Functional Neuropsychophysiological Asymmetry in Schizophrenia: A Review and Reorientation

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Abstract

In reviewing the neuropsychophysiological evidence of functional asymmetry it is proposed that schizophrenia is characterized by a greater dispersion of leftward and rightward asymmetries. The two extremes are represented by active (left greater than right) and withdrawn (right greater than left) syndromes, as is the case with psychometric schizotypy. Syndrome-asymmetry relations extended beyond fronto-temporal systems to include posterior activity, infracortical motoneuron excitability, and individual differences in interhemispheric connectivity and directional biases. Central to these are lateral imbalances in thalamo-cortical and callosal arousal systems, while centrality to schizophrenia follows evidence of reversals in asymmetry with changes in symptom profile, clinical recovery, and neuroleptic treatment. Affinities are found in intact animals from challenge-induced turning tendencies representing coordinated activity of attentional, motor, and reinforcement systems. In both patients and animals, neuroleptics have reciprocal interhemispheric effects, with a bidirectionality that depends on syndrome or endogenous turning preference. Bidirectionality implicates nonspecific thalamic system (NSTS) and not limbic projections. It is proposed that the asymmetries arise from endogenous influences of genes, hormones, and early experience including stressors on NSTS asymmetry, and these underpin approach/withdrawal behavior that is manifested in temperament, personality, and clinical syndrome, and which precedes language development.

Key words: Laterality, callosum, thalamus, syndromes, activity, withdrawal, dopamine, development.


Neuropsychophysiology provided the first modern evidence of lateralized dysfunction in schizophrenia, a perspective dormant since the last century (Harrington 1985). In a landmark and controversial report, Flor-Henry (1969) claimed that the clinical electroencephalograms (EEGs) of temporal lobe epileptic patients with schizophrenic features showed left or bilateral temporal foci. These results contrasted with the right temporal foci of epileptics with manic depressive illness. Most schizophrenia patients showed left less than right (L < R) asymmetry patterns in electrodermal orienting and habituation processes, the same asymmetry seen in neurological patients with space-occupying lesions of left temporal and frontal lobes (Gruzelier 1973; Gruzelier and Venables 1974). Gur (1978, 1979) found predominantly rightward conjugate eye movements, signifying left > right (L > R) activation in the frontal eye fields, in conjunction with right neuropsychological deficits and proposed an overactivation of left-hemisphere functions in schizophrenia. A decade later these findings prompted the first of four meetings on the topic (Gruzelier and Flor-Henry 1979; Flor-Henry and Gruzelier 1983; Takahashi et al. 1987; Gruzelier, in press a).

Initial research had polarized around two competing views: a disorder of the left hemisphere or a disorder of interhemispheric pathways. Within each viewpoint was a conflict of evidence: left hemisphere loss of function contrasted with overactivation in the left hemisphere, and interhemispheric hyperconnectivity with hypoconnectivity. This evidence could not be explained by the discrete intrahemispheric or interhemispheric structural lesion models, and the way ahead was thought to lie with a disorder of "functional systems with a working rather than anatomical unity" (Gruzelier and Flor-Henry 1979, p. 671). This perspective, reaffirmed a decade later by Levin et al. (1989) on the basis of clinical neuropsychological investigations, will be the conclusion of this review. For while the past decade has seen a preoccupation with structural asymmetry, this ignores the fact that the symptoms
of schizophrenia are rarely fixed but fluctuate, that is, the disorder is essentially functional in nature.

This review, which is largely confined to neuropsychophysiological evidence, will begin with two factors—syndromes and medication—that may help unravel the conflicting nature of the evidence and shed light on underlying mechanisms. These two factors tend to have been neglected in contemporary research designs. Two others—handedness and sex—are better recognized as fundamental to individual differences in lateralization. Most investigators in the field have selected dextral patients so that handedness has not been a confound, and while sex differences are receiving more attention, so far the literature is scant.

**Syndrome-Asymmetry Relations**

**A Data-Driven Model: Electrodermal Orienting Response Asymmetry.** The importance of syndrome-asymmetry relations first arose as a data-driven finding from research with electrodermal responses. This finding led to a model of the hemispheric basis of important positive and negative syndromes in schizophrenia and personality dimensions in schizotypy. We reversed the conventional procedure of looking at brain-behavior features of clinically defined subgroups and instead classified unmedicated patients by a psychophysiological variable—the lateral asymmetry of auditory evoked electrodermal responses. We then examined clinical symptoms as the dependent variable (Gruzelier 1981a, 1984; Gruzelier and Manchanda 1982). These measures were originally chosen to probe amygdaloid and hippocampal functions (Gruzelier and Venables 1972; Gruzelier 1973). In two studies, one a replication, patterns of asymmetry were disclosed in both directions. The opposite lateral asymmetries delineated two clinical syndromes, which were distinguished by activity and withdrawal. The terms “active” and “withdrawn” were popular descriptors of schizophrenia subgroups in 1960s and 1970s research (Wing and Brown 1970; Depue 1976; Gruzelier 1996a), but the distinction was lost in later definitions of positive and negative symptoms. The patients were independently examined with the 140-item Present State Examination (PSE; Wing et al. 1974) and the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962). Patients with the L > R asymmetry in electrodermal orienting responses—the active syndrome—were characterized by positive symptoms of behavioral overactivity, pressure of speech, manic grandiose and paranoid ideas, exaggerated or inappropriate labile affect, and affective delusions. Patients with R > L asymmetry in orienting responses—the withdrawn syndrome—were characterized by negative symptoms of social and emotional withdrawal, blunted affect, poverty of speech, and motor retardation. It was noteworthy that the syndromes did not hinge on a simple positive-negative symptom dichotomy. All patients had positive symptoms in the form of Schneiderian first-rank symptoms (Schneider 1959) that were unrelated to asymmetry pattern in type or severity. These symptoms constituted the unreality syndrome. The three syndromes had affinities with the three-factor structure of one negative and two positive syndromes in schizophrenia (Bilder 1985; Liddle 1987; Liddle and Barnes 1990; Arndt et al. 1991; Gur et al. 1991). At the same time there were important differences (Gruzelier 1996a).

The nature of the asymmetries—L > R activation in the active syndrome and R > L activation in the withdrawn syndrome—was consistent to some extent with a neuropsychological translation of the symptoms. Pressure of speech in the active syndrome contrasted with poverty of speech in the withdrawn syndrome, which is compatible with opposite states of activation of the left-sided speech production mechanism. The positive affect of the active syndrome contrasted with the emotional and social withdrawal, blunted affect, and motor retardation of the withdrawn syndrome, which was consistent with extensive evidence of hemispheric specialization for aspects of positive versus negative affect. The syndromes had affinities with social interaction/withdrawal models of left versus right hemispheric specialization (Kinsbourne 1982; Tucker and Williamson 1984; Ehrlichman 1987; Davidson and Tomarken 1989; Turner and Ortony 1992; Wheeler et al. 1993). The model was also in keeping with ipsilateral excitatory limbic influences on electrodermal orienting activity (Gruzelier 1973), a view that was controversial (Hugdahl 1984), but has been strengthened by a report of lateralized intracranial stimulation in patients with epilepsy who were undergoing surgery (Mangina and Beuzeron-Mangina 1996). Excitatory influences on electrodermal activity were found to be ipsilateral with stimulation of the amygdala, posterior and anterior hippocampus, and cingulate, in contrast to negligible effects from a representative cortical location.

**Validation of the Model With Tests of Learning and Memory.** The syndrome-asymmetry model was validated in two investigations of *DSM-III* (American Psychiatric Association 1980) and *DSM-IV* (American Psychiatric Association 1994) schizophrenia patients. The research used complementary lateralized tests of learning and memory. These tests met double dissociation criteria in distinguishing between neurological patients with unilateral left- and right-sided lesions of temporohippocampal and frontohippocampal function (Milner 1982;
In the first investigation, schizophrenia patients were classified as active or withdrawn on the basis of symptom ratings and were compared with affective psychotic patients and controls (Gruzelier et al. 1987, 1988). Schizophrenia patients were found to be deficient in both temporohippocampal and frontothalamic tests of learning and memory. Tests included Hebb’s recurring supraspan digit test, the Corsi block-span right hemisphere analog test (Milner 1971), and Petrides’ tests of spatial and nonspatial conditional associative learning (Petrides 1985). The impairments were found predominantly in the hemisphere with the lower level of activation—the right in the active syndrome and the left in the withdrawn syndrome (see also Kemali et al. 1987). These findings further justified the construct of lateral imbalance: the losses of function in learning and memory corresponded to the temporal-frontal system on the side that was less implicated in generating the majority of symptoms, as in Gur’s (1978) original study. The left-sided impairment was greater in the group as a whole. If the syndrome analysis had not been done, this would have masked the right-sided deficits and led to the mistaken conclusion that schizophrenia was characterized by only a left-sided deficit.

In the second investigation, 104 schizophrenia patients were classified as having active/withdrawn or mixed active/withdrawn syndromes and were examined for asymmetry patterns in recognition memory for words versus unfamiliar faces (Gruzelier 1994; Gruzelier et al., in press a). The tests had been validated in patients with unilateral lesions of the temporal and parietal lobes (Warrington 1984), and there was electrophysiological validation in patients and normal subjects with the same or similar words and faces tests (Halgren et al. 1994; Burgess and Gruzelier 1997a, 1997b). Males showed the predicted word advantage in recognition memory in the active syndrome, whereas some females had severe word memory deficits. The prediction of a face advantage in the withdrawn syndrome was supported in both sexes. Patients with a mixture of both syndromes tended to share the face advantage of withdrawn syndrome patients. Patients who were not on antipsychotic medication had the same asymmetry patterns as the symptomatic medicated patients. In both sexes impairments on average were comparable to neurological normative data (Warrington 1984). The recognition memory results in male patients and in females with the withdrawn syndrome, which showed reduced performance in the side with lower level of activation, were consistent with the previous study of learning and memory in schizophrenia (Gruzelier et al. 1987, 1988).

Retest reliability of cognitive asymmetry was demonstrated in patients who were tested twice in the same syndrome in different episodes or in successive states of remission (Gruzelier et al., in press b). Longitudinal investigations also endorsed the importance of functional effects on the nature of the memory deficit (Gruzelier et al., in press b). In five patients who belonged to different syndromes in different episodes, asymmetry patterns varied congruently with syndrome. In addition, both cross-sectional and longitudinal comparisons between psychotic episodes and states of remission showed differences in asymmetry patterns with recovery. Active syndrome patients showed a reversal in cognitive asymmetry such that the face disadvantage in the psychotic episode gave way to a face advantage in remission. By contrast, the withdrawn group showed improvements that were selective for verbal memory. These results disclosed subgroups with opposite reversals of functional asymmetry with treatment and recovery, and these reversals were syndrome dependent. (See Drug Influences on Functional Asymmetry for further discussion of this issue.)

