiation of divalproex treatment. A trend level increase in fasting total cholesterol was similarly observed. For subjects going on or off divalproex, no significant changes in BPRS total scores were observed. These data do not support previous reports suggesting that divalproex therapy is associated with beneficial effects on plasma lipids. The results provide further evidence that psychiatric medications that produce increases in fat mass can also increase circulating lipid fractions associated with adverse health outcomes. NARSAD (Stephen and Connie Lieber Young Investigator Award), NIMH K23 MH 067795; NIH R01 63985, USPHS, #MOIRR00036, GCRC, CNRU P30 DK56341 and P60-DK20579.

A RESEARCH-CLINICAL PARTNERSHIP TO IMPROVE SAFETY OF ANTIPSYCHOTIC MEDICATIONS

T. J. Hudson,* K. Henderson, R. R. Owen
Psychiatry, University of Arkansas for Medical Sciences, North Little Rock, AR, USA

Objective: To improve safety of patients receiving antipsychotics, clinicians and researchers from the South Central Veterans Affairs Health Care Network (SCVAHCN) Mental Health Product Line, the South Central Mental Illness, Research, Education and Clinical Center (MIRECC) and the Mental Health QUERI collaborated to 1) develop side effect monitoring recommendations; 2) develop and implement a performance measure; and 3) educate providers. Methods: Representatives from three groups worked together to develop evidence-based monitoring recommendations. After peer-review by psychopharmacology experts, the recommendations were printed in a pocket-sized booklet. The booklets and a slide set explaining the performance measures were distributed to the SCVAHCN Chiefs of Mental Health for further dissemination to clinic staff. The mental health product line used these recommendations as the basis for development of performance measures for monitoring weight and blood glucose/hemoglobin A1C. The SCVAHCN data warehouse was used to determine performance measure results. The performance measures applied to all patients receiving new antipsychotic prescriptions in a mental health clinic. To be fully successful, a facility must monitor weight of 85% of patients and blood glucose/hemoglobin A1c of 70% of patients within 180 days prior to or 30 days after initiation of an antipsychotic. Results: During FY03, 4066 patients at 10 facilities were included in the performance measure at baseline, 85% (range: 73.5%-98.9%) of the patients had weight measured and 68.3% (range: 51.4%-82.9%) had a blood glucose or hemoglobin A1C. As of August 04, 3995 patients were available for evaluation. At baseline 88% had weight (range: 80%-100%) and 74% (range: 67.8%-88.6%) had blood glucose or hemoglobin A1C measured. Eight of 10 facilities and seven of 10 facilities met the fully successful criterion for monitoring weight and blood glucose/hemoglobin A1C respectively. Weight monitoring improved in 8/10 facilities and monitoring of blood glucose/hemoglobin A1C improved in 7/10 facilities. Conclusions: This project represents a close collaboration between clinicians and researchers and is one of the first efforts to define and implement routine physical health monitoring for antipsychotic medications. Although the improvements in monitoring were relatively small, some facilities made substantial improvements. Future directions include developing a performance measuring for serum lipids.

PHARMACOTHERAPY OF METABOLIC COMPLICATIONS OF SCHIZOPHRENIA

M. Jafari,* D. E. Casey
Medicine, University of California, Irvine, Orange, CA, USA

During the last few years, concern has risen about metabolic complications such as diabetes, obesity, and dyslipidemia in patients with schizophrenia. These complications may be due to the disease state of schizophrenia or induced by medications that are used to treat schizophrenia. If untreated, they may result in cardiovascular diseases and mortality. The purpose of this presentation is to discuss the epidemiology, etiology, pathophysiology, and pharmacotherapy of these metabolic complications. For each complication an in depth discussion of the preventive measures, monitoring parameters, and

disease and patient specific pharmacotherapeutic modalities will be presented.

BEYOND WEIGHT GAIN IN SCHIZOPHRENIA: PAYING CLOSER ATTENTION TO CARDIOVASCULAR RISK WITH SECOND-GENERATION ANTIPSYCHOTICS

D. L. Kelly,* J. Shim, R. P. McMahon, R. C. Love, S. Feldman, Y. Yu, J. A. Morrison, R. R. Conley
Maryland Psychiatric Research Center, University of Maryland, Baltimore, MD, USA

Weight gain has recently been viewed as a hot topic for people treated with antipsychotics. Much less attention, however, has been paid to the relation of weight gain to metabolic sequelae and/or cardiovascular risk in people with schizophrenia (SZ). We present two studies: the first evaluated body mass index, body surface area, subcutaneous fat tissue, and coronary atherosclerosis by autopsy reports for people with SZ who were deceased to evaluate the presence of cardiac atherosclerosis and it association with body weight. The second study was an 8-week randomized double blind trial of the metabolic consequences and relationship to weight gain in people with SZ treated with olanzapine or risperidone. Cardiovascular disease (CVD) was the leading cause (46%) of death in people with SZ as well as controls (42%) (N=268). Body weight, BMI, BSA and SC fat were not different between two groups, however people with SZ who were considered underweight had higher rates of cardiac death than the controls (38% vs. 13%) (c2 = 5.79, p=0.01). No difference was noted in the number of coronary arteries occluded, however, 49% of the controls with abnormal SC fat had cardiac atherosclerosis as compared to 33% of the SZ group. In the double blind trial, greater gains in total cholesterol (TC), triglycerides (TG), and LDL were observed on olanzapine compared to risperidone (N=377). Men on olanzapine (but not women) had higher than expected increases in TC (4X) controlling for the extent of weight gain than in general population data (Z=-1.810 p=0.04). This was also true with TG for men taking olanzapine (3X)(Z=-2.622 p=0.004). TC and TG changes were expected given the observed changes in weight for risperidone. Although CVD occurs commonly in people with SZ, the risk and development may be related less to weight than in the general population. This may be related to intrinsic metabolic differences of the disease itself, lifestyle differences, or treatment with antipsychotic medications. Furthermore, certain antipsychotics may be associated with lipid changes that are greater than expected given the specific weight gain. Both studies suggest that efforts for the prevention of CVD in SZ patients should include the effort for reducing multiple risk factors such as smoking, dyslipidemia, lifestyle factors, and medication effects, not confined solely to the control of weight.

THE DIFFERENTIAL CHANGE OF BLOOD PRESSURE IN PATIENTS WITH SCHIZOPHRENIA TREATED WITH CLOZAPINE AND OLANZAPINE

W. Kim,* W. M. Bahk, J. H. Chae, T. Y. Jun, K. S. Kim
Psychiatry, The Catholic University of Korea, Seoul, South Korea

Objectives: There were reports about weight gain, hyperglycemia, diabetes mellitus and hyperlipidemia associated with atypical antipsychotics. Moreover, these adverse effects of atypical agents, especially clozapine and olanzapine were reported to be able to precipitate cardiovascular disease. So we investigated the change of blood pressure in schizophrenic patients treated with clozapine and olanzapine by retrospective chart review. Methods: We reviewed charts of patients with schizophrenia who admitted at St.Mary Hospital, The Catholic University of Korea, and selected records of patients treated with clozapine and olanzapine during at least 6 weeks. Patients treated with mood stabilizers, antidepressants, and antipsychotics other than clozapine and olanzapine were excluded. Finally, the records of 23 clozapine-treated patients and 45 olanzapine-treated patients were analyzed. Changes of systolic and diastolic blood pressure between before treatment and discharge time were analyzed by paired t-test, and group difference of changes were analyzed by repeated measures ANOVA. Results: Mean systolic and diastolic blood pressure before treatment in clozapine group were 110.87(8.48), 75.22(7.90), and mean blood pressure at discharge time were 114.35(10.80), 79.13(7.33). There was no significant change of systolic blood pressure in clozapine-treated patients(p=0.16). But, clozapine had a trend of increasing diastolic blood pressure, although not statistically significant(p=0.071). In olanzapine-treated patients, mean systolic and diastolic blood pressure before treatment were 114.22(9.88), 75.56(8.93), and mean blood pressure at discharge were 111.34(10.14), 74.44(8.13). There was no significant change in both systolic and diastolic blood pressure(p=0.102, p=0.430). As a results of repeated measures ANOVA, within-subject factors and between-subjects factors were not significant, but interaction of two factors was statistically significant for both systolic and diastolic blood pressure(p=0.36, p=0.44). Conclusions: We could see that clozapine had a trend of increasing diastolic blood pressure, although that was not significant. We also found that clozapine-treated patients and olanzapine-treated patients were different in the pattern of changes in systolic and diastolic blood pressure. This result suggests that clozapine has more tendency of increasing blood pressure, compared with olanzapine.

