Neurocognitive Correlates of Schizotypy in First Degree Relatives of Schizophrenia Patients

by Meinte G. Vollema and Belinda Postma

Abstract

We examined neurocognitive correlates of three dimensions of schizotypy in 63 healthy first degree relatives of schizophrenia patients. Neurocognitive measures of attention, verbal memory, and prefrontal functioning were combined with self-report and interview measures of schizotypy. State-psychopathology (anxiety and depression) was a strong predictor for positive schizotypy (PS) and negative schizotypy (NS). PS was slightly correlated to verbal long-term memory, therefore weakly supporting the hypothesis that temporal-limbic malfunctioning underlies PS. NS was not correlated to any prefrontal measure, and therefore no evidence was found for the hypothesis that prefrontal malfunctioning underlies NS. Disorganization schizotypy (DS) was strongly correlated to the false alarm variable of the Continuous Performance Test (CPT), probably supporting the hypothesis of orbitofrontal malfunctioning underlying DS. This correlational pattern of DS echoes closely two schizophrenia studies reporting a relationship between formal thought disorder and the false alarm CPT variable. This similarity between the dimensions of schizotypy and the dimensions of schizophrenia is striking. It may suggest that schizotypal traits and schizophrenia symptoms reflect different points on the same continuum. It may also suggest an underlying tridimensionality of etiology (Venables 1995). If these hypotheses are right, it would mean that there may be different pathogenetic determinants to the three dimensions of schizotypy and schizophrenia (i.e., positive, negative, and disorganization). For instance, both positive schizophrenia and positive schizotypy may be caused by temporal-limbic dysfunction.

For 20 years, studies have been conducted into the neurocognitive correlates of schizotypy for two reasons: (1) to investigate the construct validity of schizotypy measures (Lenzenweger and Moldin 1990), and (2) to explore the neurocognitive processes that might be related to different dimensions of schizotypy. These studies may contribute to a better understanding of specific pathogenetic factors that underlie different dimensions of schizotypy and probably schizophrenia.

In a meta-analytical review of the literature on the relationship between schizotypal dimensions and neurocognition (including 33 studies), we found that in nor-

Empirical evidence suggests that schizotypy is a multidimensional construct (Raine et al. 1994; Venables 1995; Vollema and van den Bosch 1995). Factor analytical studies provide evidence for dimensions of PS (e.g., magical ideation, perceptual aberrations), DS (e.g., odd speech, odd behavior), and NS (e.g., social anxiety, no close friends). Empirical evidence also suggests that schizophrenia itself is a multidimensional construct (review by Venables 1995). It is composed of a positive symptom dimension (hallucinations, delusions), a disorganization dimension (formal thought disorder, bizarre behavior), and a negative symptom dimension (blunted affect, poverty of speech). This similarity between the dimensions of schizotypy and the dimensions of schizophrenia is striking. It may suggest that schizotypal traits and schizophrenia symptoms reflect different points on the same continuum. It may also suggest an underlying tridimensionality of etiology (Venables 1995). If these hypotheses are right, it would mean that there may be different pathogenetic determinants to the three dimensions of schizotypy and schizophrenia (i.e., positive, negative, and disorganization). For instance, both positive schizophrenia and positive schizotypy may be caused by temporal-limbic dysfunction.

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In a meta-analytical review of the literature on the relationship between schizotypal dimensions and neurocognition (including 33 studies), we found that in nor-
mal subjects PS is more strongly associated with deviances in smooth pursuit eye movements and continuous performance tasks than DS and NS are. We also found that NS is more strongly associated with abnormal performance on the Wisconsin Card Sorting Test (WCST) than PS and DS are (Vollema et al., submitted for publication).

A neurodevelopmental model of neurocircuitry malfunction underlying schizotypy and schizophrenia is provided by Walker and Gale (1995). Two malfunctioning neural circuits are held responsible for the development of schizotypal traits. First, dysfunction of the temporal-limbic circuit may contribute to the development of PS traits. Evidence for this hypothesis is provided by Flbaum and Andreasen (1995), who report a negative correlation between hippocampal volume and PS. Hemsley (1992) argued that an inability to make use of stored information (mediated by the hippocampus) of past regularities could give rise to positive symptoms. If temporal-limbic malfunction underlies PS, one would expect correlations with the retrieval component of verbal long-term memory. In our review, we did not report on temporal-limbic dysfunction, because few studies were conducted into the relationship to schizotypy.

Second, Walker and Gale (1995) argued that malfunction of the prefrontal circuit contributes to the development of NS traits. Evidence that NS is related to prefrontal dysfunction is provided by Raine et al. (1992), who report strong correlations between NS and WCST variables. These findings suggest that prefrontal (or executive) dysfunction, including mental inflexibility and poor planning, is associated with, and probably may give rise to, the social-interpersonal deficits of NS. If Walker and Gale are right, correlations may be found between NS and neurocognitive measures of prefrontal functioning.