Trait-like qualities that may exist in the premorbid personality have also been implicated in syndrome-asymmetry relations. The recognition memory tests were given to university students classified on schizotypy scales, including the Schizotypal Personality Questionnaire (SPQ; Raine 1991) and the Oxford-Liverpool Inventory (O-LIFE; Mason et al. 1995). Subtle lateralized anomalies have been associated with schizotypy, but the pattern of asymmetries has been inconsistent from study to study (Gruzelier 1991). In factor analyses with the SPQ on two samples (Gruzelier 1996a), a three-factor solution was found depicting active, withdrawn, and unreality schizotypy personality factors related to the schizophrenia syndromes. As in schizophrenia, asymmetry patterns in recognition memory were associated with the active and withdrawn factors in both samples, and there was an inconsistent relation with the unreality syndrome (Gruzelier and Doig 1996). Turning to the O-LIFE subscales, three of the four—unusual experiences, introvertive anhedonia, and impulsive nonconformity—were related to the unreality, withdrawn, and active schizophrenia syndromes, respectively. (The fourth subscale is cognitive disorganization, which is a mixture of positive and negative features.) In line with our model, the face memory advantage was associated with introvertive anhedonia, while the word memory advantage was associated with impulsive nonconformity (Gruzelier and Richardson 1994). On the whole, relations were stronger in males, just as they were with the patients. In one male subject who subsequently had two psychotic episodes characterized by withdrawn and unreality syndromes, the extreme face > word asymmetry obtained premorbidly was predictive of the presenting withdrawn syndrome. These results in normal young
adults imply that syndrome expression in patients has a basis in the premorbid personality.

In summary, the model posited that hemispheric asymmetry underpinned the expression of active versus withdrawn symptoms. The active syndrome represented a dominance of left frontotemporal functions and an underactivation of corresponding right-sided functions. Conversely, the withdrawn syndrome represented a dominance of right frontotemporal functions with underactivation of the corresponding left-sided functions. The unreality syndrome of Schneiderian hallucinations and delusions was inconsistently associated with asymmetry. The results also indicated a functional imbalance between the hemispheres instead of opposite patterns of unilateral impairment. It follows that failure to take syndrome into account will produce inconsistencies among reports of lateral asymmetries in schizophrenia.

**Psychophysiological Asymmetries in Light of the Syndrome-Asymmetry Model**

Evidence of two asymmetry patterns in schizophrenia offered the possibility of unraveling some of the all-too-pervasive contradictions in research on lateral asymmetry and schizophrenia. Reviews undertaken in the light of this hypothesis (Gruzelier 1983, 1991, 1996b) disclosed many measures that showed left-hemisphere advantages/right-hemisphere disadvantages in patients with active syndrome characteristics, such as paranoid, acute, late-onset, reactive, or positive symptoms. The converse relation of right-hemisphere advantages/left-hemisphere disadvantages was found in patients who had withdrawn syndrome characteristics and were described as having nonparanoid, chronic, process, early-onset, or negative-symptom schizophrenia. The following section summarizes and updates this evidence, focusing on neuropsychophysiological measures. Neuropsychological evidence is found elsewhere (Gruzelier 1996b), as is early bloodflow imaging data (Gruzelier 1991). This discussion emphasizes reports in which patients are characterized by syndrome, particularly where more than one patient subgroup is characterized, so as to provide evidence of double dissociation.

**Eye Movements and Lateralized Inattention.** Directional biases in lateral eye movements, whether spontaneous or conjugate, occur contralateral to the more activated frontal eye field. These biases have been reported in both directions in schizophrenia. Gaebel et al. (1986) recorded lateral deviations from a central fixation point in partially remitted outpatients rated with the BPRS. Ratings of emotional excitement and the activation factor score of the BPRS were associated with rightward deviations, while withdrawal was associated with leftward deviations. Gaebel et al. went on to monitor eye movement pattern and reaction time (RT) during a visual search task. The two syndrome groups showed strikingly different scan paths of a letter matrix and also differed in the time taken to detect the target. It is important to note that the withdrawn patients, who typically show poorer performance on cognitive tasks, reached the target more quickly with a shorter search path, and eye movement recording showed a pattern compatible with a gestalt (right-hemisphere) perceptual style. By contrast, the high-activation patients took longer because they scanned the matrix line by line until they reached the target, which is compatible with a serial (left-hemisphere) perceptual style. As part of the same investigation, eye movements were examined while subjects looked at a picture. Patients were subclassified into minimal and extensive scanning groups, and similar syndrome associations were found as above. Extensive scanners had higher ratings on tension, suspiciousness, and conceptual disorganization. Minimal scanning was associated with withdrawal and retardation (Gaebel et al. 1987). Both studies support the syndrome-asymmetry model.

Several authors have reported on conjugate lateral eye movements (CLEMs) in response to verbal and spatial cues, but few studies have examined patient subgroups. Sandel and Alcorn (1980) reported that a leftward lateral asymmetry characterized nonparanoid schizophrenia and depressive patients, distinguishing them from schizoaffective and manic depressive patients, who disclosed no consistent asymmetry. Myslobodsky et al. (1983) have cautioned that the more commonly reported rightward asymmetry (Gur 1978; Schweitzer et al. 1978; Tomer et al. 1979) may reflect a drug effect, for they found that only schizophrenia patients on neuroleptics consistently showed a rightward asymmetry. Barkowska and Rybakowski (1997) compared paranoid schizophrenia patients (DSM–III–R) who had been drug free for a least 7 days with depressed patients and controls. Whereas the controls showed asymmetries that were in line with hemispheric specialization, the schizophrenia patients exhibited rightward CLEMs to both verbal and spatial questions, while patients with depression showed leftward CLEMs. Therefore CLEMs may be in either direction in schizophrenia, and direction may depend on positive (rightward) and negative (leftward) symptoms.

Subtle forms of lateralized inattention have been reported in schizophrenia with eye movement recording, neuropsychological tests, and Posner’s spatial-orienting RT tasks, as reviewed more fully elsewhere (Gruzelier 1996b) and discussed below in Drug Influences on Functional Asymmetry. While symptom relations have not...
been formally examined with the spatial-orienting task, eye movements have been recorded in schizophrenia patients while they performed the Benton visual retention test (Kawazoe et al. 1987). These patients were characterized as mostly in remission with blunted affect and social withdrawal. More errors of recall were found in the right visual field, and eye movement recording disclosed a relative neglect of the right visual field. In other words, the withdrawn patients showed a right-hemispheric activation advantage. Consistent with this, in a series of studies using a double-simultaneous haptic extinction test, Scarone et al. (1987) found that chronicity influenced the lateral asymmetry of neglect. Right neglect characterized chronic patients while left neglect characterized acute patients. In summary, studies of eye movements and of lateralized inattention that have documented symptoms show some consistencies with the syndrome-asymmetry model. Gaebel et al.'s (1986) distinction between emotional excitement/activation and withdrawal provides direct support, as does Kawazoe et al.'s (1987) report of more errors of recall and less time spent looking in the right hemifield in patients with social withdrawal and blunted affect. More indirect are the distinctions between nonparanoid and manic depressive/schizoaffective patients in the CLEM study of Sandel and Alcorn (1980) and the acute/chronic distinction of Scarone et al. (1987). Nevertheless, the asymmetry patterns were all found in the direction the model predicts. It is doubtful that the 7-day minimum washout was sufficient to remove neuroleptic effects on CLEMs in Barkowska and Rybakowski's (1997) study. The minimum period to shift asymmetry of attention for which controlled evidence exists is 14 days (Hammond and Gruzelier 1978). Nevertheless, should their effects be unconfounded by drug, then altogether the results are consistent with a left-hemispheric activation bias in active syndrome patients and a right-hemispheric activation bias in depression.

**Motoneuron Excitability.** Goode and colleagues found symptom-asymmetry correlates in unmedicated patients with the Hoffman reflex. This indexes spinal motor asymmetry and lower motoneuron excitability (Tan and Gurgen 1986). The Hoffman reflex is mediated by the predominantly inhibitory action of the motor cortex on contralateral extensor motoneurons (Uemura and Preston 1965). This evidence was incidentally supported through combined measurement of the reflex and cognitive asymmetries in schizophrenia patients (Goode et al. 1980). As will be seen later, the Hoffman reflex is susceptible to drug influences on asymmetry. In unmedicated schizophrenia patients Goode et al. (1981) found an association between withdrawal-retardation (BPRS) and a dominance of right-hemisphere influences (R > L leg), while the opposite asymmetry was associated with anxiety-depression in schizophrenia. Tan and Gurgen (1986) found only R > L asymmetry in their unmedicated patients diagnosed by Feighner’s criteria (Feighner et al. 1972), which requires the presence of affective blunting. Therefore negative symptoms have been associated with R > L hemispheric influences as has a mixed negative/positive picture (Feighner). Further work is required on relations with positive and “active” symptoms.

**Cardiac Vagal Tone.** Malaspina et al.'s (1997) 24-hour monitoring of high-frequency heart rate variability has disclosed both high- and low-variability subgroups of schizophrenia and schizoaffective patients. Cognitive measures indicated that opposite states of hemispheric functional imbalance characterized the low- and high-variability groups. A left functional advantage was found in the low-variability subgroup and a right advantage in the high-variability group. In the low-variability group, left-hemispheric preference was seen in a large right ear advantage on a verbal dichotic listening test, as well as in the absence of the normal left ear (right-hemispheric) advantage for complex tones, which was replaced by a significant right ear advantage. By contrast, the high-variability subgroup failed to show the normal left-hemispheric advantage on the verbal dichotic test, but did show the normal right-hemispheric advantage on the non-verbal test in keeping with an imbalance favoring the right hemisphere. The hypovagalization of the low-variability, low-vagal-tone group and their L > R imbalance are consistent with evidence of right-hemispheric control of autonomic functions (Lane and Jennings 1995) as is the compromise that would occur as a result of right hypofunction. With regard to symptoms, the low-variability group scored high on the excitement factor of the BPRS, a symptom central to the active syndrome. In terms of our model, this finding is consistent with their L > R cognitive profile. The low-variability group was also characterized by a later age at onset, which is also compatible with the active syndrome. By contrast, the high-variability group, which had a withdrawn syndrome cognitive profile, had an earlier age at onset and more diagnoses of schizoaffective depression.

**Electrodermal Orienting Responses.** Gruzelier and Davis (1995) examined relations in unmedicated psychotic patients between asymmetry in electrodermal orienting responses and the social and physical anhedonia schizotypy scales (Chapman et al. 1976). Social anhedonia has the stronger affinity with the withdrawal and social anxiety features of the withdrawn syndrome. In line with the model, social anhedonia correlated with the
rightward asymmetry; physical anhedonia was associated with reduced responsiveness. Positive symptom relations were found by Mason et al. (1997), who examined normal subjects with psychosis-proneness scales and found correlations between a leftward asymmetry in auditory evoked electrodermal responses and the positive symptom schizophrenia scales of unusual experiences (O-LIFE; Mason et al. 1995) and paranoia and suspiciousness, results which were stronger in females than males.