CHANGES IN GLUCOSE, LIPID LEVELS, AND BODY WEIGHT IN KOREAN PATIENTS WITH SCHIZOPHRENIA TREATED WITH ATYPICAL ANTIPSYCHOTICS

C. E. Kim,* M. H. Lee, J. N. Bae
Psychiatry, Inha University Hospital, Incheon, South Korea

Objective: The association of hyperglycemia, dyslipidemia and body weight gain with use of atypical antipsychotics has been documented in many studies. But, previous most studies about this topic had retrospective design and the participants of these studies were mostly western people. We aimed to assess the effect of risperidone, olanzapine, quetiapine and amisulpiride on glucose, lipid levels and body weight changes in Korean patients with schizophrenia during 12 -week prospective trial. Method:The subjects were inpatient in InHa univ hospital and they had no previous history of diabetes mellitus, hyperlipidemia and antipsychotic medication within 1 month before the assignment. The subjects were assigned to each medication groups by clinical judgment of the charge doctors. 79 patients with schizophrenia provided blood samples at baseline and at least at one point after starting antipsychotic medication. In risepridone Group, 22 patients provided blood samples at baseline and at 2 weeks after starting risperidone. 12 patients provided blood samples at baseline and at 7 week point. 12 patients provided blood samples at baseline and at 12 week point. In olanzapine group, there were 16, 7, 8 patients at 2 week, 7 week, 12 week point. In quetiapine group, there were

14, 8, 6 patients at each point. In amisulpride group, there were 14, 13, 10 patients at each point. During 12-week trial, planned assessment included fasting glucose and lipid levels (cholesterol, TG, HDL, LDL), body weight which were collected at baseline and at 2 weeks, 7 weeks, 12 weeks after antipsychotics medication. All data analyzed by paired t-test and the significance level was 0.05. Results and cnclusions: In this prospective trial, risperidone, olanzapine, quetiapine, amisulpride were significantly associated with increase in weight. In amisulpiride group, there were significant decrease in glucose level at 2 week point. but, in all medication group, there were no significant change in glucose point at 12 week. There were significant increace in cholesterol, LDL levels in amisulpride group at 12 week point and other medication groups showed trend of increase in cholesterol and TG levels.

THE SUBJECTS RESPONSES TO ANTIPSYCHOTICS EVALUATOR: SRA*E*

R. Knegtering,* H. A. Wolters, R. Bruggeman, R. J. van den Bosch, D. Wiersma
Psychiatry, University Medical Center Groningen, Groningen, Groningen, Netherlands

Most questionnaires concerning antipsychotic treatment are developed for clinical research goals. They are less suited to help clinicians and patients in optimising their pharmacotherapy. The objective of the present study was 1) to develop and 2) to validate an easy, self rating questionnaire for clinical practice to explicitly evaluate treatment effects of antipsychotic medication from a patients perspective. The instrument is designed to improve antipsychotic treatment and is named The Subjects Responses to Antipsychotics evaluator (SRA*e*). First, items were gathered through open and semi-structured interviews with patients being treated with antipsychotics, classical and atypical. All desired and undesired effects, attributable to antipsychotic treatment were collected and grouped into items. The phrasing of the items corresponded as much as possible with the original responses as verbalised by the patients. In total 77 patients reported 760 different responses to their treatment. Of these reported effects 61% were of a psychological nature (of which 52% undesired), 30% included somatic effects (93% undesired), and 9% were on social interactions (28% undesired). Then, independent clinical experts grouped all these responses, constituting a 74-item questionnaire with 6 subscales. The items could be rated: no; to a certain degree; or yes. Next, the SRA*e* was tested in a multi-centre study evaluating 1) test-retest reliability, 2) construct-concurrent- and predictive-validity and 3) sensitivity to change. For this reason, demographical and clinical data, standardised questionnaires for Quality of Life, drug adherence, subjective wellbeing, drug attitude and side effects were also included. 320 patients participated in this study. Of these, 90% completed the questionnaire without any help, all within 20 minutes. The test-retest reliability was good for all sub-scales (r= .60 - .89), except for the subscale sexual anhedonia (r= .39). The internal consistency (Cronbachs alpha) was 0.69 or higher. First analysis showed a high correlation of scores on the SRA*e* with quality-of-life scales and a moderate correlation with the subjective wellbeing. Known undesired effects of antipsychotics, were correctly identified. Data on congruent and predictive validity are under study. The SRA*e* may be an easy, reliable and useful tool assisting clinicians and patients to find optimal antipsychotic treatment.

NEUTROPENIA AND AGRANULOCYTOSIS IN TREATMENT-REFRACTORY ADOLESCENTS RECEIVING CLOZAPINE

H. N. Kranzler,* G. Gerbino-Rosen, D. A. Tompkins, D. Feryo, L. Nussbaum, D. Roofeh, G. Fisch, A. Frederickson, B. Napolitano, S. Kumra
Department of Psychiatry, Division of Child and Adolescent Psychiatry, Bronx Childrens Psychiatric Center, Bronx, NY, USA

Clozapine is an atypical antipsychotic medication that is effective in the treatment of patients with refractory schizophrenia and bipolar disorder. There is some data to suggest that children and adolescents may be particularly vulnerable to the hematological adverse effects of clozapine. We conducted a retrospective chart review for May 1992 through May 2004 to determine the incidence of neutropenia (absolute neutrophil count <1500) and agranulocytosis (absolute neutrophil count <500) in children and adolescents treated with clozapine and the effects of potential risk factors such as baseline demographic characteristics and laboratory values. Each prescribing physician administered clozapine treatment in an open label fashion using a flexible titration schedule. Data were available for 172 children and adolescents who received clozapine with a median observation period of 8 months. Neutropenia developed in 23 patients and agranulocytosis in 1 patient. In total, 13 (8%) of 172 patients from this sample eventually discontinued clozapine due to hematological side effects. Twenty (83%) of twenty-four patients developed their first episode of neutropenia within the first six months of treatment; the isolated case of agranulocytosis occurred at the second month of treatment. Eleven (48%) of 23 patients who developed neutropenia were successfully retried on clozapine often with adjunctive lithium therapy to increase the absolute neutrophil count. As a group, patients who developed some type of hematological adverse effect while on clozapine therapy (e.g., neutropenia, agranulocytosis) had significantly lower baseline absolute neutrophil counts and also were younger at clozapine initiation relative to patients who did not develop a hematological adverse effect. A logistic regression was used to determine whether baseline absolute neutrophil count or age at clozapine initiation, considered in a single model, could predict group status (presence/absence of hematological adverse side effect). Only baseline absolute neutrophil count predicted likelihood of developing a hematological adverse side effect on clozapine therapy. The occurrence of hematological adverse events is a significant hazard associated with the administration of clozapine, however, in this case series the majority of cases of neutropenia were transient and very few patients (8%) actually discontinued therapy due to this side effect.

ADVERSE EVENTS DURING ANTIPSYCHOTIC CLINICAL TRIALS OF ELDERLY PATIENTS WITH DEMENTIA

L. Kryzhanovskaya,* P. Cavazzoni, C. Young, J. Polzer, J. Jansen, R. Baker
Eli Lilly and Company, Indianapolis, IN, USA

Background: Antipsychotics are sometimes prescribed to patients with dementia-related psychosis. Deaths and cerebrovascular adverse events (CVAEs) have been reported in this population during antipsychotic clinical trials. Methods: Data from seven studies of olanzapine (OLZ) in elderly patients with dementia were analyzed for incidence of mortality and CVAEs. Data was taken from five double-blind placebo (PLC)-controlled studies (OLZ N=1184, PLC

N=478; and OLZ N=204, risperidone (RISP) N=196); an open-label study (OLZ N=149, conventional antipsychotics (CONV) N=143), and an overall-OLZ database (N=1610, data from these studies and an open-label OLZ-only study, N=81). Results: In this integrated analysis, incidence of CVAEs was approximately three times higher in olanzapine- than in placebo-treated patients (1.3% vs. 0.4%; pooled data, Fisher's exact test p=.177; meta-analysis on incidence rate difference, stratified by protocol, fixed-effects model p=.016); there was no difference between OLZ- and RISP- (2.9% vs. 2.0%, p=.751), or CONV-treated patients (14.8% vs. 16.1%, p=.871). The higher rate of mortality did not appear to be associated with duration of OLZ treatment. Across all treatments, mortality risk factors in PLC controlled studies included age >80, low baseline MMSE score, benzodiazepine use, treatment emergent (TE) ≥7% weight change, TE sedation, TE malnutrition/dehydration, TE dysphagia, and TE pulmonary conditions. Risk factors associated with a higher mortality incidence in OLZ- treated patients included age >80, benzodiazepine use, TE sedation, or TE pulmonary conditions. Incidence of CVAEs was approximately three times higher in OLZ- than in PLC-treated patients (1.3% vs. 0.4%). There were no significant differences between OLZ- and RISP- (2.5% vs. 2.0%, p=1.0), or CONV-treated patients (3.4% vs. 4.3%, p=.765). Risk factors for CVAEs in OLZ-treated patients included age ≥80 (vs. PLC), vascular/mixed dementia (vs. PLC and RISP; OLZ overall group), or baseline MMSE <14 (vs. CONV). Conclusions: In this analysis, incidence of mortality and CVAEs was higher in OLZ- than in PLC-treated patients, but there were no significant differences between OLZ and RISP-, or CONV-treated patients. OLZ and other antipsychotic agents are not approved for the treatment of dementia in the U.S., and these findings should be considered carefully if prescribers elect to treat dementia-related psychosis in the elderly with OLZ or other antipsychotics.

