Indicators of Genetic Liability to Schizophrenia: A Sibling Study of Neuropsychological Performance

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Despite clear evidence of important genetic influences on schizophrenia, identifying the genes involved has been difficult because of the genetic complexity of the phenotype. The use of additional phenotypic measures that are more sensitive to the genetic liability than is the clinical diagnosis should enhance the power to detect small individual genetic effects. The present study assessed the neuropsychological performance of 30 male schizophrenia probands, 30 of their unaffected male siblings, and 20 well controls matched on age, sex, and education in order to identify measures that may be particularly sensitive to the genetic liability to schizophrenia and thus may be useful in gene mapping studies. Siblings showed impaired neuropsychological performance compared to controls on four out of the five measures used. Additional results suggested that Trails B was especially effective at discriminating index siblings from controls, thus supporting its potential utility as a candidate quantitative phenotype to aid in gene mapping studies of the disorder.

Key Words: Schizophrenia/genetics/family study/neuropsychological tests/Trail Making Test/Wisconsin Card Sorting Test

Twin and adoption studies have clearly indicated that genes have a major role in the etiology of schizophrenia (Gottesman 1991). Despite suggestive findings for some chromosomal regions (Pulver 2000; Baron 2001; O’Donovan et al. 2003), researchers have been unable to identify which genes contribute to schizophrenia (Moises et al. 1995; Owen 2000). Several features of the genetic epidemiology of schizophrenia conspire to make the task of identifying such genes difficult. First, observed familial risk patterns for schizophrenia suggest that multiple genes contribute to liability (McGue and Gottesman 1989; Risch 1990; Pogue-Geile and Gottesman 1999). In addition, the discordance rate among monozygotic twins (Gottesman 1991) supports an etiologic role of non-shared environmental influences, implying that there are individuals who possess some genetic liability to the disorder but do not develop clinical schizophrenia (Gottesman and Bertelsen 1989). As initially pointed out by Gottesman and Shields (1967), these features suggest that although liability to schizophrenia is itself highly heritable ($h^2$ estimated at approximately 0.80; Cardno et al. 1999), the effect on the diagnosis of any single specific genetic locus may be relatively small. The slow progress of mapping specific genes for schizophrenia to date reinforces the plausibility of some sort of multifactorial threshold model.

The difficulties for gene mapping efforts presented by such genes of relatively small effect arise from the presence of both false negatives (i.e., individuals with a specific risk allele for schizophrenia who do not meet diagnostic criteria) and false positives (i.e., individuals diagnosed with schizophrenia without a specific risk allele for schizophrenia). Both of these classification errors reduce the power to detect genetic linkage and association in current study designs, although the “cost” of each varies with the design.

Along with increasing sample size, improvements in measurement could increase the statistical power to detect such small effects. Identifying additional phenotypic measures that are more affected by individual schizophrenia liability genes than is the clinical diagnosis would help reduce the false negative and/or false positive errors and thus be especially useful to genetic linkage and association studies. At present, one of the best screening strategies to identify such potentially useful endophenotypes (Gottesman and Shields 1972; Gottesman and Gould 2003) is to search for characteristics that discriminate nonschizophrenia relatives of schizophrenia probands from controls. Because such relatives should show higher rates of risk-increasing alleles for schizophrenia compared to the general population, characteristics that maximally discriminate relatives of patients from controls may be especially sensitive to specific genes and/or overall genetic liability for schizophrenia. The current study used this strategy in an effort to identify quantitative traits that may be particularly sensitive to the genetic liability to schizophrenia and thus may be useful in increasing the power in genetic linkage and association studies of schizophrenia.

Numerous psychological abnormalities have been detected in unaffected first degree relatives of schizophrenia
probands, ranging from eye-tracking deficits (e.g., Holzman 1987) to schizotypal symptoms (e.g., Grove et al. 1991). The present study, however, focused on neuropsychological assessments of cognitive functioning as being potentially sensitive to genetic liability for several reasons. First, aside from the defining symptoms of schizophrenia (e.g., hallucinations and delusions), one could argue that various abnormalities of cognitive functioning are the next most discriminating feature of the diagnosis itself, with differences of 1.5 standard deviations (SDs) between the means of patients and normal controls being commonly observed, depending on the specific task (Johnson-Selridge and Zalewski 2001). In general, these neuropsychological impairments remain during periods of remission (Nopoulos et al. 1994), are not solely medication artifacts (Saykin et al. 1994), and on average are more severe in schizophrenia compared to other diagnoses (Johnson-Selridge and Zalewski 2001). In addition to their robust empirical association with the schizophrenia diagnosis, cognitive abnormalities have theoretical attractions. Although the specifics are not yet established, brain abnormalities are universally hypothesized as the pathophysiology of schizophrenia signs and symptoms (e.g., Gur and Pearson 1993; Willner 1997), and neuropsychological assessments of cognitive functions have the advantage that many were developed to be sensitive (although rarely specific) to known brain abnormalities among neurological patients. Thus, such assessments may be sensitive to aspects of the pathophysiology of schizophrenia and, if so, may be better at indicating genetic liability to schizophrenia than the diagnosis itself. Although it is clear that the pathophysiology of diagnosed schizophrenia is only a fallible guide to the pathophysiology of genetic liability to schizophrenia given the importance of environmental risk factors, it is nevertheless a plausible heuristic strategy.

