Neurocognitive Impairments in Nonpsychotic Parents of Children With Schizophrenia and Attention-Deficit/Hyperactivity Disorder

The University of California, Los Angeles Family Study

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Background: We tested the hypotheses that certain neurocognitive impairments index genetic liability to schizophrenia and that childhood-onset schizophrenia (COS) is a variant of adult-onset schizophrenia (AOS) by determining whether parents of COS probands show the types of neurocognitive impairments found in relatives of AOS probands.

Methods: Parents of COS probands (n = 79) were compared with parents of attention-deficit/hyperactivity disorder (ADHD; n = 190) and community control (CC; n = 115) probands on 3 neurocognitive tasks shown in previous research to detect impairments in patients with AOS and ADHD and in the relatives of patients with AOS. Parents with a diagnosis of psychosis were excluded from the study.

Results: On the Degraded Stimulus–Continuous Performance Test and the Trail-Making Test B–Adolescent Version, the parents of COS probands performed significantly worse than the parents of CC and ADHD probands, who did not differ significantly from each other. On the Span of Apprehension, we found no significant group differences. Using rigorous cutoffs, a combination of scores on certain neurocognitive tasks identified 16 (20%) of the mothers and fathers of COS probands compared with 0% of the mothers and fathers of CC probands. There was diagnostic specificity of the neurocognitive impairments. A combination of neurocognitive scores identified 6 (12%) of the mothers of COS probands vs 0% of the mothers of ADHD probands. A cutoff that identified 2 (2%) of the fathers of ADHD probands classified 5 (17%) of the fathers of COS probands. We found no significant differences in neurocognitive functions between the parents of ADHD and CC probands.

Conclusions: The aggregation of neurocognitive impairments in the parents of COS probands provides further evidence of etiologic continuity between COS and AOS. A substantial subgroup of parents of COS probands had a worse neurocognitive performance than that of any of the parents of ADHD and CC probands. Receiver operating characteristic curves showed that when rigorous cutoffs define neurocognitive impairments, the combination of scores on certain neurocognitive tasks produced a level of diagnostic accuracy in the parents of COS probands that is sufficient for use in genetic linkage studies.

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that COS is a variant of AOS and that these impairments index genetic liability to both COS and AOS.

Some previous studies that found neurocognitive impairments in relatives of schizophrenic patients did not exclude relatives with overt psychosis. We excluded parents with schizophrenia to determine the extent to which the presence of neurocognitive impairments is independent of the presence of schizophrenia.

Statistical power in linkage studies is directly related to the relative incidence of a phenotype in relatives of schizophrenic probands (true-positive findings) compared with its incidence in the general population (false-positive findings).20 Given the familial risk and population base rate of schizophrenia, to improve on the clinical diagnosis of schizophrenia as a phenotype, indicators must have ratios of true- to false-positive findings of at least 10:1.21 Therefore, to be useful in linkage studies, cutoff scores on neurocognitive tasks should produce low false-positive rates (high specificity).20 With a notable exception,8 previous studies reported group differences between the relatives of AOS and control probands and did not examine the diagnostic accuracy of neurocognitive measures. “For neurocognitive measures to be useful indices of a genetic liability to schizophrenia, group differences are not sufficient to show that a measure is useful for classification, rather what is needed are diagnostic accuracy analyses which specify the sensitivity and specificity . . . of measures.”8 The present study performed diagnostic accuracy analyses of 3 neurocognitive tasks to determine whether they are useful indices of liability to schizophrenia in linkage studies.

Given the central role of cognitive impairments in the diagnosis and pathophysiology of ADHD and the growing evidence of a familial aggregation of ADHD, surprisingly little research has examined neurocognitive functioning in relatives of individuals with ADHD. Nonhyperactive siblings of ADHD probands have decreased intelligence and achievement test scores23,24 but are similar to control subjects on measures of executive functioning, attention, and verbal learning.25 The present study provides a further test of the hypothesis that certain neurocognitive impairments index liability in ADHD probands by examining neurocognitive functioning in their parents on 3 tasks that detect impairments in patients with ADHD.