Gruzelier et al. (1996) recorded bilateral electrodermal activity in schizophrenia patients in a study aimed at contrasting syndrome characteristics with tests of (1) orbital frontal functions (visual discrimination reversal learning and rate of habituation of electrodermal orienting responses), (2) dorsolateral frontal functions (Wisconsin Card Sort; Nelson 1976), and (3) lateralized limbic functions (auditory evoked electrodermal asymmetries). Medicated DSM-IV schizophrenia patients were rated on the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987) and a scale specifically designed to detail the active-withdrawn syndromes (Schizophrenia Rating Scale; Gruzelier and Doig, in preparation). Some relatively distinct syndrome relations were disclosed: anxiety-depression with both the frontal orbital measures, conceptual disorder with the dorsolateral prefrontal measure, and conceptual and motoric disorganization with both frontal measures. An electrodermal response amplitude asymmetry in the direction of larger left-hand responses was associated with active symptoms. These included excitement, pressure of speech, ecstatic thinking, grandiosity, hypomania, stereotyped behavior, positive thought disorder, conceptual disorganization, and active social withdrawal. However, unlike the earlier study, these symptoms extended beyond the active syndrome to encompass positive unreality symptoms, including the unreality syndrome total score and subscores of first-rank delusions and hallucinatory activity. No relationships were found with the withdrawn syndrome.

In conclusion, support for associations between leftward asymmetry and the active syndrome was found, but this was a general positive symptom relationship that included both active and unreality symptoms (Gruzelier et al. 1996), as was the case in schizophrenia (Mason et al. 1997). Support for an association between the rightward asymmetry and the withdrawn syndrome, which in the original investigation was the best replicated relationship (Gruzelier and Manchanda 1982), was found only in unmedicated patients (Gruzelier and Davis 1995). Medication may have been a confound in the other patient study (Gruzelier et al. 1996); the fact that negative symptoms reached only the 30th percentile on the PANSS may also have affected the results.

**EEG Spectral Power.** Considering first the “resting” EEG, Etevenon et al. (1983) compared drug-withdrawn paranoid with residual schizophrenia patients (DSM-III) and controls who were classified on the basis of high versus low alpha activity (with parietal-occipital derivations). Paranoid patients had more affinities with low alpha controls and were distinguished by elevated slow- and fast-wave activity on the left side. By contrast, the residual schizophrenia patients were more like the high alpha controls and were distinguished by right-sided elevations. Coger and Serafetinides (1983) used BPRS ratings to classify male dextral medicated patients on “hypothesized hemisphericity.” Asymmetries in fast-frequency activity were among the distinguishing features of the groups. The putative left-hemispheric group had an asymmetry favoring the left frontotemporal region in the 20–32-Hz band, whereas the right-hemispheric group had an elevation in 26–30-Hz activity in the posterior central occipital leads. Merrin and Floyd (1992) examined unmedicated schizophrenia patients and reported a relation between the degree of negative symptoms recorded with the BPRS and a reduction in alpha power (greater activation), an effect that though bilateral was greater in the right hemisphere. The right-sided relationships also extended to EEG coherence (Merrin and Floyd 1996). No relations with positive symptoms were found.

EEG telemetry recorded from temporoparietal derivations have disclosed subgroup differences in ambulatory activity on the ward, an interview, and verbal and spatial tasks (Stevens and Livermore 1982). Among these findings were abnormalities in right temporal activity in catatonic patients and in left-sided placements in chronic paranoid patients with auditory hallucinations. Guenther et al. (1986, 1989, 1991) compared motor tasks that varied in complexity and dependence on sensorimotor integration, all involving the right hand. In the first two reports, which involved mixed groups of medicated schizophrenia patients, subjects failed to show the normal increase in power in primary sensory and motor areas of the left hemisphere but often showed overactivation of the right hemisphere. It is noteworthy that in the third study, which involved medicated chronic patients with predominantly negative symptoms, and included a resting EEG condition, the asymmetry in the form of raised right temporal beta activity was exhibited at rest and activation with the task produced no further reliable changes. The direction of the asymmetry in the negative syndrome patients is consistent with the syndrome-asymmetry model.

Gruzelier et al. (1990) recorded EEGs in active syndrome DSM-III schizophrenia patients and controls during cognitive activation with lateralized memory and iterative finger movement tasks. Patients differed from...
controls in the right-hemispheric tasks, that is, in recognition memory for faces but not recognition memory for words, and in left-hand (nondominant hand) but not right-hand finger movements. During faces recognition in the temporoparietal region, a region relevant to the face recognition process (Burgess and Gruzelier 1997b), the active syndrome patients showed an absence of the focal beta (17–30 Hz) power reduction that was exhibited by controls in the task. A similar absence of focal power reduction was found in the left finger movement task involving the left anterior and right-posterior regions. The underactivated right hemisphere in the active syndrome was the one in which neuropsychological deficits had been reported with learning and memory tests.

The syndrome-asymmetry model was tested in an EEG and electrophysiological study with unmedicated active and withdrawn schizophrenia patients and controls. EEG amplitude spectra of visual evoked potentials, which were presented in an augmenting-reducing paradigm, were examined at O1, O2, T3, and T4 preceded by electrodermal orienting responses to auditory stimuli (Gruzelier et al. 1993). Syndrome-electrodermal asymmetry relations were in the direction predicted by the model. Occipital EEG asymmetries were found in beta activity (18–22 Hz), with higher power on the left in the active syndrome and on the right in the withdrawn syndrome (in which stimulus intensity relations were abnormal). By contrast, abnormal stimulus intensity relations in the active syndrome were found in the high alpha range (10–14 Hz) and were located in the temporal region. This abnormality was coupled with an abnormal asymmetry in slow-wave activity (2–6 Hz), with more slow-wave activity on the right (T4). These lateralized effects were consistent with the syndrome-asymmetry model and extended the model to include posterior brain activity. Additionally, both syndromes were characterized by an abnormal L > R temporal asymmetry in beta activity (18–22 Hz). Controls showed the opposite asymmetry, indicating a homogeneous lateral imbalance (unilateral comparisons did not distinguish the groups).

In summary, aside from affirmative EEG results in studies that set out to test the syndrome-asymmetry model (Gruzelier et al. 1990, 1993), there were reports of relations between positive symptoms and the left hemisphere (Stevens and Livermore 1982; Coger and Serafetinides 1983; Etevenon et al. 1983) and negative symptoms and the right hemisphere (Stevens and Livermore 1982; Etevenon et al. 1983; Guenther et al. 1989; Merrin and Floyd 1992). The locus of the syndrome-asymmetry relations proved to be widespread, which in the majority of reports included posterior brain activity extending as far as the occipital lobe, and in the case of the withdrawn syndrome, did not require a task-activated EEG to produce the EEG asymmetries. Thalamocortical involvement was implied by abnormalities in the activated EEG, as shown by failures in desynchronization (Guenther et al. 1986, 1989, 1991; Gruzelier et al. 1990) and in abnormal stimulus intensity relations (Gruzelier et al. 1993). Together, these results imply the involvement of subcortical arousal mechanisms that have generalized cortical influences rather than discrete module-specific cortical asymmetry.

Cortical Evoked Potentials and the P300. Among cortical event-related potential measures, hemispheric asymmetry has been most widely examined with the P300. Before considering syndrome-asymmetry relations, it should be noted that clinical correlates of P300 reduction, independent of asymmetry, are diverse and controversial, though it is often assumed that P300 attenuation goes with negative symptoms. Ebmeier et al. (1990), who recorded from Cz and parietal sites bilaterally, found associations with nonspecific symptoms such as poor attention, distractibility, and impersistence, but none with key positive and negative symptoms. St. Clair et al. (1989), recording from a single electrode (Cz), found no differences between paranoid and nonparanoid patients classified on Research Diagnostic Criteria (RDC). By contrast, Louza and Maurer (1989) found that patients with the paranoid-hallucinatory syndrome showed an overall reduction in somatosensory P300 amplitude compared with nonparanoid (mainly disorganized type) patients, whose acute symptoms were all in remission. Similarly, Egan et al. (1994) reported associations with positive symptoms that included paranoia as well as positive verbal and positive behavior scores, as did Kawasaki et al. (1997). But associations have also been reported with negative symptoms rated with the BPRS (Merrin and Floyd 1994), while Eikmeier et al. (1992), recording from the midline in remitted patients, found associations with the global SANS and its anhedonia-asociality subscale, but no associations in acute patients. Associations have also been found with thought disorder (Roth et al. 1981) and with the BPRS symptom severity score (Pfefferbaum et al. 1989). In sum, no consistent relationship has been found between P300 amplitude reduction and positive and negative symptoms, though both classes of symptoms have been implicated in different studies.

Can topography and syndrome differences explain these varied results? Harvard researchers have reported a homogeneous left-sided deficit in the auditory oddball P300 in chronic patients with predominantly positive symptoms of schizophrenia. This deficit tends to have a temporal locus, although the precise location within the left hemisphere has varied between anterior temporal, central middle, and posterior temporal electrodes (Morstyn et al. 1983; Faux et al. 1987, 1990, 1993;
McCarley et al. 1989, 1993). However, these findings are beset with methodological ambiguity. In their initial research, the authors used a procedure in which responses to tones were presented while the subject read a simple story—an “inattentive” condition giving rise to a P3a component—were subtracted from responses in the traditional “attend” condition in which the subject counted silently or pressed a button, giving rise to a P3b component. Aside from the involvement of different P300 components, the use of the subtraction technique complicates interpretation of the results. This is seen by the fact that before subtraction, patients had either a L > R asymmetry or symmetry in the attentive condition and an even larger L > R asymmetry disadvantaging the right hemisphere in the inattentive condition (Faux et al. 1987, 1988). In both conditions the greatest single contribution to group differences was made by the amplitude attenuation in patients at the right temporal electrodes (T4 and T6). In other words, the schizophrenia patients showed right temporal decrements in P300 in both the attentive and inattentive conditions. Only after subtracting the inattentive from the attentive responses did the asymmetry reverse to produce the left-sided effect, which better differentiated patients from controls than either condition did before subtraction—hence the author’s focus on a left-sided “deficit.” A further question is raised by Shenton et al.’s (1989b) report of positive correlations between positive symptoms and P300 over left temporal areas. In other words, the less the “deficit,” the greater the positive symptoms. As Faux et al. (1988) acknowledged, theirs was an empirical result and its theoretical and neurophysiological significance was unclear.

Syndromes have had a bearing on attempts at independent replication. These efforts have produced either no evidence of asymmetry for the schizophrenia group as a whole (Pfefferbaum et al. 1989; Egan et al. 1994; Ford et al. 1994) or evidence of both asymmetries when the data of individual patients were examined (Gruzelier et al., in press c; Strik et al. 1993). In fact, Shenton et al. (1989a) reported opposite asymmetries in P300 amplitude in 2 patients from the Faux et al. (1987) sample (n = 11), who were compared with 2 subjects with the left-sided reduction. The right-sided reduction was associated with more positive symptoms and thought disorder, although the 2 subjects also had a malignant form of illness with earlier onset, poorer premorbid history and response to treatment, and more severe and diffuse impairment. However, in 9 patients from the same sample McCarley et al. (1989) found that positive symptoms rated with the Scale for the Assessment of Positive Symptoms (Andreason 1984) correlated positively with the amplitude of the P300 at T3 (both variables also correlated positively with L > R Sylvian fissure enlargement). Methodological ambiguity aside, positive symptoms per se do not explain asymmetry relations in this sample. Strik et al. (1993) examined controls and remitted (DSM—III—R) schizophrenia patients subcategorized according to Leonhard’s classification of “core schizophrenia,” or “cycloid psychoses” in whom symptoms had fully remitted (Leonhard 1979). Only the core schizophrenia group had a reduction and asymmetry of P300 amplitude; this was lateralized to the left hemisphere as shown by a parietal maxima displaced to the right. The results in patients with core schizophrenia and residual symptoms were replicated (Strik et al. 1994), though there were no control group differences on temporal electrodes (T3 and T4).