A number of studies over the past decade have followed this general approach and have reported a variety of neuropsychological abnormalities in first degree relatives (for review, see Kremen et al. 1994). However, many specific findings have been mixed (e.g., Stratta et al. 1997; Egan et al. 2001), and their interpretation is often complicated by methodological factors. For example, studies often have not included analyses that controlled for index relatives’ psychopathology (e.g., Roxborough et al. 1993; Cannon et al. 1994; Harris et al. 1996). Such comparisons between index relatives with diagnosable psychopathology and control participants without diagnoses are sensitive to nonspecific effects of psychopathology on neuropsychological performance and thus may overestimate deficits in index relatives. Studies have also often combined more than one class of relative in their first degree relative sample (e.g., Keefe et al. 1994; Faraone et al. 1995; Mirsky et al. 1995; Stratta et al. 1997; Koren et al. 1998; Toomey et al. 1998). Classes of relatives (i.e., siblings, parents, and offspring of patients) differ on several factors, such as age, genetic effects (siblings share dominance effects, but parents and offspring do not), and environmental experiences (e.g., offspring reared by a parent with schizophrenia) that could influence their neuropsychological performance. Combining multiple relative classes may cloud attempts to detect genetic liability to schizophrenia and could produce spurious results to the extent that it erodes matching with the control group on age.

The current study therefore sought to investigate neuropsychological deficits among unaffected relatives of schizophrenia probands with the ultimate goal of aiding linkage studies of schizophrenia. Specifically, a multivariate approach was employed to address questions about which neuropsychological measures may most effectively discriminate unaffected siblings of patients from control participants. In addition, the study had methodological advantages that included the use of only siblings of patients for the first degree relative sample, analyses that controlled for index sibling psychopathology, and close control group matching on age, sex, and education.

The primary questions addressed were as follows:

1. Do nonschizophrenia siblings of patients show significantly impaired neuropsychological performance compared to control participants on the selected neuropsychological tests?
2. Of these tests, which best discriminate between siblings and control participants?
3. Do nonschizophrenia siblings of patients display greater variance on and covariance between neuropsychological measures than control participants?
4. Do index siblings without any psychiatric diagnosis show performance deficits compared to control participants?

Method

To address these questions, neuropsychological tests were administered to three groups of subjects: schizophrenia or schizoaffective male probands, their male full biological siblings, and unrelated well male controls. (See the following for reports on samples that overlap with the current sample: Steinhauser et al. 1991; Condray and Steinhauser 1992; Condray et al. 1992, 1995, 1996; Steinhauser and Hakerem 1992.)

Participants

Index patient probands. Index patient probands were ascertained from the outpatient Mental Hygiene Clinic of the Highland Drive Division, Veterans Administration Pittsburgh Healthcare System, in Pittsburgh, PA. Screening criteria were as follows: male gender, DSM–III (APA 1980) chart diagnosis of schizophrenia or schizoaffective
disorder, age between 18 and 56 years, no history of substance abuse substantial enough to question the diagnosis of schizophrenia, no history of a diagnosed neurological disorder or medical condition known to be associated with neuropsychological impairment (e.g., epilepsy, stroke), and availability of at least one full biological brother residing in the greater Pittsburgh area. Patient probands also needed to have been clinically stable on their current medication for at least 1 month prior to time of assessment, to minimize performance variation due to clinical state. Potential probands who met these criteria were assessed with the Schedule for Affective Disorders and Schizophrenia–Lifetime Version (SADS–L; Spitzer and Endicott 1975) by trained interviewers and were selected for participation if they met Research Diagnostic Criteria (RDC; Spitzer et al. 1981) for definite lifetime diagnosis of schizophrenia or schizoaffective disorder—mainly schizophrenia. Thirty index patient probands were recruited.

Index siblings. For each of the 30 index probands, one randomly selected full biological male sibling was recruited. For those cases in which the index proband had more than one brother, brothers were ranked by birth order and a table of random numbers was used to determine the order in which to approach them for recruitment. Sibling screening criteria were age between 18 and 56 years and no history of a diagnosed neurological disorder or medical condition known to be associated with neuropsychological impairment. Potential index siblings were assessed by trained interviewers with the SADS–L, the Structured Interview for DSM–III Personality Disorders (SIDP; Stangl et al. 1985), and the Drug and Alcohol section of the Diagnostic Interview Schedule (DIS; Robins et al. 1981) for DSM–III substance abuse diagnoses. Siblings were excluded from participation if they met RDC for schizophrenia or schizoaffective disorder. Otherwise, psychopathology was free to vary. Thirty siblings were recruited and assigned to one of three groups, based on their psychopathology status. The Schizophrenia Spectrum Disorder group comprised siblings who met criteria for DSM–III Cluster 1 personality disorder (i.e., schizotypal, paranoid, or schizoid, according to the SIDP). The Non-spectrum Disorder group included siblings who met criteria for an RDC diagnosis or a DSM–III Axis II disorder that was not a schizophrenia spectrum disorder. The Nondiagnosed group comprised siblings who did not meet criteria for any RDC diagnosis or DSM–III Axis II disorder.