METHODS

SUBJECTS

The University of California, Los Angeles Family Study consists of parallel studies of biological relatives of 3 child (principal investigator, R.F.A.) and 3 adult (principal investigator, K.H.N.) proband groups. This report presents data on the parents of the 2 child proband groups with COS and ADHD, and of a group of community control (CC) probands. We ascertained COS probands by screening 9 Los Angeles County treatment facilities and the University of California, Los Angeles Neuropsychiatric Hospital and school-based programs for seriously emotionally disturbed children in Los Angeles County. We ascertained ADHD probands through outpatient pediatric clinics and support groups for the families of children with ADHD located in Los Angeles County.

Lists of potential CC probands living in the same ZIP codes as COS probands were obtained from a scientific survey research firm (Survey Sampling, Inc, Fairfield, Conn). Parents of potential CC probands were contacted by telephone to explain the purpose of the study and to screen out probands who had schizophrenia or ADHD or were gifted or learning disabled. All participants in the study provided a written, informed consent and assent (if a minor).

A child psychologist used the Schedule for Affective Disorder and Schizophrenia for School-Aged Children–Epidemiologic Version (K-SADS)30 to interview the parent about the proband’s psychiatric symptoms and then conducted a psychiatric interview of the proband. The psychologist then reviewed the medical and school records and K-SADS interviews with a child psychiatrist to reach consensus diagnoses.27 Fifty-one children with consensus diagnoses of DSM-III-R schizophrenia and with first onset of psychosis before 13 years of age constituted the schizophrenic probands. One hundred eighteen children with consensus diagnoses of DSM-III-R ADHD (at least 8 ADHD symptoms rated as definitely or probably present) constituted the ADHD probands. Of these, 106 had at least 8 ADHD symptoms rated as definitely present, whereas 12 children had at least 6 or 7 ADHD symptoms rated as definitely present and 1 or 2 ADHD symptoms rated as probably present.

Children were excluded from the CC group for a personal diagnosis of schizophrenia or ADHD, but not for any other psychiatric diagnoses. Nineteen (31%) of the 61 CC probands received at least 1 DSM-III-R diagnosis. The most frequent diagnoses were separation anxiety disorder (n=4), adjustment disorder (n=4), oppositional defiant disorder (n=3), oppositional defiant disorder (n=3), overanxious disorder (n=3), and simple phobia (n=3).

Children were excluded from all 3 proband groups if they had a Full-Scale IQ of less than 70 or a central nervous system disease or had taken psychoactive drugs that may have induced psychosis.

Parents of probands were given structured diagnostic interviews (the Diagnostic Interview Schedule34 supplemented with the psychosis section of the Present State Examination30) for Axis I disorders and the Structured Clinical Interview for DSM-III-R Personality Disorders35 for Axis II disorders by a different set of interviewers than the proband diagnostic team. Interviewers of parents were masked to the proband’s diagnosis. Family history information was collected on all first- and second-degree relatives, usually from 2 informants using the Relative Family History Interview.32 Direct interviews, family history, and medical record information were reviewed to make consensus DSM-III-R diagnoses. Consensus diagnoses were reviewed by senior clinicians (R.F.A., K.H.N., and D.L.F.) who were always masked to the diagnoses of probands and relatives. Previous reports from our project11,33 described the background and training of family interviewers, the interrater reliability on key diagnoses, and the diagnostic process in more detail.

Five parents of COS probands and 1 parent of an ADHD proband were excluded from this report because they had personal diagnoses of schizophrenia, and 2 parents of COS probands were excluded because of personal diagnoses of schizoaffective disorder with depression. None of the parents of CC probands had diagnoses of schizophrenia or schizoaffective disorder.33

NEUROCOGNITIVE TASKS

The neurocognitive tasks were administered to participants in a fixed order of presentation by research assistants who were masked to the diagnoses of the probands and parents.

The Trails B, from the Halstead-Reitan Battery,12,35 requires subjects to connect numbers and letters in sequence on
a page as quickly as possible, alternating between the 2 sets of characters correctly. The dependent variable is the time to complete the page. This paper-and-pencil test requires efficient visual search, maintenance of the task set, and the ability to alternate between and maintain sequences for 2 series of stimuli.