We examined 20 DSM—IV schizophrenia patients rated as active or withdrawn with the conventional P300 procedure (Gruzelier et al., in press c), comparing measures across the posterior temporal-parietal coronal chain (T3, P3; P2, P5, T6). When the patients were categorized as withdrawn or with predominantly active symptomatology, opposite asymmetry patterns were disclosed between T3 and T6 placements in the amplitudes of the P300, and also of the N100, N200, and N200-P300. Negativity of evoked potentials was higher and positivity was lower on the right in the withdrawn group, while the opposite relation was found in the active/mixed group, whose parietal maxima were also displaced to the right. Therefore, the active patients showed the left-sided P300 reduction and they also had lower P300 amplitudes overall, while the withdrawn patients had the right-sided P300 reduction. These relations did not hold for anterior temporal T1 and T4 derivations. The results with active patients were compatible with a posterior temporal left-sided reduction reported in DSM—III—R schizotypy (Salisbury et al. 1996) in subjects who were characterized by high scores on the positive symptom scales of magical ideation and perceptual aberration (Eckblad and Chapman 1983) and not the negative scale of physical anhedonia (Chapman et al. 1976).

Heidrich and Strik (1997) examined the relation between P300 asymmetry and lateralized cognitive tests. Their measure involved the deviation of the P300 maxima located over the central parietal region rather than the asymmetry in the temporal region. They examined 13 catatonic and paranoid medicated outpatients who were either fully remitted or had residual symptoms. A correlation was found between the degree of P300 deviation to the right and relative impairment of memory for words versus abstract designs, tests sensitive to left and right temporal lobe functions—the greater the deviation to the right, the greater the verbal impairment. In fact, all the cognitive tests showed correlations that tended toward significance between rightward asymmetry and poorer performance. In keeping with their remitted status, the patients did not differ from the test norms on the conditional associative learning tests, indicating that they were cognitively a fairly
intact group. Unlike the symptomatic patients of Gruzelier et al. (1988) and Kemali et al. (1987), they showed no evidence of differential deficit on the same tests in active/withdrawn or withdrawn syndrome patients. It is also the case, as will be shown below, that right-hemispheric electrophysiological advantages have been found to accompany symptom remission on drugs.

McCarley et al. (1989) investigated structure-function-syndrome relations. First, a reciprocity of hemispheric influences was indicated between P300 laterality amplitude measured in the inattentive (reading a story) condition and the left and right Sylvian fissure size measured with computed tomography (CT). This was seen in the progressive reduction in the size of the correlation across the central chain until there was a reversal at the right temporal electrode (T4). The greater the L > R asymmetry of the Sylvian fissure, the greater the L > R (T2/T4) P300 asymmetry. Second, the L > R Sylvian fissure asymmetry related to positive symptoms consisting of delusions, positive thought disorder, and bizarre, whereas the R > L asymmetry related to alogia, avolition-apathe, affective flattening, and the total negative symptom score.

In summary, evidence of both L > R and R > L P300 asymmetry patterns and of reciprocal relations between P300 asymmetry and Sylvian fissure asymmetry has been found in schizophrenia. However, differences in methodology and topography hamper interpretation of these conflicting results. In our data the syndrome-asymmetry relations were as pronounced with the earlier N100 and P200 components as they were with the P300. Egan et al. (1994) also found that correlations between the P300 and N200 distinguished patients from controls. Consistency of effects across components from N100 and to P300 would be in keeping with generalized imbalances in hemispheric activation arising from thalamocortical mechanisms. This proposition is compatible with accumulating evidence in this review of a fundamental basis for the asymmetry patterns in lateralized arousal processes. As such, the results cast a different light on the significance of P300 amplitude reduction in schizophrenia than in a circumscribed memory deficit. When the functional significance of negativity (neuronal excitation) and positivity (neuronal inhibition) (Birbaumer et al. 1990) is considered, associations of the active syndrome with the left-sided reduction and the withdrawn syndrome with the right-sided reduction are consistent with the syndrome-asymmetry model.

Cortical Evoked Potentials: Mismatch Negativity (MMN). Javitt et al. (1993) have reported a trend toward asymmetry in a negative component that precedes the P300 in the 50–150 ms range and represents an earlier stage of processing localized to the superior temporal plane of the primary auditory cortex. The MMN was reduced at midline electrodes Fz, Cz, Pz, left precentral F7/C7, and left temporal T7/T4 placements, with the greatest reduction (compared with controls) at the temporal sites. An analysis of MMN with variation of the interstimulus interval (Baldeweg et al. 1998) supports a predominantly left-sided MMN reduction for the patients as a whole. A preliminary syndrome analysis found that the active and withdrawn syndromes were differentiated by abnormal interstimulus intervals decay functions in opposite hemispheres. This decay involved the right hemisphere of the active syndrome and the left hemisphere of the withdrawn syndrome, which in each case are the hypofunctional hemispheres as defined by the syndrome-asymmetry model and other cognitive measures.

Magnetoecephalography (MEG). The importance of anomalous event-related potential (ERP) asymmetries in earlier components is also endorsed by MEG evidence with the auditory N100m component, which is the counterpart of the EEG N100 wave although not isomorphic with it. The MEG studies include evidence of abnormal function-structure relations. Reite and Rojas (1997; Reite et al. 1997) have examined patients with DSM-III diagnoses of paranoid schizophrenia. They set out to extend earlier evidence obtained with a single-channel gradiometer in which normal asymmetry, which is characterized by a more anterior location on the right, was absent in male but not female schizophrenia patients (Reite et al. 1988, 1989). Source locations determined with magnetic resonance imaging (MRI) were traced to generators in the transverse gyri of Heschl’s left and right superior temporal gyri. The absence of normal asymmetry in male patients was replicated, whereas the asymmetry was found to be more pronounced in female patients, such that it had a more anterior location on the right. Reite et al. went on to show that there was no alignment between the M100 asymmetry and the left-right plane asymmetry of Heschl’s gyrus; in fact, in the male patients relations were reversed in the left hemisphere. This finding indicates that the abnormal auditory N100m asymmetry does not reflect a shift in the location of Heschl’s gyrus and may suggest an alteration of structure-function relations in the primary auditory cortex.

Other investigators have not found the same uniformity of results in schizophrenia, which may indicate that the asymmetry reported by Reite et al. may be specific to the paranoid subgroup. In a more diverse sample of 18 DSM-III schizophrenia patients including paranoid, undifferentiated, disorganized, residual, and catatonic subgroups, Tiihonen et al. (1992) found a greater dispersion of M100 asymmetries in both directions. Six subjects showed an abnormal left anterior locus not seen in controls while three had a right anterior locus more extreme.
than in controls. The abnormal left anterior locus was associated with higher levels of general psychopathology rated by the PANSS, as well as more guilt feelings and motor retardation. There was also a shift of the left auditory cortex toward the anterior tip of the temporal lobe. Hajek et al. (1997) examined eight DSM-III-R female schizophrenia patients and found a lack of the asymmetry demonstrated in controls. This was because the patients had a more horizontal orientation of the right hemisphere dipole than the controls.

Thus both hemispheres have been implicated in auditory M100 abnormalities. While reports of sex differences are contradictory (Reite et al. 1989; Hajek et al. 1997), there are hints that syndrome relations with positive symptoms may be associated with the right-sided abnormalities (Reite et al. 1989) and negative symptoms with the left-sided abnormalities (Tiihonen et al. 1992). Research thus far has not demonstrated in patients the alignment with structure that was found in controls, which may imply abnormal structure-function relations in schizophrenia.

Syndrome-Related Asymmetries in Interhemispheric Connectivity

Syndrome-Related Hyperconnectivity Versus Hypoconnectivity. The syndromes may also be linked with differences in interhemispheric connectivity via the corpus callosum, the active syndrome with hyperconnectivity and the withdrawn syndrome with hypoconnectivity. Considering hyperconnection and the active syndrome, using MRI, Guenther et al. (1991) found a larger callosal area in positive-symptom than in negative-symptom patients. Enlargement coexisted with increased bilateral blood flow measured by single photon emission computed tomography following dominant hand motor activation in those with positive symptoms. However, there were no task-induced changes in blood flow in those with negative symptoms, a result endorsed with topographical EEG (Guenther et al. 1989). Abnormalities of movement aftereffects indicative of an abnormal increase in callosal transmission have been reported in patients with case-note evidence of first-rank symptoms (Tress et al. 1983). Siegel et al. (1993) found an association between positive symptoms and metabolic activity in the corpus callosum, coexisting with a L > R frontal metabolic asymmetry, the active syndrome signature. The evidence of a thicker callosum in anterior regions of female schizophrenia patients, a characteristic shared with affective disorder patients (Raine et al. 1990), may also be relevant to the active syndrome given the more positive symptoms of an affective type in female schizophrenia patients (Lewine 1981; Goldstein and Link 1988) and the involvement of anterior brain regions in the expression of affect (Heller 1993). Thus it is proposed that positive syndrome features are associated with functional and structural hyperconnection.

Hypoconnection in the withdrawn syndrome has been supported by electrophysiological evidence. In the somatosensory modality, there is controversial yet reasonable evidence (Gruzelier 1996b) that unilateral stimulation of either the finger, wrist, or arm produces both an abnormally short ipsilateral latency and an apparent bilateral symmetry of somatosensory evoked potential amplitude (Jones and Miller 1981; Tress et al. 1983; Cooper et al. 1985; Andrews et al. 1986). One explanation is that the phenomenon represents an abnormal development of ipsilateral pathways, perhaps secondary to a developmental abnormality of the callosum and failure of interhemispheric transmission. Some support for this hypothesis was forthcoming from auditory ERPs, where in recording the N120 from T3 and T4, 80 percent of normal controls showed the expected contralateral pathway advantage compared with only half of the patients. The other half of the patient group showed ipsilateral dominance (Connolly et al. 1985). However, a functional origin was indicated by evidence (Tress et al. 1983) that the abnormal pattern of somatosensory evoked potentials was reduced with symptom improvement (as measured by total BPRS score). Andrews et al. (1986, 1987) examined the phenomenon in association with subgroups, in this instance the active and withdrawn syndromes. The withdrawn syndrome exhibited the abnormal symmetry, whereas active syndrome patients had the normal asymmetry favoring contralateral pathways. Furthermore, while neuropsychological tests showed no difference between schizophrenia subjects as a group and patient controls, subdivision by syndrome indicated that those with the symmetrical evoked potential pattern showed the characteristic R > L neuropsychological asymmetry of the withdrawn syndrome. Negative symptoms and right-sided anomalies have been associated with reduced interhemispheric EEG coherence. In the resting EEG of unmedicated patients, Merrin and Floyd (1996) found that negative symptoms were associated with less interhemispheric coherence between homologous electrodes. Less coherence was also found between the right parietal region and both frontal regions, a relation no longer evident when the patients were retested on neuroleptics. Thus callosal hypoconnection may characterize chronic, negative, withdrawn syndrome schizophrenia.