Walker and Gale did not hypothesize about neural circuits underlying DS. It was argued by Frith et al. (1991) and Allen et al. (1993) that formal thought disorder in schizophrenia is related to the production of incorrect words during a verbal fluency task. Problems in suppressing incorrect responses seem to be associated with formal thought disorder in schizophrenia, which made Liddle and Morris (1991) suggest that orbitofrontal dysfunction may underlie formal thought disorder. If this holds for DS as well, it would be expected that DS is associated with cognitive disinhibition (indicated by premature and incorrect responses during attention and memory tasks).

Schizotypy can be assessed with questionnaires and with structured interviews. Questionnaires are mainly used for screening purposes, because they take less time to administer (review in Vollema and van den Bosch 1995). Structured interviews are more time-consuming and therefore are mainly used as a second line for classification of schizotypal traits and schizotypal personality disorder (review in Benishay and Lencz 1995). However, it remains to be seen whether questionnaires and interviews (with identical items) for schizotypy are equivalent and assess schizotypy similarly. Kendler et al. (1996) argued that questionnaires are not well suited to measuring all schizotypal signs (e.g., goal directedness of thinking), which can be rated reliably by only a well-trained interviewer. In a confirmatory factor analysis, using a schizotypy interview and a schizotypy questionnaire (see Instrument portion of Method section), we predicted that five factors would describe the data the best: three trait factors (PS, NS, and DS) and two method factors (interview and questionnaire). Questionnaire and interview PS and NS (respectively) loaded onto the same trait and method factors, suggesting that they are highly equivalent. Self-report and interview measures for PS assess PS similarly. Self-report and interview measures for NS assess NS similarly. However, questionnaire and interview DS loaded onto different trait factors, suggesting that they are not equivalent, both measuring very different aspects of schizotypy (Vollema and Ormel, submitted for publication). A high level of trait variation indicates that the trait of interest (e.g., positive schizotypy) is a main determinant of the test score. A high level of method variation indicates that the format of the test is a main determinant of the test score.

The aim of this study was to test some hypotheses and to further explore the neurocognitive correlates of dimensions of schizotypy assessed by questionnaire and interview. We hypothesized that (1) PS would correlate negatively with the retrieval component of verbal memory, (2) DS would correlate positively with cognitive disinhibition, and (3) NS would correlate positively with perseverative errors, as part of executive functioning.

Method

Subjects. First degree relatives of schizophrenia patients have a 5 to 15 percent chance of developing schizophrenia and therefore are considered a biological high-risk group (Gottesman 1991). First degree relatives were selected for this study because more variation in scores on measures of schizotypy (questionnaire, interview, and neurocognitive tests) was expected to occur than in a general population sample or a college student sample known by their restricted range of neurocognitive abilities (Lencz et al. 1995).

The subjects were 63 (28 males and 35 females) healthy first degree relatives of schizophrenia patients. The schizophrenia patients, classified according to DSM-IV (APA 1994), were admitted to our hospital, and all of their first degree relatives were asked to participate.
Subjects were recruited in two phases. First, we asked the Family Board of our hospital to assist in recruiting the first degree relatives. Second, by letter we asked all families of schizophrenia patients in our hospital to participate. Letters (including three application sheets) were sent to 140 families, and we received 139 in return: 85 relatives agreed to participate and 54 relatives refused. Sixty-three relatives fulfilled the inclusion criteria and participated.

Exclusion criteria were as follows: age over 65 years, IQ lower than 70, organic cerebral or neurological disorder, and chronic alcohol or drug abuse. The mean age of the relatives was 46 years (range 17–64 years), their mean IQ was 102 (standard deviation 14), the mode of educational level was secondary (18 subjects), most subjects (45) were married, and subjects did not use psychiatric medication.

We cannot be sure whether this is a representative sample of first degree relatives of schizophrenia patients. Some relatives remarked that the relative most similar to the patient refused to participate. This was in line with expectations put forward by Lenzenweger (1993), who argued that the most severe schizotypal subjects are too avoidant or too anxious to participate in research. Those who participated seemed surprisingly cooperative and compliant.

Instruments

Schizotypy. The Schizotypal Personality Questionnaire (SPQ; Raine 1991) is a 74-item self-report questionnaire with a dichotomous response format (yes/no). The SPQ is developed to measure all nine DSM-III-R criteria for schizotypal personality disorder (referential thinking, social anxiety, magical ideation, unusual perceptual experiences, odd behavior, no close friends, odd speech, constricted affect, suspiciousness). The SPQ is used as a screening instrument in the general population for identification of individuals with schizotypal traits. It can also serve as a measure of individual differences in schizotypal personality. Recent factor analytical studies with the SPQ suggest that the nine original subscales can be reduced to three schizotypal dimensions (Raine et al. 1994; Vollema and Hoijtink 2000). The first dimension is called PS and contains symptoms of delusional thinking, unusual perceptual experiences, odd behavior, no close friends, odd speech, constricted affect, suspiciousness. The second dimension is called DS and contains symptoms of referential thinking, delusional mood, magical ideation, illusions, and suspiciousness. The last SIS-R dimension concerns PS and contains symptoms of referential thinking, delusional mood, magical ideation, illusions, and suspiciousness. The second SIS-R dimension concerns DS and contains symptoms of goal directedness of thinking, loosening of associations, and oddness. The last SIS-R dimension concerns NS and contains symptoms of social isolation, social anxiety, introversion, restricted affect, paranoid ideation, and referential thinking. The variables are further referred to as Interview Positive Schizotypy (IPS), Interview Disorganization Schizotypy (IDS), and Interview Negative Schizotypy (INS).