Well controls. Potential control participants were recruited via advertisements in local newspapers. Initial screening criteria, assessed via a brief telephone interview, were as follows: male gender, age between 18 and 56 years, no history of a diagnosed neurological disorder or medical condition known to be associated with neuropsychological impairment, and no history of obvious psychopathology or substance abuse. Those who met initial criteria were assessed via in-person interviews with the SADS–L, the SIDP, and the Drug and Alcohol section of the DIS. Potential controls were excluded if they met criteria for any RDC diagnosis or DSM–III Axis II disorder, or had a family history of psychosis as assessed by Family History–RDC (Andreasen et al. 1977). Selection of control participants was further guided by the goal of matching the controls to the siblings at a group level on age and years of education. Twenty unrelated control participants were included in the study.

The structured interviews of all subjects were conducted by one of two trained interviewers. Lifetime RDC and DSM–III Axis II diagnoses were assigned by an experienced diagnostic committee using the SADS–L and SIDP interviews and hospital charts, if available.

Neuropsychological Measures

The following five neuropsychological tests were selected because they have been shown to discriminate between individuals with schizophrenia and controls and as a group assessed several cognitive domains while emphasizing frontal lobe functions. Specifically, the Block Design subtest from the Wechsler Adult Intelligence Scale–Revised (WAIS–R; Wechsler 1981) was used to assess spatial abilities. The Trail Making Test–Part B (Army Individual Test Battery 1944; administered and scored according to Reitan 1958) was used as a measure of attention, sequencing ability, and visual scanning. Time in seconds to complete the task was recorded. The Wisconsin Card Sorting Test (WCST; Berg 1948), a measure of executive processes (e.g., abstraction, inhibition, perseveration), was administered and scored according to the WCST manual (Heaton 1981). Two measures were used from the WCST: perseverative errors, as the test’s indexes of perseveration are considered to be sensitive to frontal lobe damage (Lezak 1995), and nonperseverative errors (as an index of nonspecific errors). Two verbal reasoning subtests from the Receptive Speech Scale of the Luria-Nebraska Neuropsychological Battery were used (Golden et al. 1980): the Relational Concepts test, which assesses verbal reasoning and comprehension, and the Verbal-Spatial Relations test, which taps both verbal comprehension and spatial orientation. Scoring of both tests followed the Luria-Nebraska manual, with higher scores reflecting increased errors and thus poorer performance.

The WAIS–R Information subtest (Wechsler 1981) was also administered as a control measure of general verbal intelligence.

Procedure

After the clinical interviews, participants completed several computerized cognitive tasks and event-related
potential measurements, the findings of which are reported elsewhere (Steinhauer et al. 1991). After a brief break, the participants were then administered the neuropsychological tests by a trained examiner, with testing lasting approximately 1 hour. The examiner was not blind to group membership. Tests were administered in the following fixed order: Information, Block Design, Relational Concepts, Verbal-Spatial Relations, Trail Making Test–Part B, and WCST.

Results

Sample Characteristics. Table 1 provides demographic and clinical characteristics of the participant groups. In the absence of any directional hypotheses, the probability values for the tests of group demographic differences presented below are all 2-tailed.

Index probands. Of the 30 index probands, 21 were diagnosed with schizophrenia and 9 were diagnosed with schizoaffective disorder—mainly schizophrenia according to the RDC (7 depressed type, 2 manic type). All probands also met DSM–III criteria for schizophrenia. In addition, 7 probands met DSM–III criteria for substance abuse.

Index siblings. As noted, brothers of index probands were randomly ranked to determine the order in which to approach them for recruitment. The first ranked brother was successfully recruited in 77 percent of the cases. In the remaining cases, the second (17%) or third (6%) ranked brother was recruited. The second and third ranked brothers (n = 7) did not differ significantly from the first ranked brothers (n = 23) on education, socioeconomic status, or general verbal ability (all p’s > 0.136), although they were significantly younger than the first ranked brothers (mean = 30.86, SD = 10.46; mean = 38.91, SD = 8.04, respectively; t = 2.17, p = 0.039).

The breakdown into psychopathology subgroups, as described earlier, was as follows: the Schizophrenia Spectrum Disorder group (n = 4), the Nonspectrum Disorder group (n = 15), and the Nondiagnosed group (n = 11). All four siblings in the Schizophrenia Spectrum Disorder group met criteria for schizotypal personality disorder, and two also had a history of substance abuse. The most common diagnoses among the 15 Nonspectrum Disorder siblings were (nonhierarchical): substance abuse or dependence (13), mood (3), anxiety (2), antisocial personality (2), and other nonspectrum personality disorders (2). The three sibling subgroups did not differ significantly on age, years of education, socioeconomic status, or general verbal ability as assessed by the Information subtest (analyses of variance [ANOVAs]; all p’s > 0.176).