Interhemispheric Directional Asymmetry. Directional asymmetries in the normal brain have received little attention (Hopfman and Davidson 1994). However, on the basis of a meta-analysis on RT advantages with visual
hemifield studies, Marzi et al. (1991) concluded that there was an advantage for the left visual field-right hand condition, that is, a rightward transmission advantage. A meta-analysis on evoked potential experiments also found an advantage for right-to-left transmission (Brown et al. 1994). By contrast, a review of both the cognitive and psychophysiological literature in schizophrenia (Gruzelier 1996b) has disclosed that the interhemispheric transmission deficit in schizophrenia is subject to lateral asymmetry with asymmetries reported in both directions of interhemispheric transmission. Furthermore, the asymmetry in the direction of transmission appears to be associated with the syndrome. Measures included dichotic listening and shadowing, stereognosis, somatosensory evoked potentials to median nerve stimulation, flash evoked potentials, interocular transfer of movement aftereffects, and divided visual field color naming. A dominance of left-hemispheric influences, shown by difficulty in transmitting information from right to left, has been found in patients described as acute (Green et al. 1983; Green 1985), paranoid (Bull 1972; Gruzelier and Hammond 1979b, 1980), autonomically responsive (Gruzelier and Hammond 1979a, 1979b, 1980), actively psychotic (Buchsbaum et al. 1979; Gruzelier and Hammond 1979a, 1979b; Gulmann et al. 1982), schizoaffective (Weller and Kugler 1979; Craft et al. 1987), and having first-rank symptoms (David 1987). Such a profile is consistent with the aroused, active syndrome and it follows from their characteristic L > R imbalance that rightward transmission would be dominant over leftward transmission. The opposite pattern of asymmetry, depicting a dominance of right-hemispheric influences, or a difficulty in transmitting information in a rightward direction, has been described in nonparanoid and in electrodermally hyporesponsive patients (Gruzelier and Hammond 1979a, 1979b, 1980) and in chronic patients (Craft et al. 1987), all consistent with a withdrawn profile. Again, it follows from the R > L imbalance that leftward transmission would be dominant over rightward transmission. In summary, it is proposed that the positive active syndrome is associated with functional and structural hyperconnection as well as with faster rightward transmission, while the negative withdrawn syndrome is associated with hypoconnection and faster leftward than rightward transmission.

Asymmetry, Symmetry, and Dispersion. Currently "symmetry" has as much currency as "asymmetry" in schizophrenia research. The interest in symmetry stems from structural evidence on the presence or absence of torque in the shape of the brain, specifically the planum temporale. It has been posited that schizophrenia involves a failure to develop normal asymmetry and hemispheric specialization (Crow 1995). The position taken here is that if functional asymmetry is based on structural morphological asymmetry and if the direction of structural asymmetries is heterogeneous (Yeo et al. 1997), then our supposition that opposite syndrome-dependent functional asymmetry has a basis in traits of temperament requires a greater dispersion of morphological asymmetries. The distribution will be skewed to the right, away from the normal L > R asymmetry toward symmetry and toward R > L asymmetry, with the active and withdrawn syndromes characterizing the leftward and rightward extremes, respectively.

A close inspection of Bilder et al.'s (1994) claim of structural symmetry supports this view of dispersion. They reported an absence of the normal gross hemispheric asymmetries in frontal and occipito-parietal width, known as "torque," in first-episode schizophrenia. When results for individuals categorized with "normal" L > R asymmetry, "symmetrical," or "reversed" are considered, percentages of schizophrenia (n = 53) were 54.7 percent, 7.6 percent, and 37.7 percent, respectively, compared with control (n = 45) percentages of 73.3 percent, 8.9 percent, and 17.8 percent. Most patients displayed structural asymmetry and a substantial number had reversed asymmetries. In fact the number with symmetry were small and were no larger in patients than controls.

The theory that reversed asymmetry may be characterized by the withdrawn syndrome has not been tested, but there is some limited support in the form of associations with negative symptoms or cognitive reduction (Luchins and Meltzer 1983; Bilder et al. 1994). Asymmetry of Sylvian fissure "enlargement" supports this schema. In McCarley et al.'s (1989) CT study, L > R Sylvian fissure enlargement asymmetry related to positive symptoms of delusions, positive thought disorder, and bizarre ness. R > L asymmetry related to alogia, avolition-apathy, affective flattening, and the total negative symptom score. Active-withdrawn syndrome relations have been examined with asymmetries of the lateral ventricles (Puri et al., in press a). Here strong support was found for associations between the active syndrome and an L > R asymmetry and the withdrawn syndrome and an R > L asymmetry. Recent evidence shows highly significant changes over 8 months in ventricle-to-brain ratios in first episode patients in the form of increases in the active syndrome and decreases in the active syndrome and decrease in the withdrawn syndrome (Puri et al., in press b). Thus some general relations may exist between morphological asymmetries and active and withdrawn syndromes, but none of these asymmetries have specificity for schizophrenia; nor can they account for a fluctuating functional illness.

While continuing evidence of more sinistrality or inconsistent right-handedness in schizophrenia has been
interpreted as supportive of anomalous asymmetry, two sources of evidence are incompatible with this view. First, the proportion of non-right-handed patients in all of the reports is small, and second, reports of a higher incidence of strong right-handedness are incompatible with an emphasis solely on left-handedness (Gruzelier 1981b). Are active-withdrawn syndrome differences likely to characterize the handedness subgroups? The data are scant because there has been a failure to consider clinical correlates of handedness subgroups in schizophrenia. One exception is Taylor et al. (1980), whose report of an association between strong right-handedness and paranoid schizophrenia is compatible with our proposal of active syndrome characterization of right-handedness and its accompanying left-hemispheric functional dominance. At the same time functional influences in the control of handedness have been demonstrated through inconsistencies in handedness over time in schizophrenia (Green 1998).

Of particular relevance to handedness is the Hoffman reflex, which is related to handedness and hand skill measured with the pegboard; it is supposed that fine motor control requires inhibitory functions that, along with the number of pyramidal fibers, are greater on the preferred hand (Yakovlev and Rakic 1966). Right-handers showed a greater inhibitory influence on the right-sided reflex and the opposite asymmetry was found in sinistrals and ambidextrals who showed symmetry (Tan 1985). Schizophrenia subjects display wide dispersion in both directions of asymmetry in the Hoffman reflex (Goode and Manning 1988).

Summary of Syndrome-Asymmetry Relations

Substantive evidence was disclosed of two asymmetry patterns in schizophrenia compatible with a view of greater dispersion of functional and possibly structural asymmetry in schizophrenia. Evidence where both syndromes were distinguished in a single experiment such that a L > R asymmetry was associated with the active or active-like syndrome and a R > L asymmetry with the withdrawn or negative syndrome were reported for electrodermal orienting responses (Gruzelier and Manchanda 1982), eye movement lateral deviations and search patterns (Gaebel et al. 1986, 1987), somatosensory evoked potentials (Andrews et al. 1987), EEG amplitude spectrum analysis of visual evoked potential/stimulus intensity relations (Gruzelier et al. 1993), mismatch negativity (Baldeweg et al., submitted for publication), recognition memory for words and faces (Gruzelier et al., in press a, in press b), and the P300 (Gruzelier et al., in press c). Complementary associations with features germane to the active-withdrawn distinction, such as chronicity and paranoid versus nonparanoid, were reported for conjugate lateral eye movements (Sandel and Alcorn 1980; Barkowska and Rybakowski 1997), haptic extinction (Scarone et al. 1987), motoneuron excitability (Goode et al. 1981), EEG activity (Stevens and Livermore 1982; Etevenon et al. 1983), and vagal tone (Malaspina et al. 1997). In addition, there was evidence supporting the active-withdrawn asymmetry associations, first with single subgroups (Hammond and Gruzelier 1978; Kawazoe et al. 1987; Kemali et al. 1987; Guenthier et al. 1989; Gruzelier et al. 1990; Merrin and Ford 1992; Gruzelier and Davis 1995) which extended the range of variables to include hemi-inattention, conditional associative learning, and auditory temporal discriminations, and second, from one of two subgroups examined (Coger and Serafetinides 1983; Gruzelier et al. 1996). These relations also extended to schizotypy with measures including recognition memory for words and faces, the P300, and electrodermal orienting responses (Gruzelier and Doig 1996; Salisbury et al. 1996; Mason et al. 1997). Further evidence, reviewed elsewhere (Gruzelier 1991, 1996b), was forthcoming from neuropsychological tasks and functional imaging, which included auditory thresholds, dichotic listening, dichotic and monotic shadowing, and syntax-prosody ratio and metabolism and bloodflow.

Active and withdrawn syndrome differences may also extend to individual differences in interhemispheric transmission, with hyperconnection associated with the active syndrome and hypoconnection with the withdrawn syndrome. Furthermore, there may be syndrome-related directional asymmetries such that in the active syndrome rightward transmission is dominant over leftward transmission, and vice versa in the withdrawn syndrome.

Not all results supported the model (Shenton et al. 1989a), and not all reports favored more than one functional asymmetry in schizophrenia. It is important to note that two electrophysiological studies that demonstrated opposite asymmetries in active and withdrawn syndromes also disclosed a coexisting homogeneous asymmetry: in one a left temporal abnormality in mismatch negativity to auditory stimuli (Baldeweg et al., in press) and in the other a L > R imbalance in beta desynchronization during the presentation of flashes of varying intensity (Gruzelier et al. 1993). Although in both reports the unilateral deficit was common to both active and withdrawn syndromes, the bulk of the evidence above indicates that failure to take syndrome into account will produce inconsistencies among reports of lateral asymmetries of function in schizophrenia, as will the failure to consider drug influences, considered in the next section. Aside from the theoretical significance of the syndromes for a hemispheric basis to the expression of important positive and negative symp-
toms, the data have demonstrated the importance of the functional basis of the asymmetries and of functional imbalance between the hemispheres rather than of unilateral impairment, issues that will resurface in the consideration of drug influences on lateral asymmetry.

Drug Influences on Functional Asymmetry

Neuroleptic-Induced Asymmetries in Schizophrenia. For some time there has been compelling evidence that neuroleptics have lateralized influences in schizophrenia patients. All neuroleptics have antidopaminergic action, and dopamine has been shown to produce behavioral asymmetries in the form of turning tendencies in animals. These considerations are important, first, in a purely practical sense to avoid confounding interpretation of asymmetrical deficit with drug effects; second, they may shed light on mechanisms underpinning functional asymmetry and the recovery process in schizophrenia. The empirical evidence in patients will be considered first.

In the only controlled drug study to date investigating functional lateralization in schizophrenia (single-blind), systematic influences on auditory attentional asymmetries were reported in a chlorpromazine withdrawal/reinstatement study (Hammond and Gruzelier 1978). This study assessed the ability of chronic, institutionalized, schizophrenic patients, who were characterized by withdrawal, hallucinations, and delusions, to shift attention between the ears in order to detect longer target tones that shifted from ear to ear at two rates of switching and two speeds of presentation. Patients were examined six times at biweekly intervals: two sessions after being stabilized on chlorpromazine, two sessions on placebo, and two sessions after chlorpromazine reinstatement. Ratings of symptom exacerbation off drug and symptom remission on drug reinstatement confirmed that the patients benefited from neuroleptics. On drug, the left hemisphere was superior; withdrawal of drug produced a reversal in asymmetry giving the right hemisphere the advantage. The left hemisphere regained the advantage when drug was reinstated. Reversals in hemispheric attentional advantage, both with drug withdrawal and reinstatement, were found to be related to dose (corrected for body weight). In other words, the drug produced dose-related right ear (left-hemisphere) processing advantages that were reversed by drug withdrawal. It is important to note that it was lateral asymmetry, and not overall level of performance, that was influenced by the drug, indicating that the hemispheric influences of drug withdrawal and reinstatement were reciprocal.