In the DS-CPT, subjects monitor a rapidly presented series of degraded single digits and respond as quickly as possible by pressing a button each time they see a zero-target stimulus that occurs quasi-randomly on 25% of presentations. Stimuli were presented at 1 per second for 40 milliseconds. Degradation of the stimuli resulted in digits appearing extremely blurred and indistinct. Subjects were given 480 trials in an 8-minute vigilance period. The dependent variable was sensitivity (d’), a signal-detection theory measure of signal/noise discrimination. The DS-CPT provides a sensitive measure of subtle deficits in sustained visual signal detection without burdening short-term memory.

For the Span, subjects report whether a T or O was flashed on a screen with other letters and are told to guess if in doubt. Stimuli were presented for 70 milliseconds. One target (T or O) and 0, 2, or 9 other letters were contained in each array. Each array size was presented for 40 trials. The dependent variable was the number of correct target detections for the 10-letter array size was presented for 40 trials. The dependent variable was the number of correct target detections for the 10-letter arrays. The Span provides an estimate of the rate of visual information processing.

The Trails B, Span, and DS-CPT detect neurocognitive impairments in AOS and ADHD probands and the relatives of AOS probands, whereas the Span also detects impairments in COS probands.

**EXPERIMENTAL DESIGN**

This study used a case-control design in which CC probands with index disorders (schizophrenia or ADHD) were excluded, but those with any other psychiatric disorder were included. This resulted in the parents of CC probands being more representative of the general population than they would have been if all CC probands with any psychiatric diagnoses were excluded.

**DATA ANALYSIS**

One-way analyses of variance (ANOVA) and χ² tests were used to test for group differences in demographic characteristics.

Scores on the 3 neurocognitive tasks were screened for validity by review of summaries of medical history and test results by 2 investigators (R.F.A. and K.H.N.) who were masked to proband and parent diagnoses. The Span data of 8 parents (of 3 COS, 2 CC, and 3 ADHD probands) and the DS-CPT data of 6 parents (of 4 COS, 1 CC, and 1 ADHD probands) were excluded because of poor visual acuity, medical conditions, or equipment failures or because the parents could not read English. Scores corrected for normal age effects were used to test for group differences on the 3 neurocognitive tests. Age corrections were developed by creating a best-fitting model of aging in parents of CC probands. Age-corrected scores were the residuals after the model of normal age effects was applied. We converted Trails B raw scores to reciprocals to normalize distributions, resulting in speed scores. We found a small, linear correlation between DS-CPT scores and test date associated with a subtle fading of the contrast of the stimulus slides. We regressed out this effect by entering test date as a covariate.

Because of prior evidence of sex effects on neurocognitive functioning, we evaluated sex effects in the parents of probands. Education was entered as a covariate to statistically control for group differences in education. A mixed-effects ANOVA with groups as an interfamily factor, parental sex as an intrafamily factor, and intrafamily education as a covariate was used to test the hypotheses that parents of COS and ADHD probands perform more poorly than parents of CC probands. Significant effects were followed up by means of pairwise post hoc tests.

Logistic regression was used to evaluate the diagnostic accuracy of the neurocognitive tests in distinguishing between the parents of COS and CC probands and those of COS and ADHD probands. Separate logistic regression was performed for mothers and fathers because of significant sex differences on one of the neurocognitive tasks and because the data from mothers and fathers from the same family are not independent observations and therefore cannot be pooled. For each of the 2 contrasts (COS-CC and COS-ADHD), 3 univariate logistic regressions (the predictors were the individual neurocognitive tasks) and a multivariate logistic regression were conducted (the 3 neurocognitive variables were the predictors) with group as the criteria. These analyses were performed for mothers and fathers separately.

**RESULTS**

**SUBJECT CHARACTERISTICS**

We found small but statistically significant differences between the groups of parents in age at testing and the number of years of education. The parents of COS probands had completed fewer years of school than the parents of ADHD and CC probands, who did not differ from each other (Table 1). The parents of ADHD probands were younger than parents of CC probands, who did not differ from parents of COS probands (Table 1). The proportion of mothers interviewed did not significantly differ across the 3 groups.