Dimensions of PS and NS. We also calculated two dimensional scores for each subject, which were derived from a confirmatory factor analytical study with the same sample. Two (latent) dimensions of schizotypy, using the SPQ and the SIS–R, best described (the structure of) the data. The PS dimension score is calculated as follows: $PS = 0.76QPS + 0.55QDS + 0.76IPS$. The NS dimension score is calculated as follows: $NS = 0.84QNS + 0.84INS$ (parameter values are factor loadings from the factor analytical study). Questionnaire and interview DS were not correlated, and therefore DS did not appear as a separate dimension from this factor analytical study. QDS loaded on PS, and therefore we selected IDS as the indicator of DS.

Psychopathology. Two scales of the Symptoms Checklist–90 (SCL–90; Derogatis et al. 1973) were used—anxiety and depression. These subscales provide indications for state-related anxiety and depression. It was argued by Meehl (1990) that schizotypal subjects may suffer from high levels of anxiety and depression. These symptoms may influence the performance of schizotypes on neurocognitive tests. There are three reasons the relatives in this study might have suffered from high levels of anxiety and depression. First, they might have been anxious and depressed as a result of being a family member of a schizophrenia patient. Second, they might have devel-
oped anxiety and depression in reaction to schizotypal symptoms. Finally, they might have been anxious because they were being assessed. For these reasons, we included state-anxiety and state-depression as variables to be controlled for.

**Neurocognitive Tests.** The National Adult Reading Test (NART; Dutch version NLV; Schmand et al. 1992) was used to assess the global level of intellectual functioning. It served as a tool to assess whether subjects fulfilled the inclusion criterion of IQ higher than 70. In addition, IQ was used as a variable to be controlled for in the correlational analyses.

Tests sensitive to frontal lobe performance. We use the terms tests sensitive to frontal lobe performance and tests sensitive to temporal-limbic performance to stay close to the neuropsychological model of Walker and Gale. We are aware that performance on the selected neurocognitive tests (see below) is not restricted to malfunction of one cerebral area but has more determinants. It is not our aim to explore neuroanatomical substrates of dimensions of schizotypy but to investigate associated neurocognitive mechanisms.

**CPT.** The 3-7 version of the CPT (Nuechterlein 1991), a test of sustained attention, was used. It is a relatively easy version of the CPT without high perceptual or information processing loads, but it requires working memory activity. CPT variables used were false alarm rate (CPTF), premature responses (CPTP), and d' (CPTD). False alarm rate refers to the percentage of nontargets that are incorrectly responded to as targets. We used a restricted false alarm variable as well to distinguish between general false alarms and false alarms resulting from impulsive reactions. The premature responses variable refers to those false alarms occurring when subjects reacted immediately after a 3 was presented. Finally, the general CPT variable of d' (an indicator of perceptual sensitivity) was used, referring to the degree to which subjects discriminate between target combinations (3–7) and nontargets.

Consistent evidence suggests that there is deviant CPT performance by schizophrenia patients, their first degree relatives, and schizotypal subjects (for a review, see Nuechterlein 1991). CPT performance in schizophrenia spectrum subjects is stable; therefore, the CPT qualifies as a vulnerability indicator. We wanted to examine whether CPTD is related to PS (according to the review findings) or to NS (according to the Walker and Gale prefrontal hypothesis and the assumption that d' has strong prefrontal determinants, according to Buchsbaum 1990) and whether false alarms and premature reactions are related to DS according to the (dis)inhibition hypothesis (Frith et al. 1991).

**Wisconsin Card Sorting Test.** The Wisconsin Card Sorting Test (WCST; Heaton 1981) is sensitive to frontal lobe functioning (McPherson and Cummings 1998) and was administered in paper-and-pencil form according to the standard instructions described by Heaton. The WCST measures so-called executive functions like conceptual ability, problem solving, and mental flexibility.

WCST variables used were number of categories completed (WCC; indicates conceptual ability) and number of perseverative errors (WCP; indicates mental flexibility). WCST deviances are found throughout the schizophrenia spectrum (van der Does and van den Bosch 1992). In schizotypy studies, WCST deviances of normal subjects are related to all three dimensions, but the strongest association is with NS (Vollema et al., submitted for publication). According to the Walker and Gale prefrontal hypothesis, NS should be related to the WCST, and we investigated this. We also explored whether DS is related to number of perseverative errors, which may represent a failure to inhibit a learned response, according to the (dis)inhibition hypothesis of Frith et al. (1991).

**Verbal Fluency.** Verbal Fluency (Borkowski et al. 1967) is a letter fluency test (using N, A, and M) for reproduction of words from semantic memory. According to Lezak (1983), letter fluency tests qualitatively as prefrontal tests and are more difficult and more sensitive to problems in strategy-guided search processes in semantic memory than category fluency tests are. Variables used were total number of correct words (VFC; indicates ability to retrieve and generate words) and total number of incorrect words (VFI; indicates inability to inhibit incorrectly retrieved words).

