Neuropsychologic Functioning among the Nonpsychotic Relatives of Schizophrenic Patients: The Effect of Genetic Loading

Stephen V. Faraone, Larry J. Seidman, William S. Kremen, Rosemary Toomey, John R. Pepple, and Ming T. Tsuang

Background: We previously reported that the nonpsychotic relatives of schizophrenic patients exhibited disturbances in executive functioning, verbal and visual memory, auditory attention, mental control, and verbal ability. In a 4-year follow-up, we showed that the discriminating power of most of these tests was stable over time.

Methods: In this report we compare 41 nonpsychotic persons who have only one schizophrenic first-degree relative (simplex families) with 36 nonpsychotic persons who have two schizophrenic first-degree relatives (multiplex families). Our goal was to test a hypothesis that neuropsychologic deficits would be worse among the latter.

Results: Relatives from multiplex families differed significantly from controls on estimated intelligence, immediate and delayed logical memories, and immediate visual reproductions. In contrast, in comparisons with controls, relatives from simplex families only differed on immediate logical memories. Comparisons between relatives from multiplex and simplex families showed that the former group had significantly worse scores for estimated intelligence, immediate and delayed logical memories, and immediate visual reproductions. We also found group × gender interactions: the worse performance of the multiplex group was seen for females.

Conclusions: These results are consistent with the idea that neuropsychologic deficits in relatives of schizophrenic patients reflect their degree of genetic predisposition to schizophrenia. They also suggest hypotheses about gender differences in the familial transmission of the disorder.

Key Words: Genetics, neuropsychology, endophenotypes, multiplex families

Introduction

We previously reported that the nonpsychotic relatives of schizophrenic patients exhibited disturbances in executive functioning, verbal and visual memory, auditory attention, mental control, and verbal ability (Faraone et al 1995b; Toomey et al 1998) and that most of these findings were stable over a 4-year period (Faraone et al 1999a). These findings were consistent with the findings in relatives of schizophrenic patients reviewed by Kremen et al (1994) and with other reports (Cannon et al 1994; Keefe et al 1994). In our work, the ability of neuropsychologic tests to discriminate controls from relatives was strongest among female subjects (Kremen et al 1997) and for research participants younger than 60 years of age (Faraone et al 1995b, 1996).

Neuropsychologic studies of relatives are valuable for two reasons. First, as we have discussed elsewhere (Faraone et al 1995a; Tsuang et al 1993), finding markers of the vulnerability to schizophrenia may provide phenotypes for genetic studies. For example, studies that have incorporated eye-tracking (Arolt et al 1996) and sensory gating measures (Coon et al 1993), have shown these phenotypes to suggest genetic linkage where the clinical diagnosis did not. Second, unlike studies of patients, studies of relatives are not confounded by neuroleptic treatment, chronic hospitalization, and the potential neurotoxic effects of psychosis (Faraone et al 1999b).

For several reasons, many researchers have suggested that schizophrenia is caused by a multifactorial process comprised of several genes combined with adverse environmental factors (Gottesman 1991; Gottesman et al 1987; Tsuang and Faraone 1994). Although the number of
schizophrenia genes is unknown, most researchers agree that a single gene theory of schizophrenia is not viable, even if that theory allows for many different single gene variants (Gottesman and McGue 1990; Gottesman et al 1983; McGue et al 1983; McGuffin et al 1987). The multifactorial model of schizophrenia has found some support from segregation analysis studies (Faraone and Tsuang 1985; Faraone et al 1988) and cannot be discounted as a viable model of the etiology of schizophrenia.

Although prior studies have concluded that neuropsychologic deficits in relatives of schizophrenic patients reflect the effects of schizophrenia genes, they have not examined the implications that the multifactorial model has for the distribution of neuropsychologic deficits among family members of schizophrenic patients. If a) the multifactorial model is correct in positing the existence of a graded genetic loading for schizophrenia and b) schizophrenia genes cause neuropsychologic impairment among nonpsychotic relatives of schizophrenic patients, then the degree of impairment in relatives should be associated with their genetic loading. Because we have no gold standard measure of genetic loading, we defined that construct using family data. This approach assumes that nonpsychotic relatives having only one first-degree relative with schizophrenia have a lower genetic loading than those having two relatives with schizophrenia. Thus, to test the hypothesis that the degree of neuropsychologic impairment in relatives is associated with their genetic loading for schizophrenia, we compared relatives from families having one and two schizophrenic members.