DIFFERENTIAL EFFECTS OF ATYPICAL ANTIPSYCHOTICS ON INDICES OF METABOLIC SYNDROME

J. Meyer,* J. W. Newcomer, A. D. Loebel, G. M. Cohen
San Diego Veterans Administration Medical Center, La Jolla, CA, USA

Our objective was to determine rates of dyslipidemia and metabolic syndrome associated with atypical antipsychotic use in subjects with schizophrenia in the ziprasidone clinical trial database. As of April 30, 2003, database comprised 8243 subjects with schizophrenia or schizoaffective disorder given ziprasidone (N=5622) or comparators (N=2621) in 37 trials. Trials included 15 short-term (≤12 week) and 19 long-term (>12 week) studies with random laboratory measurements, and 3 studies with fasting measurements (2 short term, 1 long term). Per current NCEP guidelines, abnormal lipid values were defined as TChol ≥240 mg/dL, LDL-C ≥160 mg/dL, HDL-C <40 mg/dL, and triglycerides ≥200 mg/dL; metabolic syndrome was defined as ≥3 of the following: blood pressure (any position) ≥130/85 mm Hg; HDL-C <40 mg/dL (males) or <50 mg/dL (females); triglycerides ≥150 mg/dL; glucose (random or fasting) ≥110 mg/dL; and, in lieu of waist circumference, body mass index (BMI)≥30. HDL-C measurements were consistent only in those trials employing fasting measurements. At last visit in fasting studies, ziprasidone-treated subjects had a prevalence of serum lipid abnormalities comparable to that of placebo and consistently lower than that of comparators. Olanzapine was associated with a nearly 2-fold higher prevalence of lipid abnormalities than ziprasidone. In studies with random measures, differences were not as marked or consistent. When metabolic syndrome was defined by a BMI ≥30, the rate in ziprasidone vs olanzapine subjects was 3.3% vs 8.8%, respectively, in short-term studies, and 4.8% vs 12.4% in long-term studies. In fasting trials with ziprasidone and olanzapine treatment groups, rates of metabolic syndrome at endpoint in BMI ≥30 subjects were 15.2% vs 23.6%, respectively (short-term), 25.7% vs 46.4% (short-term), and 22.6% vs 19.7% (long-term). In studies including risperidone, the rate exceeded that of ziprasidone while falling below that of olanzapine. Endpoint prevalence of dyslipidemia and metabolic syndrome is reported without adjusting for status of the latter at study baseline. In conclusion, this comprehensive database review of comparative atypical antipsychotic trials shows a differential effect on dyslipidemia and metabolic syndrome rates. Observed differences at endpoint between groups indicated rates of metabolic abnormalities of ziprasidone < risperidone < olanzapine and is consistent with recent ADA/APA findings (*Diabetes Care* 2004; 27:596-601).

ATYPICAL ANTIPSYCHOTIC TREATMENT EFFECTS ON METABOLIC OUTCOME

J. W. Newcomer,* D. W. Haupt, K. S. Flavin,
J. A. Schweiger, J. Maeda, B. Patterson, S. Klein
Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA

Increased adiposity can disturb glucose and lipid metabolism, and schizophrenia patients experience an increased prevalence of overweight and obesity, diabetes mellitus, and the metabolic syndrome in comparison to the general population. Increased adiposity, plasma glucose, and increases in certain lipid fractions are known risk factors for cardiovascular disease (CV), and schizophrenia patients experience higher rates of CV. Recent interest has focused on the contribution of certain antipsychotic medications to metabolic abnormalities. Reports in this area have spanned uncontrolled observations, retrospective database analyses using surrogate indicators, and a limited number of controlled studies with rare randomized clinical trials using sensitive measures. Treatment effects on metabolic variables can be measured using sensitive techniques in the setting of randomized assignment to selected antipsychotic medications. Adiposity can be directly measured using whole body dual energy x-ray absorptiometry (DEXA) and abdominal magnetic resonance imaging. These adiposity measures can be analyzed in relation to whole-body glucose and lipid kinetics measured with stable isotope tracer methodology during hyperinsulinemic-euglycemic clamp conditions. These methods can be used to measure tissue-specific changes in insulin sensitivity that might occur independent or dependent on fat mass. In this ongoing study, schizophrenia patients undergo prospective randomized assignment to 12 weeks of treatment with olanzapine, quetiapine, risperidone, or ziprasidone, with no other medication changes allowed. Significant treatment effects on adiposity and tissue specific insulin sensitivity are observed using this approach, with different medications producing different effects on metabolic outcome. Methodological considerations, particularly concerning the baseline or pre-treatment conditions, may be important to consider in further studies in this area. The results are directly relevant to ongoing clinical and regulatory considerations in this area, and suggest opportunities to improve the overall metabolic risk profile of patients treated with antipsychotic medications. Support Contributed By: NIMH, R01 63985; NIH, (USPHS #M01RR00036): GCRC.

ASSESSING PHYSICAL HEALTH IN AN URBAN POPULATION OF PEOPLE WITH SERIOUS MENTAL ILLNESS

R. Ohlsen,* G. Peacock, S. Smith, L. S. Pilowsky
Neurochemical Imaging & Psychiatry, Institute of Psychiatry, London, United Kingdom

Background: The physical health of people with serious mental illness is a relatively neglected area of clinical focus and research (Lambert et al, 2003). Schizophrenic people are vulnerable to cardiovascular disorders, and are more likely to suffer metabolic abnormalities such as diabetes (Ryan and Thakore, 2002). While poor diet, cigarette smoking, and sedentary lifestyle (Brown et al, 1999) are significantly detrimental to the health of this group, there is no doubt that schizophrenia per se appears to be a risk factor. In addition, obesity and metabolic disorders are frequently initiated or exacerbated by treatment with antipsychotic drugs. Definitive, effective models of managing the physical health problems of the mentally ill have yet to be identified and implemented. Methods:We assessed physical health and lifestyle in a population of n=124 (66 male, 58 female) people in an inner city area of London (Brixton). Patients were weighed, had their body mass index (BMI), blood pressure(BP) and blood sugar checked. They were also asked about cigarette and alcohol consumption, diet and self esteem. Results:Baseline results showed that 89% were overweight, (BMI>25), and 38% (BMI>35) were morbidly obese. BP was higher than average (mean 139/95) and 52% were smokers compared to 19% of the general population. 13& had diabetes. 60% were assessed as having an unhealthy diet, and 58% had below average self esteem. This group was clearly an at risk population, requiring some intervention to avert further morbidity and mortality. Patients were offered an intervention comprising 6 consultations wherein dietary and lifestyle advice would be given, as well as the opportunity to attend a weekly weight management group and gymnasium/physical activity group for a year free of charge. This study is ongoing. After 3 consultations, 35% had unhealthy diets, 70% had average self esteem, and 52% had achieved some weight loss. Mean wt loss wqs 0.7kg but ranged from -19kg -+8kg. This confirms earlier research (Ohlsen et al, 2004) that psychosocial interventions can be very effective for some patients. Conclusions: Simple advice about lifestyle and diet can effect positive changes in even very unhealthy groups of people with serious mental illness. This intervention was performed by a nurse and could be replicated in other centres. The baseline findings highlight the extent of physical morbidity in the mentally ill in this urban setting.

NEW-ONSET DYSLIPIDEMIA IN CHILDREN AND ADOLESCENTS TREATED WITH SECOND-GENERATION ANTIPSYCHOTICS

V. Olshanskiy,* A. K. Malhotra, U. H. Parikh, T. Mughal, M. Moroff, J. M. Kane, C. U. Correll
Psychiatry Research, The Zucker Hillside Hospital, Glen Oaks, NY, USA

Objective: Although second-generation antipsychotics (SGAs) are used in children and adolescents for a wide variety of psychotic and non-psychotic disorders, no comparative data exist on their effects on serum lipids. Methods: 12-week, prospective, open-label study in subjects 5-19 years old with a DSM-IV diagnosis of psychotic, mood and/or disruptive behavior disorders necessitating initiation of non-clozapine SGA-treatment. At baseline and monthly, height, weight, body mass index (BMI), fat mass (bioimpedantiometry), waist circumference, as well as lipid profile, leptin and SGA levels (assessing compliance) were measured. Dyslipidemia was defined as fasting cholesterol >200 mg/dL and/or triglycerides >150 mg/dl). Results: 258 youngsters (mean age: 13.8+/-3.5 years, 62.0% male, 47.9% Caucasian) completed 8-13 (mean: 11.8+/-1.5) weeks of treatment with olanzapine (n=66), risperidone (n=81), ziprasidone (n=12), quetiapine (n=51) or aripiprazole (n=48). Although for the entire group, none of the individual lipid parameters increased significantly from baseline to endpoint, 19.2% of youths developed new-onset dyslipidemia (aripiprazole: 15.2%; olanzapine: 24.2; quetiapine: 21.6%; risperidone: 17.5%; and ziprasidone: 8.3%, p=.57). In antipsychotic-naive youths (n=120), however, significant increases from baseline to endpoint were observed in the entire sample for cholesterol (p=.04), and triglycerides (p=.001). When analyzing changes for each SGA individually, lipid increases were significant only for olanzapine (total cholesterol: p=.002), LDL-cholesterol: p=.01, triglycerides: p=.001). Correlates of total cholesterol increase (R2=.25, p<.0001) were low baseline cholesterol levels (p<.0001), weight gain (p<.0001) and antidepressant co-treatment (p=.003). Correlates of triglyceride increase (R2=.39, p<.0001) were low baseline triglyceride levels (p<.0001), BMI increase (p<.0001), antidepressant co-treatment (p=.01) and antipsychotic-naivete (p=.04). Conclusions: In youngsters, SGAs adversely affect lipid metabolism, increasing the risk for future cardiovascular morbidity. High-risk individuals are antipsychotic-naive youths with low lipid levels who experience weigh gain. The potential effect of antidepressant cotreatment on lipid levels requires further study. Careful use of SGAs, regular monitoring of these side effects, and pre-treatment dietary/lifestyle counseling are warranted.