Liddle and Morris (1991) and Allen et al. (1993) found that schizophrenia patients with negative symptoms produced few words and those with formal thought disorder produced many incorrect words. The associations of VF with NS (according to the prefrontal hypothesis of Walker and Gale) and DS (according to the [dis]inhibition hypothesis of Frith et al.) will be investigated.

**Temporal-Limbic Test, California Verbal Learning Test.** The Verbal Learning and Memory Test (VLGT; Dutch version of the California Verbal Learning Test; Mulder et al. 1996) is a verbal memory test, which is used in a shortened version. Subjects were presented the list of 16 words once. After 30 minutes they were asked which words they still knew. Variables used were total number of correct words retrieved (VLMC; indicates ability to retrieve information from verbal long-term memory) and total number of incorrect words retrieved (VLFM; indicates incorrectly retrieved information from verbal long-term memory, probably because of disinhibition).

Sass et al. (1992) found an association between retrieval from verbal long-term memory and loss of neurons in the hippocampus. The associations of the VLGT with PS (according to the temporal-limbic hypothesis of Walker and Gale) and with DS (according to the [dis]inhibition hypothesis of Frith et al.) were investigated.
Results

Correlational Analyses. We started with the usual correlational analyses (Pearson; 2-tailed), which showed many associations between schizotypy, neurocognition, and demographic variables. For instance, age and IQ correlated significantly with CPTD (r = –0.28 and 0.50, respectively) and with IDS (r = 0.32 and r = –0.29, respectively). Stratta et al. (1997) showed that age and education (and therefore IQ) also have strong effects on WCST performance. Therefore, partial correlational analyses were executed controlling for the effects of age, IQ, state-anxiety and state-depression, because these variables might influence neurocognitive performance.

Table 1 shows partial correlations (Pearson; 1-tailed because we knew in advance the directions of the correlations) between dimensions of schizotypy and neurocognitive measures. Seventy-two correlations were calculated, and ten were significant at the p < 0.05 level (including the correlation of PS with VLMC at p = 0.05) and four at the p < 0.01 level.

The highest correlations were found between disorganization and CPT. For QDS we found a significant correlation with CPTD (r = 0.33, p = 0.006). IDS was significantly correlated with CPTF (r = 0.59, p = 0.000), CPTD (r = –0.30, p = 0.011), and CPTP (r = 0.35, p = 0.004). IPS and INS were not correlated with any of the neurocognitive measures.

Multiple Regression Analyses. To investigate whether schizotypy scores could be predicted by performance on neurocognitive tests, multiple regression analyses were executed.

Variables used in the analyses (except the nominal variable of gender) were standardized to z scores in order to use standard variances in the regression analyses. For all schizotypal measures (QPS, QDS, QNS, IPS, IDS, INS, PS, and NS), multiple regression analyses were executed in two steps. First, the variables of gender, age, IQ, state-anxiety, and state-depression were used as independent variables (all model 1s). Thereafter, the neurocognitive variables CPTF, CPTD, CPTP, WCP, WCC, VFC, VFI, VLMC, and VLMI were added in the analyses for each measure of schizotypy separately (all model 2s).

For all regression analyses, values of multiple r (absolute value of correlation coefficient between dependent and independent variables), r^2 (proportion of variance explained by the model), r adjusted (r^2 for this sample, corrected for population parameters), F (test that all coefficients are 0 and that no linear relationship exists between dependent and independent variables), p (significance level for F), and beta (partial regression coefficient) are shown in table 2. Betas are provided only when their probability level is p < 0.05 and when r values are lower than –2 or higher than 2 (Norusis 1995).

Many variables were included in the model 2 analyses. In particular, the neurocognitive variables might inter-
correlate; therefore, we tested for collinearity. Testing for collinearity did not reveal condition indexes for independent variables higher than 15, indicating that the independent variables in this study did not intercorrelate significantly.

In predicting QPS, the multiple $r^2$ of 0.22 for model 1 is significant at the $p < 0.05$ level but rather low. As can be seen in table 2, only depression (beta = 0.33) contributed significantly to the prediction of QPS. Adding the neurocognitive variables (model 2) resulted in a higher multiple $r^2$ of 0.37, but the F statistic was insignificant. However, betas were significant for depression (beta = 0.43) and verbal long-term memory (beta = -0.34). The addition of neurocognitive variables to demographic and state-psychopathology variables did not improve the prediction of QPS. With respect to the significant beta for verbal long-term memory and the significant partial correlation at the $p < 0.05$ level (table

Table 2. Multiple regressions predicting scores on dimensional measures of schizotypy