Well controls. Of the 110 potential control participants screened over the telephone, 82 were ruled out, most frequently because of a history of substance abuse or depression. Several were also screened out in an attempt to match controls to index siblings on age and education. Of the 28 who were interviewed in person, 8 were ruled out because of the presence of RDC or DSM–III Axis II diagnoses.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Index probands (n = 30)</th>
<th>Index siblings (n = 30)</th>
<th>Well controls (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>36.63 (6.92)</td>
<td>37.03 (9.15)</td>
<td>34.35 (7.92)</td>
</tr>
<tr>
<td>Yrs of education, mean (SD)</td>
<td>12.60 (1.90)</td>
<td>13.50 (2.45)</td>
<td>13.65 (1.76)</td>
</tr>
<tr>
<td>Current personal socioeconomic status, mean (SD)¹</td>
<td>4.73 (0.45)</td>
<td>3.50 (1.04)</td>
<td>3.55 (0.69)</td>
</tr>
<tr>
<td>WAIS–R Information, mean (SD)²</td>
<td>9.93 (2.95)</td>
<td>10.50 (2.66)</td>
<td>10.70 (2.30)</td>
</tr>
<tr>
<td>Age at first psychiatric hospitalization, mean (SD)</td>
<td>21.17 (4.25)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Duration of illness, mean (SD)³</td>
<td>15.33 (7.77)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mos since last hospitalization, median (range)</td>
<td>18 (2–204)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>% on antipsychotic medication</td>
<td>93.33%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>% on antiparkinsonian medication</td>
<td>56.67%</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Note.—SD = standard deviation; WAIS–R = Wechsler Adult Intelligence Scale–Revised.
¹Current personal socioeconomic status as measured by Hollingshead’s Two-Factor Index of Social Position (1957; 1 = highest, 5 = lowest).
²WAIS–R age-corrected scores (mean = 10, SD = 3 in standardization sample) appear here, but raw scores were used in analyses.
³As measured by years since first hospitalization.
Group Demographic Comparisons. Index probands, index siblings, and control participants did not differ significantly on age, years of education, or general verbal intelligence as assessed by the Information subtest (separate three-group ANOVAs; all \( p > 0.124 \)). As might be expected, an overall mean difference was detected in personal socioeconomic status, \( F(2, 77) = 27.63, p < 0.001 \), with Scheffé post hoc analyses revealing that index probands had a significantly lower current socioeconomic status than both their siblings \( (p < 0.001) \) and controls \( (p < 0.001) \), probably because of the effects of the index probands’ disorder. In contrast, index siblings and controls did not differ significantly in either means or variances on socioeconomic status or any of the other demographic characteristics (pairwise t tests, all \( p > 0.159 \)). Because there was no variation in scores between the index siblings and controls, this measure was generally well matched at the group level on age, education level, socioeconomic status, and verbal intelligence.

Preliminary Analyses. The diagnosis of substance abuse or dependence did not significantly correlate with any of the test measures in either the patient or sibling groups (all \( p > 0.159 \)). Because there was no variation in scores for the Verbal-Spatial Relations test among the control participants (they all received perfect scores), this measure was not included in the remaining analyses.

Group Differences in Neuropsychological Performance. Table 2 presents the neuropsychological test performance by subject group. A one-way three-group multivariate analysis of variance (MANOVA) of the five neuropsychological tests indicated a significant overall group effect, \( F(5, 73) = 577.02, p < 0.001 \). Given the a priori questions of this study, the following presentation of results focuses on the pairwise group comparisons of theoretical interest (i.e., probands vs. controls, siblings vs. controls, probands vs. siblings). Furthermore, given our a priori directional hypotheses, all probability values presented below are 1-tailed unless noted otherwise. In addition, the Bonferroni-corrected probability level is provided in table 3.

Index probands versus controls. As a prelude to analyzing index sibling performance, index proband-control differences were assessed. Despite the comparable performance of probands and controls on the verbal intelligence measure noted above, probands showed significantly impaired performance compared to controls on all of the neuropsychological tests when considered individually. The effect sizes \( (d) \) of the proband-control differences ranged from 2.41 to 0.98 SDs, with a rank order (decreasing) as follows: WCST perseverative errors \( (d = 2.41, t = 4.23, p = 0.001) \), Trails B \( (d = 2.19, t = 4.70, p = 0.001) \), WCST nonperseverative errors \( (d = 1.63, t = 3.49, p = 0.001) \), Relational Concepts \( (d = 1.40, t = 3.19, p = 0.002) \), and WAIS–R Block Design \( (d = –0.98, t = –3.05, p = 0.002) \). Logistic regression was used to investigate these data from a multivariate perspective. As expected, this analysis indicated that the five neuropsychological measures as a set significantly discriminated between index probands and control participants, \( \chi^2 (5, n = 50) = 25.93, p < 0.001 \). Stepwise logistic regression was then performed with the goal of identifying the most parsimonious subset of the five measures that could significantly discriminate between the index probands and controls. Here, Trails B, WCST perseverative errors, and Relational Concepts were all selected to discriminate between probands and control participants when using a probability criterion for inclusion of 0.05, 1-tailed.