CHANGES IN BODY COMPOSITION IN CHILDREN AND ADOLESCENTS TREATED WITH SECOND-GENERATION ANTIPSYCHOTICS

U. Parikh,* A. K. Malhotra, V. Olshanskiy, T. Mughal, M. Moroff, J. M. Kane, C. U. Correll
Psychiatry Research, The Zucker Hillside Hospital, Glen Oaks, NY, USA

Objective: Although second-generation antipsychotics (SGAs) are widely utilized in youths, limited comparative data exist on their effects on body composition in this vulnerable population. Methods: 12-week, prospective, open-label study in subjects 5-19 years old with a DSM-IV diagnosis of psychotic, mood and/or disruptive behavior disorders necessitating initiation of non-clozapine SGA-treatment. At baseline and monthly, height, weight, body mass index (BMI), fat mass (bioimpedantiometry), waist circumference, as well as leptin and SGA levels (assessing compliance) were measured. Results: In 258 youngsters (mean age: 13.8+/-3.4 years, 64.3% male, 47.3% Caucasian) who completed 8-13 (mean: 11.8+/-1.5) weeks of SGA-treatment, weight, BMI, fat mass, and waist circumference increased significantly for olanzapine (e.g., 7.4+/-4.5kg, 2.6+/-1.5 BMI-units, n=66), risperidone (4.8+/-3.9kg, 1.6+/-1.4 BMI-units, n=81), ziprasidone (3.8+/-3.9kg, 1.2+/-1.3 BMI-units, n=12), and quetiapine (2.7+/-5.3kg, 0.7+/-1.9 BMI-units, n=51), but not for aripiprazole (0.7+/-3.5kg, 0.01+/-1.5 BMI-units, n=48) (p<.0001, respectively). Extreme weight gain (>/=7%) occurred in 83.3%, 60.5%, 36.4%, 43.1% and 12.5% of patients, respectively (p<.0001). However, in antipsychotic-naive youths (n=120), body composition parameters increased significantly with all SGAs, including aripiprazole. Correlates of BMI increase (R2=.38, p<.0001) were

antipsychotic-naivete, receiving olanzapine treatment, not receiving aripiprazole treatment, being of Hispanic, Asian or mixed ethnicity and having a diagnosis of schizophrenia-spectrum or mood disorders. When intra-treatment changes were included in the model, correlates of weight gain included weight gain at 4 weeks, antipsychotic-naivete, higher baseline leptin levels, and divalproex co-treatment (R2=.71, p<.0001). Conclusions: In youngsters, SGAs adversely affect all components of body composition, which increases the risk for future development of diabetes and cardiovascular morbidity. High-risk individuals are antipsychotic-naive, minority youths with schizophrenia or mood disorders, treated with olanzapine who are relatively leptin-resistant and experience significant early weight gain. Careful use of SGAs, regular monitoring of these side effects, and pre-treatment dietary/lifestyle counseling are warranted.

THE METABOLIC SYNDROME IN SCHIZOPHRENIC PATIENTS TREATED WITH ANTIPSYCHOTICS

J. Peuskens,* M. De Hert, D. Van Eyck, M. Wampers, A. de Patoul, L. Hanssens, A. Scheen
Psychotic Disorders, UC St Jozef, Kortenberg, Belgium

Epidemiological studies have demonstrated relevant increased risk of metabolic abnormalities in schizophrenic patients treated with antipsychotics, irrespective of concomitant weight gain. The study aims to evaluate the frequency of the metabolic syndrome in treated schizophrenic patients. Extensive metabolic data, including an Oral Glucose Tolerance Test and fasting serum lipids, are being collected in a large cross-sectional naturalistic sample of treated schizophrenic patients, who will be followed prospectively for 1 year. Preliminary baseline data on 200 schizophrenic patients (average age 37.2 years), stable on medication (88.5% on atypical antipsychotics) for at least 12 months, have been analyzed. The metabolic syndrome (ATPIII-criteria) is present in 27% op patients. 38% of patients are overweight, 20.5% are obese. The prevalence of individual metabolic risk factors is: 44% hypertriglyceridemia, 39% increased waist circumference, 29.5% low HDL, 42.5% hypertension, 6.5% impaired fasting glucose. Elevated cholesterol was present in 53.5% of patients. In patients with prospective serum lipid assessments 1 out of 3 meets criteria for treatment with statins. The metabolic syndrome is frequent in treated schizophrenic patients. Analysis of covariance will be performed with and specific drugs and duration of exposure to antipsychotics. The evolution over time will be evaluated prospectively. Data at 6 months follow-up will be presented.

A CROSS-SECTIONAL STUDY OF FASTING PLASMA GLUCOSE IN INDIVIDUALS WITH EARLY PSYCHOSIS

K. E. Pierson,* C. A. Beck
Psychiatry, Foothills Medical Centre, Calgary, AB, Canada

Little is known about the prevalence of impaired fasting glucose and diabetes in individuals diagnosed with early psychosis. The objectives of this study were: 1. To determine the distribution of fasting plasma glucose (FPG) levels in patients with early psychosis treated in a population-based outpatient early psychosis treatment service; 2. To determine the prevalence of impaired fasting glucose and diabetes in such patients; 3. To explore demographic and clinical variables associated with impaired fasting glucose and diabetes in patients with early psychosis. A precision-based calculation of sample size determined a needed sample of 200 participants to provide a prevalence estimate with a 95% confidence interval no wider than 0.1. We report preliminary results in a sample of 77 patients accrued over the first 6 months of recruitment. The average age of the sample was 30 years (SD=10), with an average body mass index (BMI) of 27 (SD=4.5). The average fasting plasma glucose was 5.0 mmol (SD=0.47) (92.5 mg/dl (SD=8.7)). There were 3 of the 77 patients (3.9%) with impaired fasting glucose (FPG 6.1 to 6.9 mmol/L) while no patients met criteria for diabetes mellitus (FPG > 6.9 mmol/L on 2 occasions). At this preliminary stage it would be premature to analyze for possible associations between FPG and measured diabetes risk factors due to the incomplete patient sample for which recruitment is ongoing. In conclusion, although no cases of diabetes were identified, 3.9% of patients were found to have impaired fasting glucose which is an established risk factor for diabetes. In addition, the patients in our clinic present with high BMI, which is another recognized risk factor for diabetes. Hence it would seem prudent to screen early psychosis patients for diabetes mellitus until subsequent data are available to determine the role of routine screening in this patient population. This study is supported by a grant from the Adult Research Committee of the Calgary Health Region. Dr. Beck is supported by a Fellowship from the Canadian Institutes for Health Research and a Clinical Fellowship from the Alberta Heritage Foundation for Medical Research.

ANTIPSYCHOTICS ASSOCIATED WITH INSULIN RESISTANCE IN NEW ZEALAND MAORI

N. R. Poa,* P. F. Edgar
Psychological Medicine, University of Otago, Christchurch, New Zealand

New Zealand Maori descend from Polynesians, which arrived in New Zealand 800-1200 years ago. They comprise approximately 15% (557 700) of the total New Zealand population. Y chromosome and mitochondrial lineage analysis point to a genetic origin for Polynesian people in South East Asia and Polynesian and Asian people share a similar high risk for type II diabetes. In New Zealand, the prevalence of type II diabetes in Maori is 10.8% and in non-Maori is 2.5%. The aim of this study was to determine whether antipsychotic treatment was associated with an increased prevalence of insulin resistance in New Zealand Maori as this ethnic group may be particularly vulnerable to antipsychotic induced impaired glucose metabolism. A group of 21 Maori patients taking antipsychotics (olanzapine, clozapine or risperidone) for at least three months and 21 untreated Maori control subjects were examined by fasting blood tests to measure serum levels of insulin, glucose, HbA1c, triglycerides and cholesterol. Data on ethnicity, weight, age, gender, personal and family history of diabetes was also recorded. Antipsychotic-treated Maori had significantly higher insulin plasma levels, 177 pmol/L (SD=160), than control Maori, 76 pmol/L (SD=46) (p=0.01). Antipsychotic-treated Maori had significantly higher homeostasis model assessment (HOMA) index 5.5 (SD=5.7) than control Maori 2.4 (SD=1.6) (p=0.03). However, antipsychotic-treated Maori did not have significantly different mean body mass index (BMI), plasma glucose, HbA1c, triglycerides or cholesterol plasma levels than control Maori. In conclusion, Maori treated with antipsychotic medication were significantly more insulin resistant than control subjects but had similar BMI to control Maori. Therefore, ethnicity is likely to be an important factor in susceptibility to antipsychotic induced impaired glucose metabolism and needs to be taken into account in prescribing practice and the general care of this ethnic group.