**Methods and Materials**

Research participants in this study were first-degree, nonpsychotic relatives of schizophrenic patients and control subjects. The patients were recruited from inpatient and outpatient units at three Boston area hospitals specializing in the care of chronically ill psychotic patients: the Brockton/West Roxbury Veterans Affairs Medical Center, the Taunton State Hospital, and the Massachusetts Mental Health Center. Inclusion criteria for patients were as follows: a diagnosis of schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised (DSM-III-R; American Psychiatric Association 1987); age greater than 17 years; English as the primary language; at least an eighth grade education; and available first-degree relatives.

For probands, DSM-III-R diagnoses were derived from structured interviews using the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer 1978). Relatives were interviewed with the Structured Clinical Interview for DSM-III-R (SCID; Spitzer et al 1987) for Axis I disorders and the Structured Interview for DSM-III Personality Disorders (SIDP; Stangl and Zimmerman 1983).

To be eligible for the study, relatives and controls had to be between 18 and 59 years of age, have at least an eighth grade education, have English as their first language, and be free of psychosis during their lifetime. The exclusion criteria for both controls and relatives also required absence of 1) substance abuse within the past 6 months; 2) history of head injury with any documented cognitive sequelae or with loss of consciousness greater than 5 min; 3) neurologic disease or damage; 4) brain surgery; 5) mental retardation; and 6) medical illnesses that may significantly impair neurocognitive function. We recruited 41 relatives from families having only one schizophrenic relative (simplex families, 29 male relatives, 12 female relatives) and 36 from families having two schizophrenic relatives (26 male relatives, 10 female relatives). For simplex families, we ruled out schizophrenia in first-degree relatives by direct interviews and in second-degree relatives by the family history method. For multiplex families, the two schizophrenic relatives and the nonschizophrenic relatives were all first-degree relatives of one another.

We recruited 100 control subjects through advertisements in the catchment areas of the hospitals from which the probands had been ascertained (58 male subjects, 42 female subjects). Control subjects went through the same screening process as the relatives, with one exception. Instead of using a structured interview, we screened control subjects for psychopathology using the short form of the Minnesota Multiphasic Personality Inventory (MMPI-168; Vincent et al 1984). Potential control subjects were excluded if any MMPI scale, except Masculinity-Femininity, was above 70.

This report focuses on the following tests, which our prior studies implicated as risk indicators in schizophrenia families: the Wisconsin Card Sorting Test (WCST), the immediate and delayed recall conditions of the Wechsler Memory Scales-Revised (WMS-R) Logical Memory stories, the immediate and delayed recall scores on the WMS-R Visual Reproductions, and a dichotic (digits) listening task. We also estimated intelligence from the vocabulary and block design subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) and measured academic achievement with the reading, arithmetic, and spelling subtests of the Wide Range Achievement Test-Revised (WRAT-R).

The psychiatric interviews of relatives were blind to the neuropsychologic test results from the relative. Diagnoses of probands and relatives were blind to all other psychiatric and neuropsychologic data.

We used logistic regression, linear regression, and ordinal logistic regression to make comparisons among groups. Because our prior work had demonstrated gender effects in differences between relatives of schizophrenic patients and control subjects, we also included gender and its interaction with relative group in our statistical models. Our statistical analyses addressed the non-independence of observations within families by adjusting variance estimates with Huber’s formula (Huber 1967), a “theoretical bootstrap” that produces accurate statistical tests for clustered data. The method, as implemented in STATA (Stata Corporation 1999) works by entering the cluster scores (i.e., sum of scores within families) into the formula for the estimate of variance using the linearization method (Binder 1983; Kish and Frankel 1974). All tests were two tailed and used the .05 level of significance.
Table 1. Group Comparisons on Neuropsychologic Test Scores