Total index siblings versus controls. Table 3 presents the comparisons of neuropsychological performance between the index siblings and controls. Despite the similar verbal intelligence scores obtained by the siblings and control participants (table 1), siblings showed significantly impaired performance compared to controls on all of the neuropsychological measures when considered individually, with the exception of WAIS–R Block Design. The effect sizes of the sibling-control differences...
Box’s M indicated that the Sibling covariance structure controls (Table III). The neuropsychological measures employed here were sensitive to the genetic liability to the disorder. Siblings compared to controls would be expected on measures sensitive to the genetic liability to schizophrenia, greater performance variance among siblings compared to controls, \( F(15, 6625.23) = 2.32, p = 0.003 \). Specifically, several of the correlations between the neuropsychological measures were significantly greater in the sibling group than the control group according to Fisher’s \( z \) tests. Such findings suggest the presence of some additional latent source of performance covariance present in the sibling but not in the control group (e.g., genetic variation that affects more than one test).

**Sibling psychopathology subgroups.** Because of the low number of siblings in the Schizophrenia Spectrum group, the Spectrum and Nonspectrum groups were combined to form the Diagnosed group for these analyses. A two-group MANOVA of the five neuropsychological test measures indicated no significant overall differences between the Diagnosed and Nondiagnosed siblings, \( F(5, 24) = 0.70, p = 0.623 \).

Of special theoretical importance is the comparison of the nondiagnosed index siblings and the control participants. This is a particularly conservative test of neuropsychological abnormalities among siblings because any possible nonspecific effect of diagnosable psychopathology is controlled. At the univariate level, nondiagnosed siblings performed significantly more poorly than controls only on Trails B (mean = 95.36, SD = 29.27, and mean = 72.30, SD = 20.37, respectively), \( t(29) = 2.58, p = 0.008, d = 1.13 \). The effect sizes of the other nondiagnosed sibling-control comparisons were 0.87 (WCST perseverative errors), 0.76 (WCST nonperseverative errors), 0.43 (Relational Concepts), and 0.33 (WAIS–R Block Design). Consistent with the total sibling-control results, Trails B was also the only measure to enter a stepwise logistic regression analysis. In contrast to results for the total sibling group, WCST nonperseverative and perseverative errors were the only measures on which the nondiagnosed siblings showed significantly greater variance than controls (both \( p’s < 0.05 \)).

**Index probands versus siblings.** The comparison of proband performance to that of their siblings is useful in that it reflects genetic and environmental influences that are not shared in discordant sibling pairs (e.g., nonserved genetic and environmental effects that contribute to schizophrenia itself, as well as environmental consequences of having schizophrenia). Paired \( t \) tests indicated that probands showed significantly impaired performance compared to their siblings on two of the five measures: WCST perseverative errors, for which the largest effect size was obtained (\( d = 2.78, t = 4.62, p = 0.005 \)), and WAIS–R Block Design (\( d = –0.46, t = –1.89, p = 0.035 \)). The effect sizes for the measures for which group differences were nonsignificant were 0.052 (Relational Concepts), 0.38 (WCST nonperseverative errors), and 0.36 (Trails B).

Logistic regression indicated that as a set, the five neuropsychological measures significantly discriminated between index siblings and control participants, \( \chi^2 (5, n = 50) = 13.39, p = 0.010 \). However, Trails B was the only measure selected to enter the equation in a stepwise logistic regression when using a probability criterion for inclusion of 0.05, 1-tailed. This suggests that this neuropsychological test alone was the most parsimonious “subset” of the five performance measures in differentiating between siblings and controls.

As siblings are not at uniformly increased genetic risk for schizophrenia, greater performance variance among siblings compared to controls would be expected on measures sensitive to the genetic liability to the disorder. With the exception of WAIS–R Block Design, the variances on the neuropsychological measures employed here were significantly greater among siblings than among controls (Table III).

### Table III. Neuropsychological performance: Index siblings versus controls

<table>
<thead>
<tr>
<th>Measure</th>
<th>( t )</th>
<th>( p^1 )</th>
<th>Effect size(^2)</th>
<th>( F^3 )</th>
<th>( p^1 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>WAIS–R Block Design (raw score)</td>
<td>(-1.45)</td>
<td>0.077</td>
<td>(-0.46)</td>
<td>1.89</td>
<td>0.088</td>
</tr>
<tr>
<td>Trails B (sec)</td>
<td>3.10</td>
<td>0.002</td>
<td>1.41</td>
<td>5.33</td>
<td>0.013</td>
</tr>
<tr>
<td>WCST nonperseverative errors</td>
<td>2.20</td>
<td>0.017</td>
<td>0.91</td>
<td>6.55</td>
<td>0.007</td>
</tr>
<tr>
<td>WCST perseverative errors</td>
<td>2.40</td>
<td>0.010</td>
<td>0.83</td>
<td>9.10</td>
<td>0.002</td>
</tr>
<tr>
<td>Relational concepts (errors)</td>
<td>2.87</td>
<td>0.003</td>
<td>1.29</td>
<td>6.81</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*Note.—WAIS–R = Wechsler Adult Intelligence Scale–Revised; WCST = Wisconsin Card Sorting Test.*

\(^1\) One-tailed \( p \) values for \( t \) tests and \( F \) due to a priori hypotheses. The Bonferroni-adjusted alpha level, 1-tailed, across the five variables is 0.01.