QTC-VARIABILITY IN SCHIZOPHRENIA PATIENTS TREATED WITH ANTIPSYCHOTICS AND HEALTHY CONTROLS

M. A. Rettenbacher,* U. Eder-Ischia, A. Bader, M. Edlinger, A. Hofer, M. Hummer, G. Kemmler, E. M. Weiss, M. Hochleitner, W. W. Fleischhacker
Biological Psychiatry, Medical University Innsbruck, Innsbruck, Austria

In this prospective investigation we analysed ECGs in 61 patients suffering from a schizophrenic disorder who were treated with different antipsychotics (Haloperidol, Clozapine, Olanzapine, Risperidone, Quetiapine, Sertindole or Amisulpride) and in 31 healthy controls. Mean age in patients was 43.6 years (+/-10.2) mean age in controls was 36.2 years (+/-7.7). In the patients group 40 were male and 23 were female whereas the control group consisted of 18 men and 13 women. Neither patients nor controls suffered from a cardiac disease or took cardiac medication when being included in the study. We found QTc variability which was not different between patients and controls. As changes during treatment might represent normal random variability rather than a drug effect our findings suggest to obtain a second ECG if a prolongation of QTc is observed in patients treated with antipsychotics. Our results further raise the question of the clinical relevance of a single ECG for diagnostics of cardiac complications in schizophrenia patients.

NEUROMUSCULAR DYSFUNCTION IN SCHIZOPHRENIA AND SCHIZOAFFECTIVE PATIENTS DURING ANTIPSYCHOTIC TREATMENT

I. Reznik,* L. Volchek, M. Reznik, A. Weizman, H. Y. Meltzer
Psychiatry Division, Herzog Memorial Hospital, Jerusalem, Israel

Treatment with both typical (TN) and atypical neuroleptic agents (ANA) have been associated with increased serum creatine kinase (SCK) activity which serves as an indicator of the possible skeletal muscle cell membrane damage and neuromuscular toxicity. The purpose of this study was to estimate prospectively the actual incidence and clinical picture of neuromuscular dysfunction in schizophrenia (Sch) or schizoaffective disorder (SAD) treated with various TN/ANA. During the two years of study we have screened 480 adult patients. Patients suffering from any non-stabilized physical disorder or receiving parenteral medication were excluded from the study. Blood samples for CK determinations were collected at baseline, weekly during first month, at weeks +8, +12 and every 3 months thereafter, up to one year of follow-up. Sch or SAD patients with persistent (at least in 3 determinations) hyper-CKemia were assessed neurologically for possible muscular and peripheral nervous systems involvement. The study group comprised 204 eligible Sch and SAD patients receiving clozapine [n=50], olanzapine [n=43], risperidone [n=42], quetiapine [n=24], haloperidol [n=18] or perphenazine [n=27]. During the study, more than 1600 blood samples were collected and 11 evaluated patients, treated with clozapine (n=6), olanzapine (n=3), perphenazine (n=2) were found having persistent hyper-CKemia - 545.5 (230.7) IU/L, in range 250-950 IU/L. Five of these patients had complaints of some muscular weakness and in two of them clinical assessment revealed mild general muscular weakness, especially in the proximal parts of the limbs. Results of this comparative study indicate that the incidence of persistent hyper-CKemia in Sch and SAD patients in our sample (5.3%) is compatible with previous reports (2-10%). However, the magnitude of hyper-CKemia is less than reported previously (1000-10000 IU/L). It is of note, that the vast majority of hyper-CKemic patients were treated with ANA (clozapine and olanzapine); however, only in few of them some neuromuscular (mostly myopathic) dysfunction was found. Further investigation of neuromuscular dysfunction, its mechanisms and pathophysiological significance in Sch and SAD patients is certainly warranted.

THE IMPACT OF HALOPERIDOL, A DA D2 ANTAGONIST, ON COGNITION AND MOOD

H. Saeedi,* G. Remington, B. Christensen
Centre for Addiction and Mental Health, Toronto, ON, Canada

All antipsychotics block dopamine (DA) D2 receptors, with clinical efficacy linked to blockade of > 60% of DA D2 receptors (Seeman, 2002); in contrast, D2 occupancy in excess of 80% has been linked to an increased risk of EPS. It remains unclear though as to other negative consequences that might result from DA D2 blockade. The literature has consistently demonstrated a relationship between DA and both cognition and mood, with decreased DA linked to deficits in each of these domains. However, the precise nature of the relationship is unclear. Research in this field is limited, and studies to date have been hampered by methodological problems, inconsistent results, and a paucity of human data. The current study was designed to evaluate the impact of DA D2 antagonism on various aspects of cognition and mood. Healthy participants (N=59) were randomized to receive a single oral dose of either 1, 3, or 5 mg of haloperidol, or placebo. Participants were tested on cognitive and mood measures at baseline, 4 and 24 hours post-administration of medication. The testing sessions involved a variety of computerized and paper-and-pencil tasks, as well as self-report questionnaires that addressed different components of cognition and mood. Several areas of cognition and mood were significantly affected by DA D2 blockade. In terms of cognition, sustained attention and reaction time were particularly influenced. Regarding mood, the most notable changes occurred on measures of anger and contentment. In order to control for the number of comparisons, a factor analysis was conducted and results indicated an overall deficit in cognition and mood at 4 hours post-administration of haloperidol, an effect that was dose-dependent. The present results suggest that DA D2 blockade, as induced by haloperidol here, produces important deficits that extend beyond motor or endocrine changes. These findings have important implications for the role of DA and the impact of antipsychotics, which have as part of their pharmacological profile D2-blocking properties. This study provides evidence to suggest that antipsychotic medications can negatively impact domains such as cognition and affect, aspects of global functioning that can profoundly affect functional recovery. References: Seeman, P., 2002. Atypical antipsychotics: mechanism of action. *Can. J. Psychiatry*. 47, 27-38.

DIRECT MEASURES OF CHANGES IN ADIPOSITY IN SCHIZOPHRENIA PATIENTS DURING ATYPICAL ANTIPSYCHOTIC TREATMENT

J. A. Schweiger,* D. Haupt, K. Flavin, A. Luber, P. Fahnestock, J. W. Newcomer
Psychiatry, Washington University School of Medicine, St. Louis, MO, USA

Increased adiposity can disturb glucose and lipid metabolism, and schizophrenia patients experience a higher prevalence of overweight

and obesity, diabetes mellitus, and the metabolic syndrome in comparison to the general population. Increases in fat mass, plasma glucose and certain lipid fractions are known risk factors for cardiovascular disease (CV), and schizophrenia patients experience higher rates of CV. Recent interest has focused on the contribution of certain antipsychotic medications to metabolic abnormalities. Reports in this area have spanned uncontrolled observations, retrospective database analyses using surrogate indicators, and a limited number of controlled studies with rare randomized clinical trials using sensitive measures. Treatment effects on metabolic variables can be measured using sensitive techniques in the setting of randomized assignment to selected antipsychotic medications. Adiposity can be directly measured using whole body dual energy x-ray absorptiometry (DEXA) and abdominal magnetic resonance imaging (MRI). Both adiposity measures can be analyzed in relation to whole-body glucose and lipid kinetics, with stable isotope tracer methodology during hyperinsulinemic-euglycemic clamp conditions. These methods can be used to calculate tissue-specific changes in insulin sensitivity that might occur independent or dependent on fat mass. In this ongoing study, schizophrenia patients undergo prospective randomized assignment to 12 weeks of treatment with olanzapine, quetiapine, risperidone, or ziprasidone, with no other medication changes allowed. Covarying baseline DEXA total fat mass (to control for baseline differences in fat), significant time X treatment group interactions for glycerol rate of appearance (Ra) ($F[1,3]=194$, $p=0.005$) are observed. Exemplifying changes in relation to changing fat mass, ziprasidone treated subjects experienced predicted changes in glucose Ra ($p=.03$), rate of disappearance ($p=.04$) and glycerol Ra ($p=.01$). These results indicate treatment-induced changes in insulin sensitivity in liver, skeletal muscle, and adipose tissue, respectively. These sensitive measures can be used to evaluate medication-induced changes in glucose and lipid metabolism, relevant to the risk of diabetes and cardiovascular disease. Support Contributed By: NIMH, R01 63985; NIH, (USPHS #M01RR00036): GCRC.

WEIGHT GAIN AND LIPID METABOLIC ABNORMALITIES INDUCED BY SECOND-GENERATION ANTIPSYCHOTICS IN DRUG-NAIVE SCHIZOPHRENIC PATIENTS WITH A FIRST EPISODE OF PSYCHOSIS

S. M. Sengupta,* R. Klink, E. Stip, T. Baptista, A. Malla, R. Joober
Douglas Hospital Research Center, Verdun, QC, Canada

Objective: To evaluate the extent of body weight gain and associated metabolic changes following treatment with risperidone and olanzapine in previously untreated (less than 7 days) schizophrenic patients with a first episode of psychosis (FEP). Method: Weight gain, fasting glucose, insulin and lipid profile were assessed in fifteen FEP patients treated with risperidone or olanzapine at baseline, 3-4 months and 6-8 months after treatment. Results: Average weight gain with risperidone and olanzapine was 5.28 and 3.68 kgs (1 month), 12.72 and 9.67 kgs (3-4 months) and 9.87 and 15.8 kgs (6-8 months), respectively. Total blood cholesterol and LDL increased significantly. Triglyceride, HDL and fasting insulin levels did not change significantly. Fasting glucose increased significantly with olanzapine ($p=0.01$) after 3 to 4 months of treatment. Conclusions: Both risperidone and olanzapine cause an alarming increase in body weight and BMI along with a significant increase in total cholesterol and, in the case of olanzapine, an increase in fasting glucose in drug naive FEP patients. The full extent of these changes with novel antipsychotic drugs may have been underestimated in previous reports, possibly due to lack of a valid pre-medication baseline.