<table>
<thead>
<tr>
<th>Test scores: mean (SD)</th>
<th>Multiplex (n = 36)</th>
<th>Simplex (n = 41)</th>
<th>Controls (n = 100)</th>
<th>Statistic</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Intelligence and achievement</td>
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<tr>
<td>Estimated IQ</td>
<td>101 (15.9)a</td>
<td>102 (10)</td>
<td>109 (14.3)</td>
<td>F(2,148) = 4.4</td>
<td>.01</td>
</tr>
<tr>
<td>WRAT-R reading</td>
<td>97 (13.9)</td>
<td>98 (11.4)</td>
<td>103 (12.4)</td>
<td>F(2,149) = 2.9</td>
<td>.06</td>
</tr>
<tr>
<td>WRAT-R arithmetic</td>
<td>92 (9.5)</td>
<td>95 (13.3)</td>
<td>97 (13.6)</td>
<td>F(2,113) = 0.9</td>
<td>.38</td>
</tr>
<tr>
<td>WRAT-R spelling</td>
<td>100 (8.3)</td>
<td>98 (13.1)</td>
<td>100 (13.5)</td>
<td>F(2,113) = 0.5</td>
<td>.62</td>
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<td>Abstraction</td>
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<td>WCST categories</td>
<td>5.1 (1.6)</td>
<td>5.2 (1.7)</td>
<td>5.6 (1.2)</td>
<td>χ²(2) = 2.4</td>
<td>.31</td>
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<tr>
<td>WCST total perseverations</td>
<td>14.9 (17.8)</td>
<td>10 (15)</td>
<td>9.5 (14.9)</td>
<td>F(2,149) = 1.0</td>
<td>.36</td>
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<tr>
<td>Verbal memory</td>
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<td>WMS-R logical memories, immediate</td>
<td>22.6 (7.3)p-b</td>
<td>26.6 (6.7)p</td>
<td>29.8 (5.6)</td>
<td>F(2,150) = 12.1</td>
<td>&lt;.001</td>
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<tr>
<td>WMS-R logical memories, delayed</td>
<td>19.6 (7.7)p-b</td>
<td>23.7 (7.6)</td>
<td>26 (6.4)</td>
<td>F(2,150) = 7.7</td>
<td>&lt;.001</td>
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<td>Auditory attention</td>
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<td>Dichotic listening, digits detected</td>
<td>97.4 (23.5)</td>
<td>96 (22)</td>
<td>101.2 (21.3)</td>
<td>F(2,145) = 0.9</td>
<td>.42</td>
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<tr>
<td>Visual memory</td>
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<tr>
<td>WMS-R visual reproductions, immediate</td>
<td>29.4 (6.1)p-b</td>
<td>33 (4.8)</td>
<td>34.7 (4.5)</td>
<td>F(2,149) = 7.8</td>
<td>&lt;.001</td>
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<tr>
<td>WMS-R visual reproductions, delayed</td>
<td>26.9 (8.7)</td>
<td>30.7 (6)</td>
<td>31.2 (5.9)</td>
<td>F(2,148) = 2.1</td>
<td>.13</td>
</tr>
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</table>

a p < .01 vs. control subjects.
b p < .05 vs. simplex.
c p < .05 vs. control subjects.

WRAT-R, Wide Range Achievement Test-Revised; WCST, Wisconsin Card Sorting Test; WMS-R, Wechsler Memory Scale-Revised.

Results

The three groups did not differ in parental education (χ²[2] = 0.1, p = .9), ethnicity (χ²[10] = 11.6, p = .3), gender (χ²[2] = 3.5, p = .2) or age (F[2,150] = 1.9, p = .2). Table 1 shows the results of group comparisons on neuropsychologic test scores. We found significant three-way group differences for estimated intelligence, WMS-R immediate and delayed logical memories, and WMS-R immediate visual reproductions.

Pairwise comparisons showed that the relatives from multiplex families differed significantly from controls on all of these variables, even after correcting for the group difference in estimated intelligence. In contrast, in comparisons with control subjects, relatives from simplex families differed only on one test score: WMS-R immediate logical memories. Comparisons between relatives from multiplex and simplex families showed that the former group had significantly worse scores for WMS-R immediate and delayed logical memories, and WMS-R immediate visual reproductions. The multiplex and simplex subjects did not differ in the sizes of their families of origin (6.5 vs. 5.0, Wilcoxon z = 1.5, p = .13). Thus, the neuropsychologic differences between these groups cannot be attributed to difference in family size. Notably, age could not account for group differences given the similar ages in our three groups: 40 ± 9 for multiplex, 41 ± 11 for simplex, and 38 ± 11 for control subjects (F[2,150] = 1.9, p = .2).