**GROUP MEAN DIFFERENCES**

Because of group differences in the number of years of education, and because there is frequently a significant effect of education on neurocognitive tasks, education was entered as a covariate in the ANOVAs for the age-adjusted scores for the 3 neurocognitive tasks (Table 2).
Table 2. Performance of Mothers and Fathers of 3 Proband Groups on Neurocognitive Tasks

<table>
<thead>
<tr>
<th></th>
<th>Parents of COS Probands</th>
<th>Parents of ADHD Probands</th>
<th>Parents of CC Probands</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mothers (n = 49)</td>
<td>Fathers (n = 38)</td>
<td>Mothers (n = 108)</td>
</tr>
<tr>
<td></td>
<td>Corrected</td>
<td>Raw</td>
<td>Corrected</td>
</tr>
<tr>
<td>DS-CPT, d1</td>
<td>0.09 (0.97)†‡§</td>
<td>2.51 (0.97)</td>
<td>0.51 (1.03)†‡§</td>
</tr>
<tr>
<td>Trails B</td>
<td>–1.28 (0.34)†‡</td>
<td>41.77 (33.15)</td>
<td>–1.48 (0.26)‡</td>
</tr>
<tr>
<td>Span, No. correct</td>
<td>0.68 (0.03)†‡</td>
<td>33.25 (2.93)</td>
<td>0.68 (0.04)‡</td>
</tr>
</tbody>
</table>

|                      | Group, F2,230 = 6.04   |
|                      | (P = .003); sex, F1,142 = 4.02 |
|                      | (P = .046) |
|                      | Group, F2,228 = 7.23   |
|                      | (P < .001); sex, F1,138 = 0.43 |
|                      | (P = .51) |
|                      | Group, F2,228 = 0.61   |
|                      | (P = .546); sex, F1,138 = 1.77 |
|                      | (P = .19) |

*Data are reported as mean (SD). COS indicates childhood-onset schizophrenia; ADHD, attention-deficit/hyperactivity disorder; CC, community control; DS-CPT, Degraded Stimulus–Continuous Performance Test; d1, sensitivity; and Trails B, Trail-Making Test B–Adolescent Version.
†Results of analysis of variance are reported for age-corrected scores, with education as a covariate. For all 3 tasks, the group × sex interaction was not statistically significant.
‡Indicates age- and education-adjusted score.
§Indicates scores were adjusted to correct for subtle change in slide contrast over time.
|Corrrected scores are speed scores (ie, time to complete the test [1/seconds]); raw scores are in seconds.

For the d1 index of the DS-CPT, we found statistically significant main effects for group and parental sex, but the group × sex interaction was not significant (Table 2). The fathers obtained significantly better scores on the DS-CPT than the mothers. The parents of COS probands obtained significantly poorer scores than the parents of CC (t238 = 3.33; P = .001) and ADHD (t238 = 2.99; P = .003) probands. The parents of ADHD and CC probands did not differ significantly from each other.

For Trails B, we found a significant main effect for group, but the main effect for sex and the group × sex interaction were not significant. The parents of COS probands were significantly slower completing Trails B than the parents of CC (t231 = 3.64; P < .001) or ADHD (t231 = 3.27; P = .001) probands. The parents of CC and ADHD probands did not differ significantly from each other.

For the Span, the main effects of group and sex and the group × sex interaction did not attain statistical significance.

DIAGNOSTIC ACCURACY ANALYSES

We tested the hypothesis that these neurocognitive tasks measure a schizophrenia endophenotype by using age-adjusted neurocognitive scores as predictors in a series of logistic regression analyses to test their ability to discriminate the parents of COS probands from the parents of CC and ADHD probands. Logits generated by the logistic regression analysis indicate the probability that a particular parent has a child with COS. Cutting points can be placed on logits to classify individuals as the parents of COS, CC, or ADHD probands. The effects of varying the cutoff on the sensitivity and specificity of the classification of individuals as parents of COS probands are depicted as receiver operating characteristic curves in Figure 1 and Figure 2. Sensitivity refers to the probability that a parent of a COS proband is classified correctly, whereas specificity is the probability that a parent of a CC proband is incorrectly classified as a parent of a COS proband. The cutoffs reported below optimize the ratio of specificity to sensitivity. Because we found no statistically significant differences on any of the neurocognitive tasks between parents of ADHD and CC probands, diagnostic accuracy analyses were not performed for this contrast.