METABOLIC CHANGES DURING 5 MONTHS TREATMENT WITH OLANZAPINE OR RISPERIDONE: PRELIMINARY RESULTS FROM RANDOMIZED TRIAL

R. C. Smith,* J. P. Lindenmayer, A. Buga, M. Matute, S. Vaidhyanathaswamy, E. Butler
Psychiatry, NYU Medical School, Hewlett, NY, USA

Atypical antipsychotics have been reported to be associated with glucose and lipid abnormalities and increased risk of diabetes. In a previous large cross-sectional study we reported no differences in most metabolic measures in comparisons of conventional antipsychotics, clozapine, olanzapine, and risperidone, except for increased triglycerides in the clozapine and olanzapine treated groups, and higher 1 hr glucose in glucose tolerance test(GTT) for risperidone. We are conducting a study of patients randomly assigned to treatment with olanzapine (OL) or risperidone (RIS) for five months, who are tested at baseline and several points during treatments, for fasting glucose and lipid metabolic levels, 75 gm 2 hr glucose tolerance test, and metabolic evaluation after a fatty meal. Preliminary results form the first 19 patients show a trend for the increase in fasting glucose levels and c-peptide levels to be higher for OL than for RIS treated patients (with some of these differences statistically significant), but no significant differences for changes in cholesterol, triglyceride or leptin levels comparing the OL vs RIS treatment groups. 2 OL and 1 RIS patients had at least 1 fasting glucose level >126 mg/dL during study drug treatment. There were no significant differences in 1 hr or 2 hr mean glucose levels during GTT's between OL vs. RIS treatment groups, and no differences in insulin levels during GTT when these were covaried with differences in baseline insulin before beginning study drug treatment. The frequency of 2 hr GTT glucose > 200 mg/dL were as follows: at baseline zero OL and zero RIS, after 1- month treatment zero OL and 1 RIS, after 2- month treatment 1 OL and 2 RIS; after 5 months (reduced sample size) 2 OL and 1 RIS patient. Both olanzapine and risperidone produced an increase in weight but there were no significant differences in weight gain in patients treated with olanzapine vs. risperidone, although the mean increase in weight was slightly higher for olanzapine. Mean prolactin levels increased on risperidone and decreased on olanzapine, and the difference was statistically significant. These results suggest that a small percent of patients treated with both OL and RIS develop potentially clinically significant abnormalities in glucose metabolism during treatment with these medications over several months, but only RIS patients showed prolactin elevation.

IMPLEMENTING GUIDELINE RECOMMENDATIONS FOR MANAGING METABOLIC ADVERSE EFFECTS OF ANTIPSYCHOTIC MEDICATIONS

E. M. Stirewalt,* D. D. Miller, B. Singer, J. Arena, P. F. Buckley
Psychiatry and Health Behavior, Medical College of Georgia, Augusta, GA, USA

There is intense scientific interest and growing public concern regarding the risk of developing weight gain, diabetes mellitus, and

related metabolic disturbances during treatment with antipsychotic medications. Hyperglycemia, hypertriglyceridemia, new onset diabetes and even diabetic ketoacidosis have been reported (through case reports and series, pharmacovigilance and various pharmacoepidemiologic studies) in patients receiving antipsychotic medications. This emergent information has recently prompted the Food and Drug Administration to request changes in the labeling of such medications. Additionally, several expert groups and consensus panels have provided guidance on this issue. Various approaches have been promulgated to inform the detection, monitoring, and management of weight gain and metabolic disturbances during antipsychotic therapy. To address this burgeoning interest in a manner complementary to current information and guidelines, we sampled the perceptions and clinical 'readiness' to detect and manage these adverse effects among general and specialist psychiatrists in 3 U.S. states. Clinicians indicated that some assessment measures (eg. personal and family history, height and weight) were readily attainable and routinely evaluated, while others (fasting blood glucose, fasting lipid profile) were more difficult to obtain; the latter were evaluated on a more inconsistent basis across the psychiatrists sampled. Clinicians expressed concern over weight gain and metabolic effects, with some indicating that these considerations have now altered the way they prescribe second generation antipsychotic medications. This presentatin will share details on clinician's perceptions of an evolving standard of care and the current extent to which actual practice reflects recently developed guidelines.

TYPE 2 DIABETES AMONG PERSONS WITH SCHIZOPHRENIA IN A FINNISH GENERAL POPULATION SURVEY

J. M. Suvisaari,* A. Reunanen, J. Ukkola, S. Saarni, J. Lonnqvist
Department of Mental Health and Alcohol Research, National Public Health Institute, Helsinki, Finland

Background: Previous studies suggest that schizophrenia is associated with impaired fasting glucose tolerance and increased risk of Type 2 diabetes. Based on the Health 2000 study, a national Finnish health survey, we compared fasting glucose concentrations and the prevalence of type 2 diabetes in persons with schizophrenia and the general population. Methods: The Health 2000 study is based on a nationally representative two-stage cluster sample of 8028 persons aged 30 or over, 6288 of whom participated in a detailed medical examination. The sample included 85 persons with a hospitalization because of schizophrenia according to the Finnish Hospital Discharge Register, 51 of whom participated in the health examination. Using linear regression, we examined whether the fasting glucose concentration of persons with schizophrenia was elevated after controlling for the effects of age, sex, and body mass index (BMI). We compared the proportion of persons with schizophrenia and other members of the study population who had received the diagnosis of Type 2 diabetes in the health examination, and who receive reimbursement of medicine costs due to diabetes, and investigated the prevalence of undiagnosed diabetes based on the fasting glucose concentration. The SUDAAN statistical software was used in the analysis, and a weighting adjustment was made to take account of the sampling design and non-participation. Results: Persons with schizophrenia had higher fasting glucose concentration (mean 107.6 vs. 99.5 mg/dL), and the effect of diagnosis of schizophrenia remained significant after controlling for age, sex, and BMI (beta 0.43, t=2.08, p=0.038). The proportion of persons with schizophrenia who received a diagnosis of Type 2 diabetes in the medical examination was 4.0% compared with 3.7% in other members of the study population, and the proportions of those receiving reimbursement of medicine costs due to diabetes were 2% and 3.1%, respectively. When we excluded persons with diagnosed Type 1 or 2 diabetes, 8.6% of persons with schizophrenia vs. 9.5% of other members of the study population had impaired fasting glucose (serum glucose between 110 and 126 mg/mL), and 11% vs. 1.9% had diabetes (serum glucose greater that 126 mg/mL). Conclusions: The results suggest that Type 2 diabetes is more common among patients with schizophrenia than in the general population, yet it remains underdiagnosed and undertreated.

SUBJECTIVE RESPONSE TO ANTIPSYCHOTICS: THE IMPACT OF A QUESTIONNAIRE ABOUT NEUROLEPTIC SIDE EFFECT

M. Taira,* T. Hashimoto, T. Takamatu, M. Fukutake, O. Shirakawa, K. Maeda
University of Kobe, Kobe, Japan

We prepared a questionnaire comprised of 17 about neuroleptic side effects and 10 questions about attitudes toward medication (Drug Attitude Inventory (DAI-10)). We also prepared a short informational booklet about antipsychotics and conducted psychoeducational sessions for patients who filled out the questionnaire. We administered this questionnaire to 219 outpatients with a diagnosis of schizophrenia or schizoaffective disorder as defined by DSM-IV. They were divided into Subject and Control groups. Patients of the Subject group filled out the questionnaire four times and took four short information booklets about antipsychotics during 6 months in addition to routine clinical practice. Thirty-four patients of Subject group attended psychoeducational sessions. Patients of the Control group had routine clinical care. Neuroleptic side effects were evaluated with the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) and objective psychotic symptoms were evaluated with the Brief Psychiatric Rating Scale (BPRS) at the beginning of this study and 6 months later. After 6 months, the DAI-10 and DIEPSS total score improved in the Subject group, while BPRS total score remained unchanged. In the Control group, the DAI-10, DIEPSS and BPRS scores did not change.

CYP2D6 GENE DOSAGE AND TYPICAL ANTIPSYCHOTIC INTOLERANCE, DRUG-INDUCED PARKINSONISM, AND TARDIVE DYSKINESIA

E. M. Tsapakis,* J. H. Zhao, P. Wright, S. Smith, J. Munro, A. J. Makoff, R. M. Murray, D. A. Collier, R. W. Kerwin, K. J. Aitchison
Section of Clinical Neuropharmacology, Institute of Psychiatry, London, United Kingdom

Adverse effects following treatment with typical antipsychotics (TAs) include drug-induced parkinsonism (DIP) and tardive dyskinesia (TD). Evidence of an association between cytochrome P450 2D6 metaboliser status and susceptibility to adverse effects of antipsychotics has been shown previously, but most studies have not included genotyping for ultrarapid metabolisers. Our objective was to ascertain whether or not there was a correlation between TA intolerance, DIP, or TD, and number of functional *CYP2D6* genes. Data

regarding a history of TA intolerance was obtained for 246 patients. A separate sample of 72 patients treated with TAs was examined for the presence of TD, and 66 of these were also examined for DIP. All patients were genotyped for the *CYP2D6* alleles **3-5* and gene duplications, whereas patients rated for TD were also genotyped for the *CYP2D6 *2* and **41* alleles. Data were analysed by Fisher's exact or chi-squared test, comparing genotype and allele data in intolerant vs. non-intolerant groups, those with and without DIP, and those with and without TD. In addition, for the sample rated for TD, logistic regression and multiple linear regression vs. *CYP2D6* gene dosage, controlling for potential confounding variables, was performed. Genotyping for *CYP2D6* alleles **3-*5*, **2*, **41* and *CYP2D6* gene duplications was undertaken as previously described[1, 2]. Results on the association between TD and the *CYP2D6 *2* and **41* will be reported later. Twenty-six (10.6%) of the patients taking clozapine had a history of TA intolerance; 35 of 66 patients (53%) met the criteria for DIP; and 13 of 72 (18.1%) met the criteria for RDC probable TD. The main outcome measures were *CYP2D6* gene dosage, and presence or absence of TA intolerance, DIP, and TD. We found no association between *CYP2D6* gene dosage and either TA intolerance or DIP. However, we found a positive association between *CYP2D6* gene dosage and TD (P = 0.04 for N = 72 rated for probable TD, P = 0.14 for N = 66 rated for persistent TD), i.e. an association with a different direction of effect than that found previously. 1. Aitchison KJ, et al. Failure to respond to treatment with typical antipsychotics is not associated with *CYP2D6* ultrarapid hydroxylation. *Br J Clin Pharmacol* 1999;48:388-394. 2. Løvlie R, et al. Polymorphisms in *CYP2D6* duplication-negative individuals with the ultrarapid metabolizer phenotype: a role for the *CYP2D6*35* allele in ultrarapid metabolism? *Pharmacogenetics* 2001; 11:45-55.