Turning to uncontrolled psychophysiological and cognitive studies, emphasis is given to longitudinal investigations because it is difficult to interpret evidence based on within-group correlations in the absence of an off/on drug design, because this may reflect the policy of prescribing higher doses to more severely disturbed patients. This interpretation is exemplified by Harvey et al.'s (1993) report of a positive correlation between neuroleptic dose and right-sided attentional neglect measured with a tactile-kinesthetic task; but dose was also found to correlate with severity of symptoms.

Several investigators have reported attentional asymmetries. Tomer and Flor-Henry (1989) found that unmedicated patients made more errors in a cancellation test on the right side of space, indicating left-hemisphere inattention. On retest those patients who were medicated for more that 3 weeks made more errors on the left side of space; the asymmetry had reversed to favor the left hemisphere. In a report of lateralized anomalies in spatial orienting, Posner et al. (1988) described two sources of evidence of drug influences on hemi-neglect. These occurred when attentional cues were endogenous, that is, were dependent on verbal or spatial hemispheric specialization. The cues consisted of words or arrows presented in pairs so that they were symbolically compatible or incompatible. One source of evidence arose from comparing medicated and unmedicated patients where there was a significant interaction between medication status and task (whether the instruction cue was a word or an arrow). Never-medicated patients manifested a linguistic but not a spatial impairment, that is, performance was reduced when the word instruction conflicted with the direction of the arrow and not vice versa. By contrast, the medicated group showed the opposite tendency, suggesting that medication improved performance on the word condition (left hemisphere) and impaired performance on the arrow condition (right hemisphere). These results imply reciprocal hemispheric changes in which neuroleptics advantaged left-hemispheric attentional processes.

The second source of evidence arose from examining the unmedicated patients after a course of medication. Performance on the attend-word condition improved, especially in the conflict condition. Again neuroleptic treatment advantaged left-hemispheric processes. Maruff et al. (1995) replicated the effect of drug on reversal of asymmetry in spatial orienting. They found slower RTs in the right visual field in unmedicated patients, but asymmetry followed a normal distribution in either direction in patients on long-term medication. In summary, the results of Posner et al. (1988) and Maruff et al. (1995) were consistent with those of Tomer and Flor-Henry (1989) and Hammond and Gruzelier (1978) in showing that neuroleptics changed the direction and in most studies the balance of hemispheric activity, giving rise to left-hemispheric processing advantages on drug.
However, reciprocal but predominantly right-hemispheric neuroleptic influences have been reported with some electrophysiological measures, including visual evoked potentials (VEPs), EEG power (Morihisa et al. 1983), and the Hoffman reflex (Tan and Gurgen 1986). Mintz et al. (1982) found that neuroleptics, particularly piperazine derivatives, influenced the late components of the visual evoked response recorded from parietal electrodes. On drug, they found dose-dependent increases in positivity in the right hemisphere (P2) that reversed the left-sided asymmetries (P3) of some patients when unmedicated. In a sample composed mainly of hebephrenic patients, those with a longer illness duration showed predominantly right-sided VEP enhancement on drug. Morihisa et al. (1983) disclosed asymmetry of fast-frequency beta activity (28–31.5 Hz) in the resting EEG. In unmedicated patients this activity was left-sided and localized to the parietal region, whereas in medicated patients it was right-sided and localized to central and temporal electrodes. Predominantly right-hemispheric drug influences were endorsed with the Hoffman reflex recovery curve, which indexes spinal motor asymmetry and lower motoneuron excitability (Tan and Gurgen 1986). The Hoffman curve is mediated by predominantly inhibitory action of the motor cortex on contralateral extensor motoneurons (Uemura and Preston 1965). Tan and Gurgen (1986) reported that unmedicated, strongly dextral schizophrenia subjects had a higher Hoffman reflex on the left than on the right leg and this reversed after 3 weeks of chlorpromazine treatment. Although the larger influence, here inhibitory, was on the right hemisphere, reciprocal interhemispheric drug influences were again disclosed.

In summary, evidence indicates that neuroleptic medication has asymmetrical influences on cognition and neurophysiology. Three reports found asymmetries to be dose dependent, and these included both behavioral (Hammond and Gruzelier 1978; Harvey et al. 1993) and physiological (Mintz et al. 1982) measures. This asymmetry occurred despite individual differences in the metabolism of neuroleptics. Failure to acknowledge the role of neuroleptics in experimental designs could seriously confound interpretation of lateralized anomalies of function in schizophrenia.

Regarding the nature of the effects, much of the earlier work was interpreted as showing a restitution of left-hemispheric functions on drug (Serafetinides 1972; Gruzelier and Hammond 1979a, 1979b; Wexler and Heninger 1979; Johnson and Crockett 1982; Myslobodsky et al. 1983). Now this assumption appears to be an oversimplification. Evidence has been cited of asymmetric right-hemispheric effects of drug as well as shifts in hemispheric balance from the left to the right hemisphere, shown by VEP late components, EEG power, and the Hoffman reflex. In an earlier section, we reported word and face recognition memory data disclosing reversals of asymmetry in both directions that were associated with active and withdrawn syndromes and occurred with recovery from symptoms (Gruzelier et al., in press b). These data are similar to an earlier finding of reversals in both directions of asymmetry in auditory evoked electrodermal orienting responses that occurred with clinical recovery on drug (Gruzelier et al. 1981). Awareness of the reciprocity of action may help reconcile other findings in the literature such as leftward activational biases in blood-flow in severely symptomatic patients, which contrasted with symmetry in treated patients (Gur et al. 1985). Common to the behavioral and electrophysiological domains of measurement, drug influences have involved interactions between the hemispheres that may be reciprocal, altering balances of activity between the hemispheres rather than improving or reducing function overall or representing a unilateral drug action. In sum, neuroleptic influences have been shown to be asymmetrical and bidirectional and involve reciprocal interhemispheric influences. The following section examines these features through consideration of the neuroanatomy and neurochemistry of drug influences on asymmetrical turning tendencies in animals, adopted as a model of neuroleptic action (Pycock et al. 1980) and in turn applied to schizophrenia (Bracha 1989; Early et al. 1989).

Implications for Neuroanatomical and Functional Substrate

**Dopamine, Rotational Behavior, and Hemi-Spatial Inattention.** Asymmetric circling behavior is a behavioral marker of nigrostriatal dopaminergic asymmetry in animals (Ungerstedt 1971; Pycock et al. 1980; Glick and Ross 1981). In the lesioned animal, turning is generally contralateral to the side with the higher level of striatal dopamine and coincides with attentional neglect of the ipsilateral side of space. The phenomenon includes asymmetry of posture, ipsilateral orienting and rotational preferences, intentional neglect or a slowing of contralateral movements, and a failure to disengage from ongoing appetitive behavior to attend to contralateral stimulation. The imbalance may occur spontaneously or through training to turn in one direction, but it is most marked when induced by lesion. Amphetamine, which increases dopamine turnover, enhances contralateral turning and is a common device for unmasking turning preference, while neuroleptics that block dopamine reverse the striatal asymmetry (Robinson et al. 1983). While the emphasis has been on dopamine, other neurochemical systems are...
affected as well. Indeed dopamine appears to have a modulatory role on information transmission attenuating the excitatory effects of glutaminergic cortical neurons and gamma aminobutyric acid (GABAergic) striatal-pallidal neurons. Circling has also led to an increase in serotonin in the contralateral amygdala without an increase in dopamine (Yamamoto and Fried 1984). Further, circling has been accentuated by apomorphine, t-dopa, scopolamine, LSD, phenylcyclidine, and morphine (Pycock et al. 1980). Turning tendencies, a form of spatial behavior, have been associated with overall learning ability and left-right discriminations, and also with affective behavior, in the form of thresholds of hypothalamic self-stimulation and reinforcement sensitivity. Thus turning preferences represent coordinated activity of attentional, motor, and reinforcement systems, all of which are influenced by dopaminergic action.

Exploring turning tendencies with a belt-mounted rotometer, Bracha (1987) found that a subgroup of about 25 percent of unmedicated schizophrenia patients were prone to turn to the left, whereas normals did not show a preference for either side. Bracha went on to show that the degree of left-turning correlated positively with severity of delusions, but not with total positive symptoms or with total symptoms (Bracha et al. 1993). He marshaled evidence in support of the view that the asymmetry reflected right-sided striatal dopaminergic hyperactivity rather than left-sided hypoactivity (Bracha 1989). This evidence included a R > L asymmetry of dopamine D2 receptors in striatal tissue at postmortem (Reynolds and Czudek 1988); asymmetrical right-limb manifestations of neuroleptic-induced Parkinsonism in paranoid patients (Tomer et al. 1987), interpreted as representing a greater effect of dopamine blockade on the left striatum with its lower level of dopamine; and tardive dyskinesia on the left side in two studies of schizophrenia patients (Wilson et al. 1984; Altshuler et al. 1988), representing hyperreactivity of the contralateral nigrostriatal system.

While Bracha depicted one asymmetry that was specific to a subgroup, other evidence of neuroleptic-induced pathology suggests there may be two asymmetries. Tardive dyskinesia has also been found on the right in a mixed group of schizophrenia and affective disorder patients (Waziri 1980); there is evidence of left-limb Parkinsonism in a disorganized schizophrenia patient (Tomer et al. 1987); the risk of tardive dyskinesia has been related to both extremes of handedness—sinistrality (Joseph 1990; McCreadie 1992) and dextrality (Barr et al. 1989; Kern et al. 1991; Morgenstern et al. 1996); in a cross-sectional study, neuroleptic-induced muscle stiffness of the upper extremities was found to be right-sided in newly treated patients and left-sided in those treated for more than 3 months (Caligiuri et al. 1989).

Early et al. (1989) espoused an alternative position to Bracha's, namely that left-sided orienting/right-sided hemi-spatial inattention in schizophrenia represented left-sided underactivity of the basal ganglia. As this position is concerned with the same R > L asymmetry, the opposing views may be reconciled by emphasizing hemispheric imbalance; but only the one R > L asymmetry was represented. Early et al. (1987) found a replicable hypermetabolism of the left globus pallidus in neuroleptic-naive schizophrenia patients similar to that which may occur in Parkinson's disease, a dopamine-deficient disorder involving unilateral destruction of midbrain dopaminergic neurons. But this finding is at odds with the hyperdopaminergic theory of schizophrenia. These investigators went on to examine schizophrenia patients for evidence of hemineglect with spatial orienting. The results, reported in Posner et al. (1988), indicated that right-sided neglect with endogenous attentional cues was modifiable by drug. When attentional cues were exogenous, these investigators disclosed a subtle deficit of attention in the right visual field (Posner et al. 1988), an asymmetry accompanied by fewer eye fixations on the right side of space (Potkin et al. 1989). Early et al. (1989) speculated that the left pallidal hyperactivity and the right hemineglect reflected a dopaminergic hemi-deficiency involving left-sided cortico-striato-pallido-thalamic circuits (Alexander et al. 1986).