The logistic regression models testing the discrimination between the mothers of COS and CC probands were statistically significant for the DS-CPT (χ2 = 14.24; n = 110; P < .001) and Trails B (χ2 = 18.38; n = 112; P < .001), but not for the model for Span. For fathers, the logistic regression model for Trails B was a significant discriminator (χ2 = 5.53; n = 75; P = .02), whereas the models for the DS-CPT and Span were not. Multiple logistic regression models for the discrimination between the mothers (χ2 = 23.67; n = 106; P < .001) and fathers (χ2 = 13.13; n = 71; P = .004) of COS probands and CC probands were statistically significant.

The sensitivity and specificity of the cognitive measures for discriminating between the mothers of COS and CC probands are shown in Figure 1A. At 100.0% specificity, the sensitivity for the Trails B was 14.6% and for the DS-CPT was 11.1%. For the Span, a cutoff producing 97.0% specificity yielded 4.3% sensitivity. For fathers (Figure 1B), a Trails B cutoff that produced 97.9% specificity produced 10.7% sensitivity. For the DS-CPT, a cutoff producing 97.9% specificity yielded 3.4% sensitivity. For the Span, a cutoff that produced 100.0% specificity yielded 14.3% sensitivity.
For all 3 tasks, lowering the cutoff for designating neurocognitive impairment in both the mothers and the fathers decreased the ratio of specificity to sensitivity. The multiple logistic model was more efficient than any single neurocognitive task for discriminating between the parents of COS and CC probands. For mothers, 20.0% sensitivity resulted in 100.0% specificity. Lowering the cutoff to 98.4% specificity increased sensitivity only slightly to 25.0%. For fathers, a cutoff that produced 100.0% specificity resulted in 20.0% sensitivity.

**Figure 1.** Receiver operating characteristic curves of efficiency of different cutting scores on logits from logistic regression models of the Trail-Making Test B–Adolescent Version (Trails B), Span of Apprehension (Span), Degraded Stimulus–Continuous Performance Test (DS-CPT), and combined-measures discrimination (Combined) between the mothers of childhood-onset schizophrenia (COS) (n=49) and community control (CC) probands (n=67) (A) and the fathers of COS (n=30) and CC probands (n=48) (B). The straight lines indicate chance levels of discrimination of the parents of COS probands from the parents of CC and attention-deficit/hyperactivity probands. Values of the logit above the line exceed chance levels of discrimination.

**Figure 2.** Receiver operating characteristic curves of efficiency of different cutting scores from logistic regression models of the Trail-Making Test B–Adolescent Version (Trails B), Span, DS-CPT, and combined-measures discrimination between the mothers of COS (n=49) and attention-deficit/hyperactivity disorder (ADHD) probands (n=108) (A) and the fathers of COS (n=30) and ADHD probands (n=82) (B). The straight lines indicate chance levels of discrimination of the parents of COS probands from the parents of community control and ADHD probands. Values of the logit above the line exceed chance levels of discrimination. Other abbreviations are explained in the legend to Figure 1.
Decreasing the cutoff to 93.4% specificity increased sensitivity to 32.0%.

For the discrimination between the mothers of COS and ADHD probands, the DS-CPT ($\chi^2_3 = 12.21; n = 152; P < .001$) and Trails B ($\chi^2_3 = 15.01; n = 155; P < .001$) were significant, whereas the Span was not. For fathers, the Trails B was a significant discriminator ($\chi^2_3 = 5.42; n = 110; P = .02$), whereas the DS-CPT and Span were not. The multiple logistic regression models for the discrimination between the mothers ($\chi^2_3 = 21.60; n = 150; P < .001$) and fathers ($\chi^2_3 = 9.87; n = 105; P = .01$) of COS and ADHD probands were both statistically significant.

For models testing the discrimination between the mothers of COS and ADHD probands (Figure 2A), the sensitivity for the Trails B was 14.6% and for the DS-CPT was 13.3% at 100.0% specificity. For the Span, a cutoff producing 99.1% specificity yielded 4.3% sensitivity. For fathers (Figure 2B), the sensitivity for the Trails B was 3.6% at 97.6% specificity, whereas the sensitivity for the DS-CPT was 3.4% at 98.7% specificity. For the Span, a cutoff producing 98.8% specificity yielded 3.6% sensitivity.