ORAL GLUCOSE TOLERANCE TESTS IN SCHIZOPHRENIA FOR "DUMMIES," MAKING SENSE OF POTENTIALLY PREDICTIVE PRE-DIABETIC INSULIN AND GLUCOSE CURVES

D. Van Eyck,* M. De Hert, M. Wampers, L. Hanssens, A. Scheen, J. Peuskens
UC St Jozef, Kortenberg, Belgium

Epidemiological studies have demonstrated relevant increased risk of diabetes in schizophrenic patients treated with atypical antipsychotics, irrespective of concomitant weight gain. Large scale prospective studies using an Oral Glucose Tolerance Test (OGTT) are rare in schizophrenia. A large scale prospective naturalistic study on metabolic disturbances in schizophrenic patients is currently ongoing. At this moment 350 patients have entered the study, they will be followed prospectively for 1 year. To diagnose glucose abnormalities criteria of the American Diabetic Association are most often used. Apart from identifying diabetic and pre-diabetic stages, we also observed other abnormalities in the obtained OGTT data. In order to better understand changes in the glucose metabolism of schizophrenic patients treated with antipsychotics we propose a topographic analysis and classification system based both on the glucose and insulin curves obtained. Data from 329 OGTT will be analyzed to test a classification system. Using strict diagnostic criteria 2.4% of OGTT meet criteria for diabetes. Impaired glucose tolerance is present in 8.8% and impaired fasting glucose in 12.7% of OGTT. Using our classification system only 18.2% of OGTT show no abnormalities. If one allows mild abnormalities 31.6% of the OGTT can be considered as normal. Overall, 54.4% of the glucose curves have normal values whereas only 27.1% of the insulin curves have normal values. At the other end, 22.8% of glucose curves show pronounced abnormalities and 32.2% of insulin curves display hyperinsulinism and delayed insulin release. Analysis of measures of insulin resistance, areas under the curves for both glucose and insulin between the different types of OGTT curves are highly significantly different. The observed abnormalities in OGTT may be related to early stages of metabolic complications of antipsychotic treatment. The proposed classification system identifies more patients with abnormalities in glucose metabolism than using strict endocrinological criteria. The prospective nature of the study will identify the predictive value of the observed abnormalities and proposed classification system.

ADVANTAGES OF QUETIAPINE ON SEXUAL DYSFUNCTIONS: A SWITCH STUDY

J. Villeneuve,* M. Demers, N. Almeras, I. Proulx, A. Labelle, D. Bourget, J. Mottard, M. Roy, R. Bouchard
Corporation de Recherche en Neuro-Psychopharmacologie de Quebec, Quebec, QC, Canada

The purpose of this study is to evaluate the effect of switching to quetiapine in patients with schizophrenia presenting a disturbing sexual dysfunction or amenorrhea. We conducted a multicenter, open-label, prospective study in patients with schizophrenia. Patients with a subjectively disturbing sexual dysfunction or amenorrhea were included. Evaluations included the UKU rating scale, measures of psychopathology, hormones and prolactin level. Concomitant medication known to impact sexual functioning such as antidepressant, beta-blocker, anticholinergic, hormonal supplement or sildenafil were not allowed. During a 6-week run-in period, patients continued their usual antipsychotic treatment, either risperidone or olanzapine, and sexual dysfunction or amenorrhea was repeatedly assessed. If sexual dysfunction or amenorrhea persisted, then patients were switched to quetiapine and evaluation was repeated after 3 months. Results are available for thirty-one subjects (27 male). Nineteen patients were initially treated with olanzapine (mean dose 17.8 mg/day) and twelve with risperidone (mean dose 2.9 mg/day). Using the UKU rating scale, a sexual desire problem was identified in 87% (27/31) of patients. An improvement was achieved in 83% of them after switching to quetiapine (mean dose 621.4 mg/day). The second most frequent problem was erectile dysfunction in 63% (17/27) of study subjects. A complete resolution was observed after 3 months in 56% of them. An orgasm problem was identified in 35% (11/31) of patients and gynecomastia in 29% (9/31); both problems improved after the switch. Amenorrhea was present in 3 women out of 4 and corrected after the switch in all cases. These data suggest that switching to quetiapine is a valuable option to reduces sexual dysfunctions and amenorrhea.

COURSE OF WEIGHT AND METABOLIC BENEFITS 1 YEAR AFTER SWITCHING TO ZIPRASIDONE

P. J. Weiden,* A. Loebel, R. Yang, H. Lebovitz
Department of Psychiatry, SUNY Downstate Medical Center, Brooklyn, NY, USA

Our objective was to determine the time course of weight and lipid reductions over 58 weeks in outpatients switched to ziprasidone from other antipsychotics. Three open-label, flexible-dose, 1-year extension studies enrolled stable completers of 6-week trials of outpatients switched from conventionals (n=71), olanzapine (n=71), or risperi-

done (n=43) to ziprasidone. Follow-up to 1 year of ziprasidone monotherapy (median duration 34.6 weeks) permitted longitudinal assessment of improvement in weight and metabolic side effects. A mixed-model regression analysis was used to estimate LS mean change over time (58 weeks total). LOCF analysis (ITT population) over the 58-week period was also performed. Mixed-model analysis showed that patients switched to ziprasidone from risperidone or olanzapine demonstrated progressive, sustained weight loss and BMI reduction over the study period. For the pre-switch olanzapine group, estimated LS mean weight loss was −3.4 (±0.6 SE) lb at 6 weeks (P<0.0001) and −21.6 (±3.6) lb at 58 weeks (P<0.0001). For the pre−switch risperidone group, estimated weight loss was −2.1 (±0.8) lb at 6 weeks (P<0.05) and −15.2 (±4.5) lb at 58 weeks (P<0.005). Statistically significant, clinically relevant improvements in triglycerides and total cholesterol occurred rapidly during the initial 6 weeks of ziprasidone monotherapy, and were sustained through endpoint of the extension studies. For the pre-switch olanzapine group, estimated LS mean triglyceride reductions were −78.0 (±11.7) mg/dL (P<0.0001) at 6 weeks and −54.5 (±15.5) mg/dL (P<0.0005) at 58 weeks. For the pre-switch risperidone group, the respective improvements were −39.2 (±14.6) mg/dL (P<0.05) and −36.7 (±18.9) mg/dL. In conclusion, patients switched from olanzapine and risperidone to ziprasidone demonstrated progressive and sustained weight loss and BMI reduction for up to 58 weeks. Improvements in lipid parameters were substantial, occurred rapidly, and were sustained during long-term ziprasidone monotherapy.

PROLACTIN ELEVATION IN CLOZAPINE PATIENTS TREATED WITH ADJUNCTIVE RISPERIDONE

E. Weiner,* M. P. Ball, R. W. Buchanan, R. Conley
ORP, MPRC, Catonsville, MD, USA

Although classified as a new generation antipsychotic, risperidone is well known to increase prolactin levels due to its predilection for dopamine blockade. Prolactin elevation is one of the causes of sexual side-effects experienced by patients on antipsychotic medication. Clozapine is less likely to cause prolactin elevation, as it does not bind as strongly or as avidly to the dopamine receptor. There is currently no data examining prolactin elevation in patients treated with both clozapine and risperidone. As part of a larger study to assess the efficacy of adjunctive risperidone to clozapine for the treatment of persistent positive symptoms and cognitive impairments, baseline and end of study prolactin levels and plasma drug levels were obtained. It is hypothesized that the group receiving risperidone will experience significantly greater prolactin elevations from baseline to end of study and that the increase will be correlated with risperidone plasma level. The amount of increase in prolactin will be discussed relative to what is known in the literature regarding prolactin elevations due to risperidone.