However, Early et al.'s claim of a homogeneous unilateral inattention deficit conflicts with the other evidence of hemi-neglect and asymmetric orientational tendencies in schizophrenia (Gaebel et al. 1986; Kawazoe et al. 1987; Scarone et al. 1987). These conflicts may explain why attempted replications of Posner's spatial-orienting paradigm have met with mixed success, resulting in both confirmation (Potkin et al. 1989; Carter et al. 1992; Maruff et al. 1995) and failure or very weak replication (Strauss et al. 1991; Moran et al. 1992; Nestor et al. 1992; Gold et al. 1992; Liotti et al. 1993; Maruff et al. 1995). The presence or absence of the anomaly raises the question of heterogeneity. Attempts at explaining this discrepancy have largely centered on acute versus chronic patient differences, respectively, or medication, but no symptom correlates have been formally examined. Posner et al. (1988) had the impression that the anomaly was associated with hallucinations. Attempts at elucidating the nature of the underlying asymmetry have found little support for a unilateral left-structural deficit. Comparisons with patients with unilateral lesions have failed to find correspondence when results were considered as a whole (Posner et al. 1988), and the magnitude of the anomalies in schizophrenia are much more subtle. In the only report of both schizophrenia and parietal patients (Maruff et al. 1995), the data show that the right visual field impairment
characterized a group of nine right-parietal patients (though the authors overlook this). Furthermore, the order of magnitude of the asymmetry in the right-parietal patients was much greater than in the schizophrenia patients and also in a mixed group of unilateral frontal patients.

However, if schizophrenia is regarded as predominantly a functional disorder, then turning tendencies produced by stimulation challenges in the intact animal may be more appropriate than a lesion model. Indeed while this approach discloses an altogether more complex pattern of results, there are parallels with neuroleptic influences on functional asymmetry in schizophrenia, including interhemispheric reciprocity. First, in contrast to the contraversive influence of lesions, stimulation-induced turning may be either ipsiversive or contraversive, demonstrating the existence of interacting facilitatory and inhibitory systems (ipsiversive movements reflect inhibition of the substrate of contraversive turning). Second, self-regulation of dopamine cells via dopamine release from dendrites has produced the opposite effects of release between different ipsilateral structures such as the caudate and substantia nigra (Glowinski et al. 1984). Third, sensory, electrical, and pharmacological stimulation studies have demonstrated reciprocal lateralized control of dopaminergic (and GABAergic) input to the basal ganglia via nigrostriatal pathways (Glowinski et al. 1984). Fourth, limbic influences arising from infusion of dopamine into the left or right amygdala or by amygdalar kindling have produced predominantly ipsiversive turning preferences and ipsilateral inhibition/contralateral facilitation of dopamine transmission in the striatum. These effects have been shown to involve interhemispheric pathways (Bradbury et al. 1985; Csernansky et al. 1985; Mintz et al. 1987), as shown by the fact that the ipsiversive turning and contralateral striatal increase in dopamine produced by amygdalar kindling were reversed by lesioning the anterior commissure (Csernansky et al. 1985). Fifth, the direction of the resulting behavioral asymmetry depended on individual differences in endogenous turning preference (Bradbury et al. 1985). Thus, a complex interplay of subcortical-cortical and interhemispheric neurochemical effects underpins neuroleptic influences on turning preferences, and these preferences are also dependent on preexisting individual differences in behavioral asymmetry.

Two studies explored spatial orienting in normal subjects under conditions of altered neurochemistry. In a study of normal volunteers, Clarke et al. (1989) examined the effects of haloperidol and clonidine, which reduce levels of dopamine and noradrenaline, respectively. The drugs facilitated disengagement and shifting of attention, which is consistent with the hyperdopaminergia theory of schizophrenia; laterality effects were not explored. Craft et al. (1992) examined children with phenylketonuria, a congenital condition in which a deficiency in the enzyme phenylalanine hydroxylase results in low levels of dopamine, noradrenaline, and serotonin. Spatial orienting in boys showed an asymmetry of inattention consistent with the results in schizophrenia (Posner et al. 1988; Potkin et al. 1989) and a positive correlation between the right visual field deficit and phenylalanine levels. However, the correlation in girls was with the analogous left visual field deficit.

In conclusion, research on turning tendencies in animals, particularly where pharmacological, electrical, or sensory challenges have been applied to the nonlesioned animal, has shown a number of parallels with neuroleptic influences in schizophrenia. Behavioral asymmetry cannot be explained by simple global increases or decreases in hemispheric functional activation because drug action involves excitatory, inhibitory, self-regulatory, and interhemispheric actions. Reciprocal interhemispheric drug influences have been demonstrated, a recurring characteristic of drug (or recovery) effects on many behavioral and electrophysiological asymmetries in schizophrenia patients. The mechanism underlying reciprocity was elucidated by the demonstration that interhemispheric reciprocity was specific to nigrostriatal dopaminergic input to the basal ganglia and was not found for limbic dopamine. Furthermore, Glowinski et al. (1984) demonstrated that interhemispheric reciprocity in the basal ganglia was mediated via thalamic motor nuclei and/or the intralaminar nuclei of the nonspecific thalamic projection system and not mediated via mesencephalic pathways or the anterior commissure, which is involved in the contralateral effects of amygdalar kindling (Csernansky et al. 1985). There was little evidence to support homogeneous effects of neuroleptics on asymmetry. On the contrary, the bidirectionalality of the drug-induced asymmetries in patients and animals and their dependence on endogenous turning preference in the rodent supported individual differences in the influences of neuroleptics on functional asymmetry. Thus, neuroleptic influences offer insights into mechanisms underlying functional asymmetry in schizophrenia.

**Development of Behavioral Asymmetries**

Insight into the origin of functional asymmetry in schizophrenia may also be gleaned from studies of the origin of turning tendencies in animals. Glick and colleagues concluded that these indices are determined by a complex interaction of genetic, hormonal, and experiential factors (Glick and Ross 1981; Carlson and Glick 1989). To begin
with, genetic influences have been associated with strength of asymmetry and developmental influences with direction of asymmetry (Collins 1985). Proposed developmental influences include the following: testosterone, which is controlled by the major histocompatibility complex and slows the development of the left hemisphere; malnutrition during pregnancy, which has abolished asymmetries in visual evoked responses and retarded the size of corpus callosum (Soto-Moyano et al. 1993); and prenatal stress, which has altered postural asymmetry after birth, and produced in adulthood a left-turning bias after amphetamine challenge with a reduction of dopamine turnover in the left striatum (Fride and Weinstock 1987, 1989) and a marked increase in inter-hemispheric coupling in dopamine (but not serotonin) up-regulation in prefrontal cortex, nucleus accumbens, and caudate nucleus (Fride and Weinstock 1987). Prenatal stress has feminized the behavior of male rats and reduced the male R > L asymmetry in neocortex thickness (Fleming et al. 1986), while rodents given extra stimulation early in life have right hemisphere dominance and increased width and regularity of shape of the callosum (Berrebi et al. 1988).

Stress in adulthood also influences direction of rotation, and while sexually dimorphic effects have been disclosed, on the whole, the nature of sex differences has not been consistent across studies, possibly because of strain and species differences. In response to d-amphetamine challenge after uncontrollable footshock stress, male rats with a rightward bias rotated toward the left or showed an accentuation of left rotation if they were already left rotators, while females showed the opposite turning preference (Carlson and Glick 1989). Right-rotating rats have been found to be less reactive and less sensitive to the effects of footshock stress than left rotators. Levels of dopamine have been related to turning tendencies, with high levels associated with right turning and low levels with left turning. Furthermore, Carlson and Glick (1989) reported that severity of stress influenced direction of asymmetry: the stress of food deprivation increased mesocortical dopamine, as did footshock. The opposite effects were seen as deprivation lengthened. Mild stress (24-hr deprivation), which increased prefrontal dopamine, produced the right rotation previously seen in rats exposed to controllable footshock, whereas severe stress (48-hr deprivation), which decreased prefrontal dopamine, produced the left rotation seen with uncontrollable stress. Levels of stress in humans have been associated with behavioral asymmetries (Tucker 1981), as well as with a reversal of cognitive asymmetry to favor the right hemisphere (Gruzelier and Phelan 1991). In schizotypy, the latter had particular impact on the left-preference active syndrome (Gruzelier and Doig, in preparation).

Activity levels in the rodent were also associated with behavioral asymmetry in the direction predicted by the active-withdrawn syndrome-asymmetry model: the more behaviorally active rats were the right rotators (Carlson and Glick 1989). Regional metabolism has also been related to turning tendencies. Glick and colleagues (Glick 1983; Glick and Ross 1981) found that asymmetries in the midbrain and striatum were predictive of contralateral turning tendencies. But metabolic asymmetry in the frontal cortex interacted with striatal asymmetry such that turning tendencies were augmented where frontal activity was higher on the side contralateral to the striatal asymmetry. Bilateral frontal lesions reduced turning tendencies. In the hippocampus, only a left-preferent asymmetry was predictive and this was in the direction of augmented right-sided turning. Raised levels of brain metabolic activity were also associated with right-sided turning, whereas absolute differences between the sides correlated with rate of turning.

In conclusion, as Glick and Ross (1981) noted, brain asymmetry is dynamic and depends in part on the system as a whole. Both genetic and developmental factors, including nutrition, stimulation, hormones, and stress, have an impact on endogenous turning preference. All of these factors have been considered in schizophrenia research. In the case of stress, long implicated as a trigger of schizophrenia episodes, transient functional influences on turning tendencies were also disclosed. Some of these influences may be sexually dimorphic.

Finally, evidence of spontaneous asymmetries of gesture and emotion has been found in human infants that can be detected prior to the development of language and visuoconstructive skills (Trevathan 1996). These evolutionary antecedents of cerebral asymmetry appear to affect motivation, social signaling, and bimanual coordination, with secondary effects on perceptual processing and learning. This evidence in infants, along with the extensive evidence on behavioral asymmetry in animals, of which turning tendencies and associated behavior is but one example (Glick and Ross 1981; Denenberg 1983), has been overlooked in the concentration on handedness and language as the key to abnormalities of cerebral asymmetry in schizophrenia, features believed to define schizophrenia as a peculiarly human disease (Crow 1995). Cerebral lateralization is an evolutionary principle subserving emotion and arousal aside from cognitive and motoric processes.

Of direct relevance to the present thesis, as well as to the delineation of active and withdrawn syndromes, Trevathan (1996) proposes that neurochemical asymme-
tries regulate motor initiatives, exploration and attention, and the approach/withdrawal balance in social encounters. Asymmetries in emotional and communicative behavior in infancy support evidence that an Intrinsic Motive Formation emerging in embryo human brain stem regulates asymmetries in development and in the functioning of the cerebral cortex.