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<th>$r$</th>
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<td>Model 1</td>
<td>0.469</td>
<td>0.22</td>
<td>0.15</td>
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<td>0.016</td>
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<td>0.067</td>
<td>0.43 (SCL-90 depression)</td>
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<td>Model 1</td>
<td>0.500</td>
<td>0.25</td>
<td>0.18</td>
<td>3.70</td>
<td>0.006</td>
<td>0.30 (SCL-90 anxiety)</td>
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<td>Model 2</td>
<td>0.640</td>
<td>0.41</td>
<td>0.22</td>
<td>2.10</td>
<td>0.027</td>
<td>0.28 (gender)</td>
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<td>0.32 (SCL-90 anxiety)</td>
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<td>0.33 (CPTP)</td>
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<td>QNS</td>
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<tr>
<td>Model 1</td>
<td>0.610</td>
<td>0.38</td>
<td>0.32</td>
<td>6.70</td>
<td>0.000</td>
<td>0.43 (SCL-90 depression)</td>
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<td>Model 2</td>
<td>0.700</td>
<td>0.50</td>
<td>0.33</td>
<td>2.96</td>
<td>0.003</td>
<td>0.46 (SCL-90 depression)</td>
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<td>-0.30 (VLMC)</td>
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<td>Model 1</td>
<td>0.370</td>
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<td>0.06</td>
<td>1.79</td>
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<td>0.460</td>
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<td>-0.02</td>
<td>0.9</td>
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<td>Model 1</td>
<td>0.490</td>
<td>0.24</td>
<td>0.17</td>
<td>3.44</td>
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<td>0.58</td>
<td>0.44</td>
<td>4.17</td>
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<td>0.56 (CPTF)</td>
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<td>-0.29 (IQ)</td>
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<td>Model 1</td>
<td>0.450</td>
<td>0.21</td>
<td>0.13</td>
<td>2.80</td>
<td>0.024</td>
<td>0.43 (SCL-90 depression)</td>
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<td>0.510</td>
<td>0.26</td>
<td>0.04</td>
<td>1.17</td>
<td>0.333</td>
<td>0.38 (SCL-90 depression)</td>
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<td>Model 1</td>
<td>0.520</td>
<td>0.27</td>
<td>0.20</td>
<td>4.07</td>
<td>0.003</td>
<td>0.33 (SCL-90 depression)</td>
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<td>0.590</td>
<td>0.35</td>
<td>0.15</td>
<td>1.74</td>
<td>0.080</td>
<td>0.37 (SCL-90 depression)</td>
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<td>NS</td>
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<td>Model 1</td>
<td>0.580</td>
<td>0.34</td>
<td>0.28</td>
<td>5.71</td>
<td>0.000</td>
<td>0.46 (SCL-90 depression)</td>
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<tr>
<td>Model 2</td>
<td>0.650</td>
<td>0.42</td>
<td>0.25</td>
<td>2.41</td>
<td>0.013</td>
<td>0.44 (SCL-90 depression)</td>
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Note. —CPT = Continuous Performance Test; CPTF = false alarm rate (CPT); CPTP = premature responses (CPT); IDS = Interview Disorganisation Schizotypy (SIS-R); INS = Interview Negative Schizotypy (SIS-R); IPS = Interview Positive Schizotypy (SIS-R); NS = negative schizotypy, dimension score (SPQ and SIS-R); PS = positive schizotypy, dimension score (SPQ and SIS-R); QDS = Questionnaire Disorganisation Schizotypy (SPQ); QNS = Questionnaire Negative Schizotypy (SPQ); QPS = Questionnaire Positive Schizotypy (SPQ); SCL-90 = Symptom Checklist-90; SIS-R = Structured Interview for Schizotypy–Revised; SPQ = Schizotypal Personality Questionnaire; VLMC = number of correct words retrieved (Verbal Long-Term Memory Test). Model 1s: One measure of schizotypy as dependent variable and as independent variables gender, age, IQ, state-depression, and state-anxiety. Model 2s: One measure of schizotypy as dependent variable and as independent variables those from model 1 added with nine neurocognitive measures.

* Betas are provided only when $|t| > 2$ or $|t| < -2$ and their $p < 0.05$. 

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1), we argue that a modest association exists between this variable and QPS.

In predicting QDS, the multiple $r^2$ of 0.25 for model 1 was rather low but highly significant at the $p < 0.01$ level. Anxiety contributed significantly to this prediction (beta = 0.30). Adding the neurocognitive variables resulted in a significant ($p < 0.05$) and higher multiple $r^2$ of 0.41. Significant contributors in this second analysis of QDS were gender (beta = 0.28), anxiety (beta = 0.32), and CPTP (beta = 0.33).

In predicting QNS, the multiple $r^2$ of 0.38 for model 1 is highly significant at the $p < 0.01$ level and represents a modest correlation. Table 2 shows that depression (beta = 0.43) contributed significantly to the prediction of QNS. Adding the neurocognitive variables resulted in a significant and higher multiple $r^2$ of 0.50: this addition improved the prediction. It was caused by verbal long-term memory (beta = -0.30).

In predicting INS, multiple $r^2$'s of both model 1 and model 2 were insignificant. Demographic, state-psychopathology, and neurocognitive variables seemed to be unrelated to INS.

In predicting IDS, the multiple $r^2$ of 0.24 for model 1 is low but significant at the $p < 0.01$ level. The majority of the variance of IDS was contributed by age (beta = 0.24) and IQ (beta = -0.29). Adding the neurocognitive variables resulted in a higher significant ($p < 0.01$) and rather high multiple $r^2$ of 0.58. The majority of the variance of IDS in this second analysis was contributed by CPTF (beta = 0.56).