\(^2\) \( M_{sibling} – M_{control}/SD_{control} \)

\(^3\) \( F \) from Levene’s Test for equality of variances. In all cases, sibling variance was greater than control variance.

Note that ranged from 1.41 to 0.46, with a rank order of: Trails B, Relational Concepts, WCST nonperseverative errors, WCST perseverative errors, and WAIS–R Block Design.

Relational Concepts, WCST nonperseverative errors, Trails B, WCST perseverative errors, and WAIS–R Block Design.

Logistic regression indicated that the five neuropsychological measures as a set significantly discriminated between index siblings and control participants, \( \chi^2 (5, n = 50) = 13.39, p = 0.010 \). However, Trails B was the only measure selected to enter the equation in a stepwise logistic regression when using a probability criterion for inclusion of 0.05, 1-tailed. This suggests that this neuropsychological test alone was the most parsimonious “subset” of the five performance measures in differentiating between siblings and controls.

As siblings are not at uniformly increased genetic risk for schizophrenia, greater performance variance among siblings compared to controls would be expected on measures sensitive to the genetic liability to the disorder. With the exception of WAIS–R Block Design, the variances on the neuropsychological measures employed here were significantly greater among siblings than among controls (table 3).

**Sibling covariance structure.** Box’s M indicated that the overall covariance matrix differed between the siblings and controls, \( F(15, 6625.23) = 2.32, p = 0.003 \). Specifically, several of the correlations between the neuropsychological measures were significantly greater in the sibling group than the control group according to Fisher’s \( z \) tests. Such findings suggest the presence of some additional latent source of performance covariance present in the sibling but not in the control group (e.g., genetic variation that affects more than one test).
performance among patients are familial, correlations between patient and sibling performance scores were calculated. Age-adjusted performance scores were first obtained using linear regression for each group separately. The patient-sibling correlations for age-adjusted scores were Block Design, \( r = 0.14, p = 0.230 \); Trails B, \( r = 0.26, p = 0.084 \); WCST nonperseverative errors, \( r = -0.31, p = 0.046 \); WCST perseverative errors, \( r = 0.05, p = 0.399 \); and Relational Concepts, \( r = 0.46, p = 0.005 \). The significant positive correlation for Relational Concepts suggests that individual differences in performance among patients for this measure may be affected by genes or experiences that they share with their siblings. Assuming no effect of shared environment, twice the sibling correlation estimates the heritability of the trait. Thus, the above correlations suggest the following heritability estimates: Block Design = 0.28, Trails B = 0.52, WCST nonperseverative errors = 0.00, WCST perseverative errors = 0.10, and Relational Concepts = 0.92. Correlations between patients’ clinical characteristics (i.e., age at first hospitalization, mean duration of illness, and median number of months since last hospitalization) and their siblings’ neuropsychological performance were also examined; none of these correlations was significant.

Discussion

The main findings to emerge from this sibling study of schizophrenia and neuropsychological functioning were as follows:

1. Siblings of patients showed impaired neuropsychological performance compared to controls. Specifically, the total sibling group performed significantly worse than controls on all measures except WAIS–R Block Design; group differences on Trails B and Relational Concepts showed effect sizes of over one SD.

2. Multivariate analyses suggested that, of the measures employed, only Trails B discriminated independently of the other tests between siblings of patients and control participants.

3. Index siblings evidenced greater variance on and covariance between the neuropsychological measures than the control participants. Specifically, siblings showed significantly greater variance on all measures except Block Design, and several of the correlations between the measures were significantly greater among the siblings than among the controls.

4. Index siblings without any diagnosis performed significantly worse than controls only on Trails B (effect size = 1.13).

Furthermore, as expected, clinically stable schizophrenia probands showed significantly impaired performance compared to control participants on all five of the neuropsychological measures, with effect sizes greater than two SDs emerging for the proband-control differences on Trails B and WCST perseverative errors. Index patients also performed significantly more poorly than their siblings on two of the five measures: WCST perseverative errors and Block Design, with an effect size of greater than one SD emerging for the group differences on WCST perseverative errors. Individual differences in neuropsychological performance among patients were generally not strongly familial, with the exception of the Relational Concepts scale.