For each of the tasks, lowering the cutoff for cognitive impairment decreased the ratio of sensitivity to specificity for both mothers and fathers.

The multivariate models for the mothers (Figure 2A) produced 100.0% specificity with 12.2% sensitivity, whereas lowering the cutoff to produce 98.1% specificity resulted in 20.5% sensitivity. For the fathers (Figure 2B), the neurocognitive measures did not work quite as well. A cutoff producing 98.5% specificity had 16.6% sensitivity.

### COMMENT

Consistent with previous studies of relatives of patients with AOS, the parents of COS probands showed neurocognitive impairments compared with the parents of CC probands. The presence of psychophysioligic and linguistic impairments and structural and functional brain abnormalities, the response to typical and atypical antipsychotic medications, and the aggregation of schizophrenia and schizophrenia spectrum personality disorders in parents is similar in COS and AOS. The results of the current study provide important additional evidence of etiologic continuity between COS and AOS.

The analyses that adjust for education effects could have underestimated the magnitude of the differences in neurocognitive functioning between parents of COS and CC probands. The lower educational attainments of the nonpsychotic parents of COS probands may partially reflect the subtle cognitive impairments tapped by the 3 neurocognitive tasks, thereby reversing the assumption about the direction of causality that underlies statistical correction for educational differences.

By excluding parents with psychoses, this study demonstrated that neurocognitive impairments occur in the relatives of COS probands independent of the presence of schizophrenia.

The diagnostic accuracy analyses show that a combination of scores on neurocognitive tasks is better at differentiating between the parents of COS probands and those of CC and ADHD probands than scores from any single task. A useful indicator of the schizophrenia phenotype for linkage studies, an endophenotypic indicator, should have a ratio of at least 10:1 of true- to false-positive findings. A cutoff using a combination of scores across the 3 tasks correctly classifies 20.0% of the mothers and fathers of COS probands compared with 0% of the mothers and fathers of CC probands. Setting a less rigorous cutoff for neurocognitive impairment decreases the ratio of true- to false-positive findings.

Performance on the 3 neurocognitive tasks is somewhat less efficient in differentiating the parents of COS and ADHD probands, but it still shows diagnostic specificity.

A substantial subgroup of the parents of COS probands has worse neurocognitive performance than that of any of the parents of ADHD and CC probands. These results replicate and extend a previous report indicating that the combination of scores on certain neurocognitive tasks produces a level of diagnostic accuracy sufficient for use in genetic linkage studies. The levels of diagnostic accuracy in this study and the previous report are quite similar, despite the differences in neurocognitive tasks used in the studies.

In conjunction with the results of a previous study, these results have potentially important implications for genetic linkage studies. Including a rigorous definition of neurocognitive impairment as an index of the schizophrenia phenotype can add statistical power to linkage studies in 2 ways. First, when using models that dichotomize affected status, it can increase the number of individuals considered to be affected within a given family. In our study, even when neurocognitive impairment is rigorously defined so as to have very high specificity, the number of parents with neurocognitive impairments (20% of mothers and fathers) is much greater than the number of parents who obtain diagnoses of schizophrenia (4.9%). Second, neurocognitive measures yield continuous variables. When continuous scores of traits correlated with schizophrenia are used, pedigrees are more informative because "individuals can be assessed on a continuous scale that provides a greater range of information on 'unaffected' individuals who are not yet through the risk period or who are near the liability threshold for affection.""
present and previous studies and the selection of appropriate control tasks.

Consistent with the results of the major, most rigorous study examining neurocognitive impairments in the siblings of ADHD probands, we found no significant differences in neurocognitive functioning between the parents of ADHD and CC probands. This was despite the fact that the tasks administered to the parents of ADHD probands had been demonstrated in previous research to distinguish between patients with ADHD and controls. In contrast to the role of neurocognitive impairments in schizophrenia, where neurocognitive impairments appear to index the liability to schizophrenia in nonpsychotic relatives, ADHC neurocognitive impairments are present primarily in individuals with a diagnosis of ADHD and are thus only part of the active disorder. Our finding that neurocognitive impairments in schizophrenia, but not ADHD, are an expression of liability parallels the findings of a study comparing neurocognition in relatives of schizophrenia and bipolar probands.

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