In predicting IPS, the multiple $r^2$ of 0.21 for model 1 was rather low but significant ($p < 0.05$). The majority of the variance of IPS was contributed by depression (beta = 0.43). The addition of the neurocognitive variables resulted in a significant ($p = 0.033$) and slightly higher multiple $r^2$ of 0.26. But the majority of the variability of INS was contributed by depression.

In predicting PS, the multiple $r^2$ of 0.27 for model 1 was rather low but significant ($p < 0.05$). The majority of the variance of PS was contributed by depression (beta = 0.33). The addition of the neurocognitive variables to model 1 resulted in nonsignificant $t$ values ($p = 0.080$).

In predicting NS, the multiple $r^2$ of 0.34 for model 1 was highly significant ($p < 0.01$). The majority of the variance of NS was contributed by depression (beta = 0.46) and IQ (beta = -0.23). The addition of the neurocognitive variables resulted in a higher $r^2$. The majority of variance was contributed by depression (beta = 0.44).

Discussion

The aim of this study was to explore some neurocognitive correlates of dimensions of schizotypy in first degree relatives of schizophrenia patients. Three general conclusions can be drawn. First, for DS we found correlations in expected directions (for PS to a much lesser extent, and for NS we found an unexpected association). Second, the pattern of correlations differed from the pattern found in schizotypy studies with normal subjects. Third, state-psychopathology is significantly correlated to all three dimensions of schizotypy. We will discuss the general conclusions, then the limitations of this study and the implications of the findings.

Dimensions of Schizotypy and Their Neurocognitive Mechanisms. PS was hardly related to any neurocognitive measure in this study. It was only slightly related to verbal long-term memory. Self-report PS tends to go with poorer retrieval from verbal long-term memory. It converges with a report by Flaum and Andreasen (1995) reporting a reduced hippocampal volume in subjects with high PS. Our findings only weakly support the temporal-limbic hypothesis of PS postulated by Walker and Gale. This hypothesis links PS, verbal retrieval deficits, and the hippocampus. It may agree with the hypothesis of Hemsley (1992), who argued that hippocampal dysfunction, psychotic tendencies, and an obstructed access to past regularities about common-sense knowledge are related to each other. Our findings suggest that the tendency to develop psychotic-like experiences seems only weakly related to problems in retrieving information from verbal long-term memory. However, verbal long-term memory was related to (self-report) NS as well. Therefore, the (weak) association with PS is not specific. This relationship is mainly restricted to paranoid ideation, which loads on PS and NS as well, and may suggest that during the formation and maintenance of paranoid ideas subjects do not have sufficient access to stored common-sense knowledge in verbal long-term memory. Therefore, their ideas cannot be consensually validated by this inaccessible information.

NS too was hardly related to any neurocognitive measure. We found only a modest relation with verbal long-term memory. Higher scores on self-report NS tend to go with poorer retrieval from verbal long-term memory. This is mainly due to the correlation between paranoid ideation (loading on PS and NS as well) and verbal long-term memory ($r = -0.29, p < 0.05$).

NS was not related to any test sensitive to frontal lobe performance. Therefore, we found no evidence for the prefrontal hypothesis of NS. In line with our findings are earlier reports about first degree relatives by Keefe et al. (1994) and Stratta et al. (1997). They reported normal WCST performance of first degree relatives. Stratta et al. (1997) argued that the WCST is related to the disease process of schizophrenia only because of its close connection to negative symptoms.
Our findings support the hypothesis of Stratta et al. (1997) that the WCST may not be a good trait marker of vulnerability to schizophrenia. Executive dysfunction, including mental inflexibility and poor planning, does not seem to underlie the social-interpersonal deficits of NS. Our findings suggest that variables from other domains may turn out to be stronger determinants of social withdrawal and schizotypal thinking and the like. One might think of personality factors like coping and motivation.

DS had the highest correlations with neurocognitive measures. It was strongly related to cognitive disinhibition during CPT performance. The findings differ quantitatively for IDS and QDS. Premature responses were related to QDS: higher scores on this schizotypy measure (including self-judgments about odd speech and odd behavior) tended to go with an increase in premature reactions on the CPT. False alarms were strongly related \( r = 0.59 \) to interview DS: higher scores on IDS (including problems in goal directedness of thinking) tended to go with an increase of incorrect responses during CPT performance. Although both CPT measures were intercorrelated \( r = 0.56 \), the divergent findings for DS measures are not surprising because their intercorrelation was very low \( r = -0.11 \). The findings strongly support the cognitive (dis)inhibition hypothesis of DS: odd speech (by SPQ) and problems in goal directedness of thinking (by SIS-R) are related to the production of incorrect responses during CPT performance. A general failure of cognitive inhibition may underlie both the lack of goal directedness in schizotypal thinking and the premature and incorrect psychomotor responses during the CPT. Additional evidence for cognitive disinhibition associated with DS was found. Incorrect retrieval from verbal long-term memory was significantly correlated to IDS in the correlational analyses, although in the multiple regression it fell to just below statistical significance \( r = 1.9 \).