When comparing relatives from simplex and multiplex families, we found group × gender interactions for four variables: auditory attention (t[51] = 2.1, p = .04), WMS-R delayed logical memories (t[51] = 2.7, p = .01) and WMS-R immediate (t[51] = 2.1, p = .04) and delayed visual reproductions (t[51] = 2.1, p = .04). Follow-up analyses by gender revealed significant multiplex–simplex differences for female but not for male subjects. For auditory attention, female subjects from multiplex families were marginally more impaired than female subjects from simplex families (90 ± 21 vs. 105 ± 12, t[19] = 1.9, p = .07), but we found no such difference for male subjects (100 ± 24 vs. 92 ± 24, t[19] = 1.2, p = .24). The same pattern was seen for immediate visual memory (female subjects: 29 ± 6 vs. 36 ± 3, t[19] = 3.9, p = .001; male subjects: 30 ± 6 vs. 32 ± 5, t[19] = 1.0, p = .33), delayed visual memory (female subjects: 26 ± 10 vs. 35 ± 3, t[19] = 3.0, p = .008; male subjects: 28 ± 8 vs. 29 ± 6, t[19] = 0.5, p = .6) and delayed verbal memory (female subjects: 17 ± 9 vs. 29 ± 7, t[19] = 3.5, p = .002; male subjects: 21 ± 7 vs. 22 ± 7, t[19] = 0.4, p = .7).

Discussion

Our prior studies suggested that neuropsychologic impairments in relatives of schizophrenic patients are stable traits caused by the set of genes that also increases the predisposition to schizophrenia (Faraone et al 1995b, 1996; 1999a; Kremen et al 1997; Lyons et al 1995; Toomey et al 1998). The present report extends that finding by showing that relatives from families having two schizophrenic members have more neuropsychologic impairment than relatives from families having one schizophrenic member.
This new finding is consistent with the multifactorial model of schizophrenia (Gottesman 1991; Gottesman et al 1987; Tsuang and Faraone 1994). This model posits that no one gene or environmental factor causes schizophrenia. Instead, it is the sum of these genes and environmental factors that leads to the disorder. If this is true, then there must be a graded genetic predisposition to the disorder such that the probability of developing schizophrenia (or showing related neuropsychologic impairments) increases as the degree of predisposition increases. Presumably, multiplex families harbor more schizophrenia genes than simplex families. Thus, our finding of greater impairments in relatives in multiplex families is consistent with the multifactorial model.

Our results, however, do not address the genetic versus environmental causes of neuropsychologic deficits given the inferential limitations of family studies that do not include twin or adoptive relatives (Faraone and Santangelo 1992; Faraone and Tsuang 1995; Faraone et al 1999b). Also, our data cannot determine why some relatives are predisposed to schizophrenia but never developed the disorder. Further work is needed to determine if they have a low “dose” of genes or if they had not been exposed to environmental agents that trigger the disorder.

Notably, the group differences we found were strongest for the memory measures. Although we cannot draw definitive conclusions about the nature of their memory problems, we can suggest several points worthy of follow-up by future research. The memory dysfunction is seen in both visual and verbal domains, and the memory tasks used are typically considered measures of long-term memory. We have, however, previously demonstrated (Faraone et al 1995b) that, unlike patients with schizophrenia (Seidman et al 1998), the relatives do not have abnormal rates of forgetting compared with control subjects (i.e., they do not have typical long-term memory deficits). Thus, the memory deficits appear to be associated with defects in the acquisition and/or the retrieval of information. Further research is needed to shed light on the nature of the cognitive dysfunctions underlying impaired task performance. Possible processes include defects in working memory, sustained attention, and encoding processes.

We cannot attribute our findings to group differences in general intellectual functioning for two reasons. First, the relatives from simplex and multiplex families did not differ in estimated intelligence. Second, although the relatives from multiplex families showed significantly lower intelligence than control subjects, statistical corrections for this confound did not change our results.

We previously reported significant or near-significant group × gender interactions in four neuropsychologic functions: verbal memory, motor function, mental control/encoding, and auditory attention (Faraone et al 1999a; Kremen et al 1997). At the follow-up assessment (Faraone et al 1999a), the group × gender interaction was significant for delayed and immediate verbal memory, and delayed and immediate visual memory. At both assessments, the nature of the interactions was the same: the greater impairment of relatives compared with control subjects was more pronounced for female than for male subjects. The present work extends these findings by showing that the gender effect is found not only when comparing relatives of schizophrenic patients with control subjects, but also when comparing relatives from simplex and multiplex schizophrenia families.