SIBUTRAMINE IN PATIENTS WITH ANTIPSYCHOTIC MEDICATION ASSOCIATED OBESITY

D. Wirshing,* Z. Erickson, S. J. Mena, S. Mahgerefteh, J. M. Pierre, C. McNally, W. C. Wirshing
Psychiatry, VAGLAHS, Los Angeles, CA, USA

Second generation antipsychotic medications have become first line treatments in the United States for the treatment of psychoses. Although superior to first generation antipsychotic medications in terms of their neurologic side effect profile, weight gain, diabetes, and dyslipidemias have proven to be the tardive dyskinesia of this new generation of medications. Here we describe the results of a double blind study of sibutramine compared to placebo. Patients with medication associated obesity were randomly assigned to 16 weeks of treatment with either sibutramine or placebo. In addition, a modest behavioral program to help control weight gain was employed during the study. The protocol was terminated at an early stage due to administrative reasons. We elaborate here detailed case reports of the five patients who were randomized to placebo or sibutramine. Of the three participants on sibutramine, two lost a small amount of weight (0.5kg and 2.7kg) and one actually gained 8.2kg. Of the two in the placebo group, one lost 0.9kg and the other had no weight change. Two participants who lost weight on sibutramine embarked on an exercise program, whereas the participant who gained weight on the drug engaged in none and existed primarily on fast food. In two of the sibutramine treated patients we also observed a decrease in triglycerides independent of weight loss or gain with glucose following the same pattern. Sibutramine did not show a consistent weight loss effect in this small group of patients. Lifestyle changes were difficult to implement in some of the patients, in particular we noted that fast food consumption in the patient who gained 8.2kg completely thwarted sibutramine's efficacy. Exercise and diet are key elements in effecting weight loss. This study was supported by a grant from Knoll Pharmaceuticals.

QUALITY OF LIFE AND PATIENTS' EVALUATION OF ANTIPSYCHOTIC MEDICATION

H. Wolters,* H. Knegtering, D. Wiersma, R. J. van den Bosch
Psychiatry, University Hospital Groningen, Groningen, Netherlands

Introduction: Schizophrenia is a chronic disabling illness without a cure and requires a long-term therapy with antipsychotic medication. The question is how patients' evaluation of the antipsychotic intervention is associated with quality of life. Until the 80's, the evaluation of treatments in schizophrenia was mainly based on objective assessment of the psychotic symptoms. The last three decades there is in medical practise a shift from prolonging life to improved quality of life. Although, one of the major goals for patients to use antipsychotic medication is improving quality of life, patients with severe mental disorders are generally less satisfied with all aspects of their life than members of the general population. Method: Inclusioncriteria were a diagnosis in the schizophrenia spectrum, at least six weeks of antipychotic treatment and able to fill in questionnaires. Exclusioncriteria were antidepressant or lithium use. Quality of life was evaluated by the WHOQoL and the EUROQoL. Side-effects were measured by a self-report questionnaire the LUNSERS. Attitude to the medication was evaluated by the DAI-10 and patients' evaluation of the antipsychotic medication was measured by the Subject Respons to Antipsychotics evaluator. Results: Threehunderd twenty patients participated in this study. Attitude to the medication is correlated modest with quality of life (r= 0.18 - 0.32). Patients evaluation of the intervention is associated with quality of life (r=0.00 - 0.49). The negative responses are more associated with quality of life than the positive responses to the intervention. Side-effects were strongly associated with quality of life (r= 0.13 - 0.66). Conclusions: It can be concluded that the effects of antipsychotic medication have a great impact on quality of life. Noteworthy is that the negative

aspects have a greater association with quality of life than the positive responses. To evaluate the antipsychotic treatment from a patients perspective the self-reported side-effects and responses to the antipsychotics are important.

INTER-RATER RELIABILITY OF THE ANTIPSYCHOTIC NON-NEUROLOGICAL SIDE EFFECTS SCALE (ANNSERS)

B. Z. Yusufi,* S. Mukherjee, K. Aitchison, G. Dunn, E. Page, T. R. Barnes
West London Mental Health Trust, London West Mental Health R&D Consortium, London, United Kingdom

The Antipsychotic Non-Neurological Side Effects Rating Scale (ANNSERS) is a new scale, designed to systematically assess the full range of side effects (other than movement disorders), including subjective burden, recognised as occurring with first and/or second-generation antipsychotics. It is a 35-item scale, with specific criteria for scoring each side effect identified as mild, moderate or severe. The rater determines the presence of each side effect and rates its severity, based on the report of the patient, and information from their clinical team and casenotes. The source of the information is noted, allowing those side effects of which the patient is aware to be identified. We tested the inter-rater reliability of the ANNSERS in a sample of 20 subjects, recruited from inpatient units and outpatient psychiatric clinics, who had been receiving maintenance treatment with clozapine for at least 3 months. Each patient was assessed by three independent raters: two psychiatrists and a research psychologist. Inter-rater reliability coefficients (inter-class) were calculated through variance components estimates (ANOVA). The reliability coefficient for the total ANNSERS score was 0.954. The reliability estimates between raters on individual side effects were variable. An adequate level of agreement was achieved for dry mouth, daytime sleepiness, delayed ejaculation, nausea, constipation, problems with concentration, sedation, headache, loss of energy, disturbance of night sleep pattern and menstrual irregularities (coefficient range 0.826 to 0.945). The lowest reliability coefficients were for respiratory problems (0.531) and subjective dysphoria (0.610). Only 5% of the patients who had non-neurological side effects reported them spontaneously. For example, a relatively high proportion of males (40%) and females (31%) were found to have sexual side effects, although very few were spontaneously reported, and none by male patients. This study demonstrated that, in addition to its good face validity, the ANNSERS has a satisfactory level of inter-rater reliability. This scale can be used reliably by a diverse range of professionals involved in the assessment and treatment of psychotic illnesses, and has already been used successfully in a large, pragmatic, multi-centre, study in the UK examining the clinical and cost effectiveness of the second generation antipsychotics (CUtLASS).

REPORT: BELGIAN CONSENSUS ON METABOLIC PROBLEMS ASSOCIATED WITH ATYPICAL ANTIPSYCHOTICS

A. R. de Nayer,* M. de Hert, A. Scheen, L. Van Gaal, J. Peuskens
Psychiatry, Ste-Therese, Montigny, Belgium

published consensus for the management of metabolic complications associated with second generation antipsychotics (SGA) might not be sufficiently sensitive: in light of our data, it seems that screening with fasting glucose misses a number of patients with impaired glucose metabolism and taking in account the possibility of possible reversal of the metabolic complication with early withdrawal of the incriminated medication, metabolic screening should be more frequent during the first 6 months; also the importance of the hyperlipidemia demands more frequent monitoring. Therefore, a workshop was convened by Belgian psychiatrists, diabetologists and pharmacists to formulate appropriate recommendations for practising psychiatrists when initiating and maintaining therapy with SGA. The consensus statement issued recommendations for the management of the basic metabolic risk in every schizophrenic patient (risk factors and metabolic disorders to screen for and to follow), choosing the SGA, the follow-up of patients on SGA, attitude in case of SGA-associated glucose metabolism disorder. SGA with low propensity for weight gain and diabetes is to be preferred (such as amisulpride, aripiprazole, or ziprasidone). The need and the way to inform patients about the metabolic effects of SGA were discussed. Close collaboration between the psychiatrist and the GP or the endocrinologist was strongly advised. Recommendations for non-schizophrenic patients treated with SGA were also proposed. Consensus has been reached about the recommendations on the management of weight gain and dyslipidemia while on SGA therapy.

Participants

WEIGHT LOSS AFTER SWITCHING FROM CONVENTIONAL TO ORALLY DISINTEGRATING OLANZAPINE

T. V. van Amelsvoort,* L. de Haan, K. Rosien, D. H. Linszen
Department of Psychiatry, Academic Medical Centre, Amsterdam, Netherlands

Introduction: Olanzapine can induce clinically significant weight gain. Patients with schizophrenia are at increased risk for obesity-related conditions such as type II diabetes mellitus and cardiovascular disease. Weight control procedures with patients on antipsychotic medication have only modest impact. When two patients mentioned a decrease in appetite after switching from conventional to orally disintegrating olanzapine, we planned a pilot study. We wished to examine weight change in patients with recent-onset schizophrenia after switching from conventional to orally disintegrating olanzapine tablets. Methods: Seventeen males and one female with a DSM-IV diagnosis of schizophrenia were included in this non-randomized, open-label study. After a complete description of the study, written informed consent was obtained from all subjects. We compared weight change (kg) and body mass index (BMI) in nine patients 16 weeks after switching from conventional to orally disintegrating olanzapine tablets with the weight change and BMI in nine

olanzapine-treated patients who continued treatment with conventional olanzapine for 16 weeks. Between-group differences in weight change and BMI were analyzed using independent samples t-tests (two-tailed). Results: Patients who switched to orally disintegrating olanzapine lost 6.6 kg (mean), 16 weeks after the switch from conventional olanzapine. In contrast, an increase in weight of 3.7 kg (mean) in the group that continued conventional olanzapine was observed ($P<0.001$). Similarly, the BMI reduced by 2.1 in the patients who switched, compared to a 1.1 increase in those who did not switch ($P<0.001$). There were no significant differences in baseline weight, BMI, age, and dosage of olanzapine. To our knowledge, this is the first report of weight loss after switching from conventional to orally disintegrating olanzapine. Discussion: Our findings may be partially explained by subtle differences in pharmacokinetic properties between the orally disintegrating and the conventional olanzapine formulation. The limitations of our study are the small group size and the non-randomized, open-label nature. Although our findings should be interpreted with caution, we feel that our observation has potentially important clinical implications and warrants further research.

Author Index

Keyword Index