**Patterns of Neurocognitive Correlations in Different Samples.** The pattern of neurocognitive correlates of dimensions of schizotypy in this relatives study seems to differ from the pattern found in normal subjects. We found verbal long-term memory correlated to PS and NS, and CPT to DS, and we found no correlations with the WCST for NS. In a meta-analysis on neurocognitive correlates of schizotypy in normal subjects, we concluded that PS is correlated to CPT and NS to WCST (Vollema et al., submitted for publication). Few studies have investigated the neurocognitive correlates of DS.

There may be various reasons for this divergency of findings. First, studies using normal subjects mainly used one particular subscale instead of dimensional scales. Summing scores on subscales and transforming them into dimensional scores may mask associations between a neurocognitive test and subtraits. For example, the Paranoid Ideation subscale of the SPQ correlated with the CPT variable of \( d' \) \( r = -0.45, p < 0.001 \), but the correlation of the dimensional score PS with CPT \( d' \) was insignificant. Second, the current study controlled for the effects of age, gender, IQ, state-anxiety, and state-depression. As can be seen in table 2, state-depression was the strongest predictor for PS and NS. In schizotypy studies using normal subjects, these variables have seldom been controlled for, except, for instance, by Lenzenweger and Korfine (1994). Third, sample differences may contribute to the different findings. Kendler et al. (1991) and Grove et al. (1991) also did not find an association between CPT and PS in first degree relatives. This would indicate that different samples may have different patterns of neurocognitive correlations of schizotypal dimensions.

The pattern of correlations from this study seems more in line with the pattern of neurocognitive correlates of schizophrenia symptom dimensions. In schizophrenia studies, significant associations between positive symptoms and Latent Inhibition (as a test sensitive to hippocampal function; Hemsley 1992), between formal thought disorder and CPT (Frith et al. 1991), and between negative symptoms and WCST (Wagman et al. 1987) are reported. The findings diverge with respect to the WCST and the negative dimensions, but with respect to the positive and disorganization dimensions, the findings converge strongly. In particular, the findings with respect to DS and cognitive disinhibition (during CPT performance) are highly similar across both samples. Nuechterlein et al. (1986) found a strong association between formal thought disorder and false alarms on the CPT in schizophrenia patients. Frith et al. (1991) confirmed this finding and concluded that formal thought disorder is associated with the production of incorrect responses during CPT performance. This similarity of a relation between CPT and DS in first degree relatives and CPT and formal thought disorder in schizophrenia patients is striking. It supports the hypothesis that in first degree relatives, false alarms and premature reactions on the CPT and problems in goal directedness of thinking are manifestations of the familial biological vulnerability to schizophrenia.

**State-Psychopathology.** State-psychopathology (in particular depression) appeared to be the best predictor for scores on PS and NS of first degree relatives. Although depression and anxiety scores of the relatives were just above normal limits (mean for SCL–90 depression = 50th percentile and mean for SCL–90 anxiety = 60th percentile compared to normal controls), they heavily determined schizotypy scores. For example, depression correlated significantly with dimensions of PS \( r = 0.34, p < 0.01 \) and NS \( r = 0.45, p < 0.01 \). As hypothesized by Meehl...
(1990), state-psychopathology is likely to co-occur with schizotypal phenomena. Some additional explanations can be given. First, during the assessments they may fear detection of schizotypal phenomena, which they are so familiar with in their relative with schizophrenia. Second, their anxiety and depression may have a trait character. Many subjects indicated that in reaction to the schizophrenia disorder of their relative and its consequences (e.g., long-term hospitalization, medication, deterioration), they developed symptoms of anxiety and depression. For these reasons it is well advised to control for the effects of anxiety and depression in future studies into schizotypy using first degree relatives of schizophrenia patients.

Limitations and Implications. Limitations of this study are as follows. First, a type I error may have occurred: Did some of the significant relationships occur by chance, because many correlational analyses (72) were executed? We stressed only significant associations between schizotypal dimensions and neurocognitive measures that occurred in both the correlational and multiple regression analyses. The correlations between DS and CPT (CPTF and CPTP) and between PS and verbal memory (VLMC) were all in the predicted directions, therefore reducing the chance for a type I error.

Second, unfortunately we are not sure whether our sample is representative. Some subjects indicated that the relative most similar to the schizophrenia patient refused to participate. If some highly schizotypal relatives were added to the sample, correlations between schizotypal dimensions and neurocognitive measures would likely increase. We have indications that relatives differ on SPQ dimensions compared to normal controls (from Kremen et al. 1998). We found means for PS (5.2), DS (3.9), and NS (8.1); and Kremen et al. found 3.4, 1.9, and 4.9, respectively. Relatives in the Kremen et al. study reached mean scores of 3.8, 2.3, and 5.8, respectively. Although we reallocated some of the SPQ items based on a confirmatory item factor analysis (see Instruments section), our scores can be (globally) compared to those of Kremen et al. (1998). This comparison shows in particular that the scores of our relatives differ from the scores of the normal controls from Kremen et al. and even seem somewhat higher than the scores of their study’s relatives. With respect to the neurocognitive measures, our study can be compared with the study of Keefe et al. (1994), in which relatives’ scores on the WCST variables categories completed and perseverative errors were 4.8 and 18, respectively, while normal controls’ scores were 5.2 and 15.6, respectively. We found 4.4 for categories completed and 21.8 for perseverative errors. So our WCST findings are more in line with the performances of the relatives than with the controls in the study by Keefe et al. (1994). The same holds for the performance on letter fluency. Keefe et al. (1994) reported a mean amount of 1 words of 13.3 for relatives and 17.9 for normal controls. Our total amount of n words was 14.2. In sum, with respect to schizotypal traits and neurocognitive measures, our relatives performed much the way relatives in other studies did and were more deviant than controls (Keefe et al. 1994; Kremen et al. 1998).