Although we have no definitive explanation for these gender differences, they suggest that men carrying the familial risk for schizophrenia have a lower threshold for developing schizophrenia than women predisposed to schizophrenia. If that were so, then male relatives with neuropsychologic deficits would have been more likely to have developed psychosis and have been excluded from our study. In contrast, if females are able to sustain greater impairment without developing psychosis, they would have been more likely to remain in our sample. It is also possible that men with neuropsychologic deficits are less likely to participate than are women with these deficits.

The idea that females have a higher threshold for expressing psychosis is consistent with epidemiologic evidence suggesting that males might be at greater risk for the disorder and that relatives of female schizophrenic patients might be at greater risk for schizophrenia than relatives of male patients (Goldstein 1995). Both of these findings are consistent with the idea that women are less likely to develop schizophrenia than men given the same degree of familial predisposition. Yet, because epidemiologic studies have not consistently shown these gender effects, this idea requires further confirmation. Moreover, although the gender differences we found are intriguing, our inferences are limited due to the small subsamples created after stratifying the sample on gender and the fact that this issue has not been addressed by other investigators.

Notably, we did not find group differences for the Wisconsin Card Sorting Test (WCST), despite a fairly large literature showing that test to be impaired among schizophrenic patients (e.g., Braff et al 1991; Koren et al 1998; Seidman et al 1997); however, the literature about WCST deficits in relatives of schizophrenic patients is contradictory. In two different samples, Pogue-Geile et al (1991, 1989) found that siblings of schizophrenic patients did worse on the WCST than control subjects. Mirsky et al (1992) found significant WCST deficits in two different samples as well. Similar findings were reported from a twin study by Goldberg et al (1997).
findings, other studies have not found impaired WCST performance among either first-degree (Condry and Steinhauser 1992; Keefe et al 1994; Scarone et al 1997; Stratta et al 1997) or monozygotic co-twin (Goldberg et al 1990) relatives of schizophrenic patients. Moreover, in a 4-year follow-up study, we showed that WCST scores in relatives of schizophrenic patients were not stable over time, raising questions about their utility as trait measures (Faraone et al 1999a).

Taken together, these conflicting results suggest that the WCST may be a weak measure of the genetic vulnerability to schizophrenia. Notably, the WCST is relatively easy; normal children achieve adult levels by age 10–12 years (Heaton 1981; Heaton et al 1993). Unlike more discriminating measures of the vulnerability to schizophrenia, such as the identical pairs version of the continuous performance task (Cornblatt and Erlenmeyer-Kimling 1984; Cornblatt and Keilp 1994), or the Wechsler Logical Memories (Faraone et al 1999a), the WCST has no time constraint in terms of its stimulus processing load or response time. Thus, the WCST may too be easy to pick up the subtle neuropsychologic deficits seen in most relatives of schizophrenic patients.

Our work must be interpreted in the context of its methodological limitations. Our probands came from centers that specialize in the treatment of chronically ill psychotic patients. Thus, although they are likely to be representative of chronic, relatively severe cases of schizophrenia, our results may not generalize to relatives ascertained through milder cases. Another potential problem is that, although we used a broad neuropsychologic battery, we did not test all aspects of neuropsychologic functioning.

Also, as we have discussed elsewhere, defining simplex and multiplex families is subject to error (Faraone et al 1999b). Thus, some of the simplex patients may not be genetically different from the multiplex patients; but, despite this uncertainty, as a group, the simplex patients should have a lower genetic loading for schizophrenia than the multiplex group. Moreover, misclassifying multiplex families as simplex would make it more difficult to find group differences and thus cannot account for our results.

We must also be cautious when inferring specific neuropsychologic function deficits from test performance. Although it is reasonable to view each test score as primarily influenced by an underlying function, the tests are complex and their scores multidetermined. Thus, to understand more fully the nature of the deficit we have documented among the relatives of schizophrenic patients, future work should analyze these deficits in terms of more fine-grained measures of information processing components.

Despite these limitations, our results suggest that the amount of neuropsychologic impairment in relatives of schizophrenic patients increases with their genetic loading for schizophrenia. This provides further, indirect, evidence that one or more of the genes that cause schizophrenia also can be expressed as neuropsychologic deficits in relatives.

References


Endicott J, Spitzer RL (1978): A diagnostic interview: The
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