Comparisons With Other Studies of Relatives

Trail Making Test–Part B. Most studies examining Trails B performance in adult relatives of schizophrenia patients are consistent with the present results in observing significant deficits in relatives compared to controls (Pogue-Geile et al. 1991; Frank et al. 1993; Keefe et al. 1994; Kinney et al. 1994, based on the effect size of 0.60 calculated by the present authors; Pogue-Geile et al. 1994; Harris et al. 1996; Laurent et al. 1999; Ismail et al. 2000; Laurent et al. 2000; Egan et al. 2001). Similarly, two studies that have included Trails B in composite scores along with other measures have found that relatives display significantly worse performance than controls (Mirsy et al. 1992; Cannon et al. 1994). However, several studies have not found Trails B performance in relatives to be significantly worse than controls’ (Yurgelun-Todd and Kinney 1993a, based on the effect size calculated by the present authors; Farace et al. 1995; Goldberg et al. 1995; Kremen et al. 1998). Although no clear pattern was apparent from review of the studies, it is possible that the mixed results regarding Trails B are due to sampling and statistical variation. An overall weighted effect size of 0.63 was found for relative-control differences on Trails B based on the other reports that provided the necessary data (Pogue-Geile et al. 1991, 1994; Frank et al. 1993; Yurgelun-Todd and Kinney 1993a; Keefe et al. 1994; Kinney et al. 1994; Goldberg et al. 1995; Harris et al. 1996; Kremen et al. 1998; Laurent et al. 1999; Ismail et al. 2000; Egan et al. 2001), which is considered moderate to large (Cohen 1987).

The current finding that even relatives free of any diagnosable psychopathology perform significantly more slowly than controls on Trails B has been observed in other studies that have assessed performance of relatives without a diagnosis (Pogue-Geile et al. 1991; Frank et al. 1993). This is a particularly conservative test in that it controls for any potential effect of nonschizophrenia psychopathology among relatives.

Thus, of the five neuropsychological measures used in the present study, Trails B most effectively discriminated univariately between siblings of patients and controls, and it also provided the best independent discrimination multivariately. Furthermore, these findings remained unchanged when only siblings free of diagnosable
psychopathology were included. In addition, siblings displayed significantly greater variance on Trails B, which would be predicted if this measure is sensitive to the genetic liability to schizophrenia. Overall then, the current results along with other research with Trails B suggest that this measure may indeed be sensitive to the genetic liability to schizophrenia and thus may facilitate the detection of linkage in genetic studies of the disorder.

**WCST.** At least five other studies of WCST perseveration in relatives (Franke et al. 1992, 1993; Toomey et al. 1998; Saoud et al. 2000; Egan et al. 2001) are consistent with our finding of increased perseveration scores in unaffected siblings compared to controls. Two of the studies (Franke et al. 1992, 1993), however, employed the Nelson (1976) method of WCST administration, which involves using a shorter version of the test and warning participants when the sorting rule changes and thus may not be directly comparable to the traditional WCST (Heaton 1981). In contrast, at least 16 studies have reported no significant differences between relatives and controls on WCST perseverative scores (Pogue-Geile et al. 1991; Scarone et al. 1993; Yurgelun-Todd and Kinney 1993a, based on the effect size calculated by the present authors; Yurgelun-Todd and Kinney 1993b, based on the test and effect size calculated by the present authors; Keefe et al. 1994; Pogue-Geile et al. 1994; Goldberg et al. 1995; Stratta et al. 1997; Koren et al. 1998; Kremen et al. 1998; Laurent et al. 1999; Chen et al. 2000; Faraone et al. 2000; Ismail et al. 2000; Laurent et al. 2000; Kéri et al. 2001). Although not significant, Chen et al. (2000) observed a large sibling-control effect size (1.06 calculated by the present authors), as did Goldberg et al. (1995) for unaffected monozygotic twins compared to control twins (effect size = 0.9, calculated by the present authors). Furthermore, the overall effect size for WCST perseverative scores across other studies that provided the necessary information (Pogue-Geile et al. 1991, 1994; Franke et al. 1992, 1993; Scarone et al. 1993; Yurgelun-Todd and Kinney 1993a, 1993b; Keefe et al. 1994; Goldberg et al. 1995; Stratta et al. 1997; Koren et al. 1998; Kremen et al. 1998; Toomey et al. 1998; Laurent et al. 1999; Chen et al. 2000; Faraone et al. 2000; Ismail et al. 2000; Saoud et al. 2000; Egan et al. 2001; Kéri et al. 2001) was 0.45, which is considered medium (Cohen 1987). The sources of variation across studies do not appear to reflect obvious methodological differences and instead may be due to sample and/or statistical variation. Thus, although our current findings are clear in suggesting that siblings of schizophrenia patients show increased WCST perseverative errors and therefore that this measure may be sensitive to the genetic liability to schizophrenia, we are less confident of this given the mixed results from other studies.

In contrast to the present findings, of the three other studies that reported on WCST nonperseverative errors in relatives compared to controls, none found significant differences on this measure (Pogue-Geile et al. 1991; Franke et al. 1992, 1993). As noted above, however, Franke and colleagues used the Nelson method of WCST administration rather than the Heaton (1981) procedure, which renders comparisons with the present results more difficult.