Individual Differences in Callosal Connectivity and Arousal. The function and structure of the callosum, which include interhemispheric coupling of dopamine upregulation, and variations in width and shape, may also be determined by developmental factors shown in the rodent to influence turning tendencies, such as malnutrition, prenatal stress, and stimulation in infancy (Fride and Weinstock 1987; Berrebi et al. 1988; Soto-Moyano et al. 1993). In schizophrenia there has been a heterogeneity of findings regarding length, width, and the rostral-caudal dimension of the callosum, as well as the extremes of functional connectivity posited for the active and withdrawn syndromes. The latter may have a structural substrate.

Variation in callosal width is indicative of the number of fibers in the small- to moderate-diameter range (Aboitiz et al. 1992). In this range there is preliminary evidence of differences between subjects with schizophrenia (n = 5) and nonpsychiatric controls (n = 7). The diameter of fibers in the anterior and genu regions was smaller in schizophrenia patients, suggesting slower anterior information transmission. Female patients had increased width and more small to moderate fibers, a thicker myelin sheath, and glial hypertrophy. It may be that the greater number of fibers in female schizophrenia subjects reflects less axonal elimination. This assumption is in line with the earlier puberty of females, for as puberty signifies the last regressive neuronal development event, an early arrest to the pruning process could result in an overabundance of fibers (Saugstad 1994, 1997). This excess may lead to greater interhemispheric interference, which is known to decrease with maturation between 10 and 12 years (Liederman et al. 1985; Merola and Liederman 1985). Interhemispheric interference may also be facilitated by increased neuronal conduction velocity caused by the thicker myelin sheath in females. By contrast, the slower maturation of males will prolong the pruning process, leading to fewer and diffuse connections, which together with thinner myelination will give smaller callosal width. The same reasoning could apply to active (female-early maturation) versus withdrawn (male-late maturation) syndrome differences. Some support was forthcoming from pubertal timing relations in schizotypy syndromes (Gruzelier and Kaiser 1996; Kaiser and Gruzelier, in press). While both extremes of maturation were found to be associated with the positive unreality syndrome, late maturation was associated with the withdrawn syndrome. The posited relations between hypercallosal and hypocallosal connectivity and the active-withdrawn syndrome may help unravel some of the heterogeneity of the structural findings.

On the whole, clear relations between callosal anatomy and behavior are lacking, leading to the proposition that the callosum may be involved in the more general processes of inhibition and arousal (Clarke and Zaidel 1994). A role in arousal modulation had been deduced from a range of attentional deficits in split-brain patients and from developmental improvements in children's attention occurring coincidentally with decreases in interhemispheric transmission time (Levy 1985). On the basis of these findings Trevarthen (1974) and Levy (1985) concluded that the corpus callosum may be involved in the regulation of arousability to sensory input in the form of a positive feedback loop, such that the greater the connectivity, the greater the arousal (Hopman and Davidson 1994). This conclusion would be compatible with the putative basis of the syndromes in arousal processes and the prediction of greater hyperconnectivity in the more aroused active syndrome and hypoconnectivity in the less aroused withdrawn syndrome.

Arousal and the Non-Specific Thalamic System (NSTS). This review will conclude with a brief consideration of a mechanism that may underpin the functional asymmetries associated with the active and withdrawn syndromes as well as the neuroleptic-induced reversals of asymmetry in schizophrenia. Arousal differences have been implicated by the neuropsychophysiological measures reviewed as a fundamental underpinning of the syndromes as well as the neuroleptic-induced reversals of asymmetry in schizophrenia. Arousal differences have been implicated by the neuropsychophysiological measures reviewed as a fundamental underpinning of the active and withdrawn syndromes, quite apart from the bipolar character of the syndromes themselves. The neuropsychophysiology of the measures involved had wider regional implications than the original focus on fronto-temporo-limbic systems. Measures extend both posteriorly to the parietal and visual cortex and infracortically to include lower motoneuron excitability. These measures take us beyond the current emphasis on hypofrontality, working memory, and executive functions in schizophrenia, and striato-thalamic circuits that involve the frontal lobe, though these predominate anatomically (Alexander et al. 1986; Cummings 1993). The expansive character of the symptoms and personality features encompassed by the syndromes, covering cognitive, emotional, motor, and arousal processes, imply widespread cortical and infracortical involvement. As reasoned by others (Pantelis and Nelson 1994), a convergence of cortical-subcortical circuits in the striatum could cause a relatively discrete lesion within the basal ganglia to produce just such a
diversity of symptoms and signs. Evidence of the influence of neuroleptic drugs on all manner of cognitive and psychophysiological asymmetries indicated that dopaminergic and GABAergic tone in cortex, limbic system, and basal ganglia offered a starting point for elucidating cortical and infracortical neurochemical mechanisms that appear to be at the heart of functional asymmetry. Trevarthan (1996) concluded that the neurochemical asymmetries that orchestrate approach/withdrawal motivation in children arose from the brainstem.

Here it is posited that the best candidate for a mechanism with projections throughout the cortical mantle and subcortex with involvement in arousal modulation is the NSTS. Innervation from the intralaminar thalamic nuclei of the NSTS reaches the superficial layer (layer I) of all cortical regions, with spatially continuous projection. Innervation also reaches the reticular nucleus, into which all specific corticofugal loops project. It is the intralaminar nuclei together with the thalamic motor nuclei that Glowinski et al. (1984) found to be involved in the transmission via the massa intermedia of the reciprocal interhemispheric influences mediated by striatal dopamine and GABA. Damage to the NSTS results in lethargy, and, of particular note for this review, unilateral lesions produce hemi-neglect.

The NSTS has been implicated in the generation of oscillatory states responsible for conscious perception (Llinas and Pare 1991). The thalamus generates rhythmic activity in the cortex, thought to represent gating and timing operations. Thalamic neurons generate two distinct firing modes — burst firing, whereby sensory information is transmitted to the cortex, and repetitive firing, which is an oscillatory mode including both the slow-wave activity that accompanies lower states of consciousness and the fast-wave activity that has a binding function. Mountcastle (1980) has theorized that shifting between the two firing modes controls levels of alertness, consciousness, and attention. However, Llinas et al. (1994) have proposed that consciousness is a noncontinuous event, which is determined by the simultaneity of activity in the thalamocortical system. This activity consists of the coordination of 40-Hz activity in (1) the specific thalamocortical (layer IV) corticofugal loops reentering and exerting inhibition on the thalamus via the GABAergic reticular nucleus, and (2) the intralaminar NSTS projecting to cortical layers I and V and to the reticular nucleus. Llinas et al. have shown that the membrane of spiny inhibitory interneurons in cortical layer IV supports 40-Hz activity. Their inhibitory input onto pyramidal cells projecting to the thalamus can, through rebound activation, entrain the specific and nonspecific thalamic systems, which in turn project to most thalamic relay. Steriade et al. (1990) have shown that intrinsic 40-Hz oscillation resonance capabilities are found in the thalamic-relay neurons, the reticular nucleus neurons, and the pyramidal cells, allowing network resonance. Given the mosaic of independent thalamocortical connections, the unique role of the reticular nucleus, which has collateral terminals from all thalamocortical connections passing in both directions, is noteworthy.

On the basis of these intrinsic oscillatory capabilities, Llinas (1987) described the brain as a self-generating, reality-emulating, closed system, as evinced by REM sleep. To paraphrase his view, sensory cues are processed via the specific thalamocortical projection through their impact on the preexisting functional disposition of the brain — "priming" in cognitive psychophysiology. Priming is to a large extent the function of the NSTS and corticofugal negative feedback loop via the reticular nucleus. Consciousness requires the temporal conjunction of activity in the specific thalamocortical nuclei, which provides the content of experience, and activity in the NSTS, which provides both the context and alertness. The conjunction is brought about by 40-Hz oscillations for which the intralaminar NSTS cells have the strongest intrinsic 40-Hz rhythmicity. If waking consciousness is duplicated by self-generated activity in the absence of appropriate sensory input, hallucinations may result. Dreaming is regarded as a state of hyperattentiveness to intrinsic activity in which the sensory input registered via thalamocortical circuits does not enter conscious experience.

Damage to unilateral thalamic nuclei, including intralaminar, dorsomedial, and midline groups, has been associated with hallucinations (Fisher 1959; Feinberg and Rapcsak 1989; Catafau et al. 1992). We have demonstrated the coincidence between fast-frequency oscillations and conscious perception (Baldeweg et al., in press). A patient with full insight who recurrently experienced pseudosomatic hallucinations taking the form of objects and pins and needles traveling through the body simultaneously displayed oscillations in the EEG with a mean frequency of 35 Hz. They were accentuated over the right central and temporoparietal regions and lasted between 200 and 1000 ms. The patient currently has a diagnosis of schizophrenia.

Interruptions ranging from minor asynchrony to complete uncoupling between the conjunction of specific and nonspecific thalamic systems and between the content and context of consciousness could give rise to many aspects of anomalous processing in schizophrenia and schizotypy. These include disturbances of sensory processing, sensory gating, and magnocellular functions; of perceptual aberrations, hallucinations, and attributions of schizophrenia to a waking dream; of dysregulation orienting, arousal, alertness, and attention; and of mismatches between ongoing and past experiences that may lead to erroneous and delu-
sional thinking (Gruzelier, in press b). Neuroanatomical evidence is also in keeping with this perspective. Garey et al. (1998) reported in schizophrenia a diminution of spines on the inhibitory interneurons, the membrane of which has been shown to support 40-Hz oscillations (see also Andreasen et al. 1994). As Oke and Adams (1987) concluded prior to the discovery of gamma oscillations, “even minor interruptions of the timing and phasic activity of the thalamus and, especially, its corticothalamic reentry system might be responsible for the sensory-processing dysfunctions seen in schizophrenia” (p. 595).

In conclusion it is posited that the active and withdrawn syndromes represent lateral biases in the nonspecific thalamic system and the callosal arousal system. These asymmetries have their origin in the endogenous influences of genes, hormones, and early experience and in stressors in adulthood. They underpin “intrinsic motive formation” taking the form of approach/withdrawal behavior and are manifested in temperament, personality, and clinical syndrome. They precede language development. The centrality of these imbalances to schizophrenia is borne out, first by the range of symptomatology they encompass, symptomatology which is both specific and nonspecific, a necessary requirement to explain the development and onset of schizophrenia and its temporal course; and second the association of reversal of the functional imbalance with clinical recovery and neuroleptic treatment, and with shifts in symptom profile. At the same time they may coexist with a unitary left-sided deficit. The functional and dynamic nature of the syndrome-related asymmetries holds out the hope for modification, not only by neuroleptics, but also by other behavioral, neurophysiological, and neurochemical methods (e.g., Wing and Brown 1970; Depue 1976; Gruzelier et al., in press d; Richardson, in press).

References


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Gruzelier, J.H., and Venables, P.H. Bimodality and lateral asymmetry of skin conductance orienting activity in schizophrenics: Replication and evidence of lateral asym-


Joseph, A.B. Non-right-handedness and maleness correlate with tardive dyskinesia among patients taking neu-


Puri, B.K.; Richardson, A.J.; Oatridge, A.; Hajnal, J.V.; and Saeed, N. Cerebral ventricular asymmetry in schizophrenics compared to normal controls. [Abstract] Schizophrenia Research, 117.


Richardson, A.J. Laterality changes accompanying symptom remission in schizophrenia following treatment with eicosapentaenoic acid. *Schizophrenia Research*, in press.


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