Third, relatives could have responded defensively. Various authors have pointed to this particular problem (Grove et al. 1991; Lenzenweger 1993). Relatives may fear the detection of schizotypal phenomena. We have no indications that the relatives responded defensively to SPQ and SIS–R (see above). Furthermore, in a multitrait-multimethod study, method variation (including a defensive response set and the like) contributed only moderately to the total variance on schizotypy measures (Vollme and Ormel, submitted for publication). It turned out that the scores on SPQ and SIS–R are mainly determined by trait factors (i.e., PS, DS, and NS) and to a much lesser extent by method factors (i.e., the format of items and response categories as well as test-taking attitudes).

Different versions of the CPT have been used in studies of schizotypy and schizophrenia. The 3–7 version has a working memory load and is easier than, for example, the Degraded Stimulus version (Nuechterlein 1991). This latter version requires higher levels of mental effort. Nuechterlein argued that the Degraded Stimulus version would be more sensitive to deviances in high-risk samples. Therefore, it is surprising that we found strong correlations between DS and false alarms on the CPT 3–7. It suggests that the 3–7 version is able to detect subtle deviances in first degree relatives.

Future research into the neurocognition of schizotypy can be directed to the following areas. First, the discrepancy between the patterns of neurocognitive correlates of schizotypy in normal subjects versus first degree relatives deserves attention. Normal studies should control for variables like sex, age, and IQ before making more definitive conclusions. Increasing evidence for this discrepancy will lead to questions about the usefulness of normal subjects to schizotypy research. Second, the modest association between PS and verbal long-term memory needs to be firmly replicated before hypotheses about hippocampal (and verbal memory) dysfunctioning underlying psychotic-like schizotypy can be tested. Alternative tests sensitive to hippocampal dysfunction may be used. Third, studies may be executed to dissect the subcomponents of CPT performance responsible for the strong correlation with DS. Fourth, more studies are needed to assess the ability of the WCST as a vulnerability marker. Finally, it is still advised to make use of observational scores for DS. The evidence from this study supports Kendler et al.’s (1996) hypothesis.
that interviews are better suited for the assessment of schizotypal signs than questionnaires are. And we have to wait until questionnaires are available assessing disorganization in a valid way.

We investigated the neurocognitive correlates of dimensions of schizotypy in healthy first degree relatives of schizophrenia patients. This sample has many advantages (over samples of schizophrenia patients) for investigating the vulnerability to schizophrenia. Our subjects were motivated and able to participate, showed no psychotic symptoms (or any psychiatric disorder), were medication-free, and were all well-functioning citizens. However, in these healthy subjects we found some highly significant associations between dimensions of schizotypy and neurocognitive measures. The strong associations between DS and incorrect responses during an attentional task may indicate a genetic vulnerability to schizophrenia.

References


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Minority Research Training in Psychiatry

Through a five-year, $2.5 million grant from the National Institute of Mental Health, the American Psychiatric Institute for Research and Education (APIRE) is seeking through the Program for Minority Research Training in Psychiatry (PMRTP) to increase the number of minority psychiatrists entering the field of psychiatric research.

The program provides medical students with funding for stipends, travel expenses, and tuition for an elective or summer experience in a research environment, with special attention paid to trainees’ career development in research. In addition, stipends are available for a limited number of one- or two-year postresidency fellowships for minority psychiatrists. Residents may engage in full-year research training during the last year of psychiatric residency or in “year off” research training.

Training takes place at research-oriented departments of psychiatry in major U.S. medical schools and other appropriate sites throughout the country. An individual at the site (the research “mentor”) is responsible for overseeing the research training experience.

Administered by the American Psychiatric Institute for Research and Education, the program includes outreach efforts to identify minority medical students and residents who are potential researchers and to put them in touch with advisors who counsel them about careers in psychiatric research. Additional activities assist fellows and alumni in their research career development.

The director of the PMRTP is James Thompson, M.D., M.P.H.; the project manager is Ernesto Guerra. An advisory committee of senior researchers and minority psychiatrists developed guidelines for applicants and criteria for selection. The members of this committee evaluate and select trainees, oversee the research training experiences, and play a role in evaluating the effectiveness of the program.

December 1 is the deadline for applications for residents seeking a year or more of training and for postresidency fellows. For medical students, applications are due three months before training is to begin. Summer medical students who will start their training by June 30 should submit their applications by April 1.

For more information about the PMRTP, call the toll-free number for the PMRTP, 1-800-852-1390, or 202-682-6225, e-mail eguerra@psych.org, or write to PMRTP at the American Psychiatric Institute for Research and Education, 1400 K Street, NW, Washington, DC 20005.