**Relational Concepts.** To our knowledge, the Relational Concepts scale has been little investigated (but see Condray and Steinhauer 1992; Condray et al. 1992). In the present study this measure yielded a sibling versus control effect size of over one SD. Such findings suggest that the Relational Concepts scale may be sensitive to genetic liability to schizophrenia and may warrant further research on this short and easily administered measure.

**Block Design.** As noted above, siblings of patients did not show significantly impaired performance compared to controls on Block Design. Other studies are consistent with this result in failing to detect significantly impaired performance in first degree relatives of patients on this measure of spatial ability (Goldberg et al. 1990; Keefe et al. 1994; Faraone et al. 1995; Kremen et al. 1995; Harris et al. 1996). Studies that have focused more generally on the construct of spatial ability, including Block Design along with other measures of spatial ability as part of a composite score, likewise have failed to find significant differences in performance on their “spatial ability” factor between adult siblings of patients and controls (Cannon et al. 1994; Staal et al. 2000). Using the existing reports that provided the necessary data (Goldberg et al. 1990; Keefe et al. 1994; Kremen et al. 1995; Harris et al. 1996), the present authors calculated an overall effect size weighted by sample size for Block Design differences between relatives and controls of –0.26, which is defined as small by Cohen (1987). Based on the present and other findings, then, it seems that the WAIS–R Block Design test, and perhaps measures of spatial ability more generally, do not reliably discriminate first degree relatives of schizophrenia patients from healthy controls and thus may be relatively insensitive to the genetic liability to schizophrenia. This basically normal performance on the Block Design test also argues against any very general performance deficit among relatives of patients.

**Proband-Sibling Comparisons.** Although less relevant to detecting unexpressed genetic liability to schizophrenia, our analyses comparing schizophrenia probands with their siblings produced several interesting points. This comparison reflects nonshared environmental effects associated with the schizophrenia diagnosis itself (either etiologic or iatrogenic) as well as any genetic effects that are not shared between patients and unaffected siblings. In this comparison, WCST perseverative errors stood out as being most abnormal in patients compared to siblings,
suggesting that this measure is especially sensitive to such nonshared environmental and genetic effects associated with the diagnosis itself. The other tests showed more modest effects, with the Relational Concepts test interestingly showing relatively little sensitivity to such effects.

Methodological Considerations. The methodological constraints of the present study must be considered when interpreting its findings. First, only males were included in our sample, which obviously limits the generalizability of our results and does not provide for tests of possible sex effects (e.g., Kremen et al. 1997; Faraone et al. 1999).

Another potential limitation of the current study was the differential screening used for the control and sibling samples. Specifically, we screened potential control participants such that they were excluded if they met diagnostic criteria for any psychiatric disorder, but psychopathology was free to vary among the siblings (excluding the diagnosis of schizophrenia or schizoaffective disorder). The use of such “supernormal” controls (Kendler 1990) could have artifactually contributed to sibling-control group differences. However, in the absence of control groups truly representative of the general population, efforts to avoid supernormal controls need to be balanced by the likelihood that unscreened volunteer control participants may actually display increased psychopathology compared to the general population (e.g., Shtasel et al. 1991). Our analyses based on only the nondiagnosed siblings avoided this issue by matching with controls on general psychopathology.

It is also important to note that we are making no inferences regarding which “underlying” specific cognitive processes may be most sensitive to genetic liability. Neuropsychological tests require multiple cognitive processes for their execution, and the tests themselves are not matched on discriminating power (Chapman and Chapman 1973). Thus, although the tests employed may be more or less useful at detecting deficits in relatives of patients, they are limited in what they can tell us regarding specific cognitive processes that may be affected by genetic liability to schizophrenia.

Furthermore, it must be recalled that these index siblings were reared with their schizophrenia brothers. Thus any deficits observed may reflect shared genetic or environmental effects. Although there is little evidence for shared environmental effects in schizophrenia in general, in the absence of adopted-away sibling studies, such effects cannot be completely ruled out.

In the absence of studies with similar results that also included control groups comprising siblings of probands with other diagnoses, the specificity of the current findings for schizophrenia is unclear (cf. Kremen et al. 1998; Kéri et al. 2001). It is possible that the sibling deficits observed here reflect familial liability that, although contributing to schizophrenia etiology, is not specific to schizophrenia.

Conclusions. In conclusion, the present study suggests that the Trails B test may be especially sensitive to the genetic liability to schizophrenia compared to the other tests evaluated. Among the index siblings, the Trails B test had the largest effect size compared to controls, had an increased variance, remained abnormal even among Nondiagnosed siblings, showed increased covariance with other tests, made a contribution to group discrimination that was independent of the other tests, and showed a trend toward correlation among siblings. The results were also generally supportive of the Relational Concepts test and the WCST as potentially sensitive to unexpressed schizophrenia liability, although somewhat less consistently so. In contrast, the results are clear that the Block Design test is not a good candidate for detecting genetic liability to schizophrenia. Overall then, these findings especially support the potential utility of the Trails B test as a candidate quantitative phenotype, or endophenotype (Gottesman and Shields 1972; Gottesman and Gould 2003), to aid in gene mapping studies of schizophrenia.

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