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Association of neuropsychological vulnerability markers in relatives of schizophrenic patients

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Abstract

We investigated the association of neuropsychological risk indicators in a matched sample of first-degree relatives of schizophrenic patients ($n=54$) and normal controls ($n=72$). We focussed on three functions previously identified in a smaller, initial sample as putative risk indicators of the schizophrenia genotype: abstraction, verbal memory and auditory attention. The expanded sample of relatives displayed significantly lower scores than controls on abstraction, verbal memory and auditory attention. The relatives demonstrated significant intercorrelations among these three functions. The significant correlations among relatives between attention and verbal memory and between attention and abstraction differed significantly from these correlations among controls. We discuss how the use of multiple risk indicators may help us better identify those relatives that carry the schizophrenia genotype.

Keywords: Neuropsychological indicators; First-degree relatives; Schizophrenia

1. Introduction

Numerous studies suggest that relatives of schizophrenic patients exhibit neuropsychological impairments that are milder, yet similar to those seen among schizophrenic patients (Cannon et al., 1994; Levin et al., 1989; Saykin et al., 1991; Seidman, 1990; Seidman et al., 1992). We reviewed cognitive and neuropsychological studies that found relatives of schizophrenic patients to manifest subtle impairments in sustained attention, perceptual-motor speed, concept formation/abstraction, verbal memory and, to a lesser extent, mental control-encoding (Kremen et al., 1994).

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These neuropsychological deficits in relatives may represent expressions of a genetic liability to schizophrenia (Seidman, 1997).

In a previous report, we identified three neuropsychological functions that met two of three criteria for putative risk indicators of a genetic liability to schizophrenia (Faraone et al., 1995b): (1) lower group mean scores in relatives, (2) increased variability in relatives, and (3) a higher proportion of impaired relatives (at or below the second percentile of the control group). The functions meeting these criteria were: abstraction, verbal memory and auditory attention. The expectation of greater variability in relatives followed from our hypothesis that neuropsychological dysfunction among relatives was caused by the genetic liability that also increased the predisposition to schizophrenia. Because some relatives have this liability while others do not, this extra source of variability should be evident in putative measures of genetic liability. This would be true under single gene or oligogenic models of transmission, but not under the assumption that a multifactorial polygenic model causes both schizophrenia and neuropsychological dysfunction. Moreover, if neuropsychological deficits among the relatives of schizophrenic patients were due to some factor that affected all relatives (e.g., ascertainment bias, environmental exposure to a schizophrenic relative, psychosocial adversity, poor nutrition), then we would observe differences in mean performance without differences in variability.

Although there is a large literature showing that neuropsychological dysfunction is found in schizophrenia families, we know little about the mechanism of transmission. Because the genetic epidemiologic literature implicates multiple genes in the genesis of schizophrenia (Faraone and Tsuang, 1985; Gottesman and McGue, 1990; McGue and Gottesman, 1991; Risch, 1990), one reasonable hypothesis is that different domains of neuropsychological dysfunction reflect the action of different genetic defects. If this were so, then we would not expect the correlations of neuropsychological scores to be greater in relatives than in normal samples. A competing hypothesis is that the full range of cognitive impairment in relatives can be attributed to a single underlying genetic liability (or to only one gene in an oligogenic system). If this second hypothesis is correct, then measures of neuropsychological dysfunction should be more highly correlated with one another among relatives of schizophrenic patients compared with controls.

Family study data can address the competing hypotheses regarding whether deficits in relatives reflect common vs independent genetic liabilities, yet the relevant literature is small. Two studies suggest that indicators of neuropsychological dysfunction co-segregate in families. Roxborough et al. (1993) divided relatives based on normal vs abnormal P300 latency and found that the abnormal P300 subgroup performed significantly worse on both a frontal and a temporal lobe cognitive measure than the normal P300 relatives. Grove et al. (1991) reported that eye tracking and attentional dysfunction were associated among the relatives of schizophrenic patients. In contrast, Yurgelun-Todd and Kinney (1993) reported an inverse correlation between the Wisconsin Card Sorting and Trailmaking tests. Our purpose in the present study was two-fold. First, we sought to examine whether the tests comprising the functions that met our criteria for risk indicators in our initial sample would hold up in our expanded sample. Second, we sought to determine whether the pattern of test intercorrelations would be consistent with either of the competing hypotheses discussed above.

2. Methods

2.1. Subjects

Subjects in this study were relatives of schizophrenic probands who were inpatients or outpatients at three Boston area hospitals (Brockton/West Roxbury Veterans Affairs Medical Center, Massachusetts Mental Health Center, and Taunton State Hospital). Inpatients were consecutively screened for eligibility; outpatients were sequentially screened from a register of outpatients. Inclusion criteria were: a diagnosis of schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders-Revised (DSM-III-R; American Psychiatric Association, 1987); age over 17 years; English as the primary language;

a minimum eighth grade education; and available biological first-degree relatives. All probands gave informed consent to participate in the study, including permission for us to contact relatives.

For this 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 required absence of: (a) substance abuse within the past 6 months; (b) history of head injury with any documented cognitive sequelae or with loss of consciousness for more than 5 min; (c) neurological disease or damage; (d) mental retardation; and (e) medical illnesses that may significantly impair neurocognitive function. Of the 133 relatives enrolled in the study, 84 were related to a schizophrenic proband. Eight of these relatives were excluded, leaving 76 relatives. This study reports on the 54 subjects under age 60. We previously reported on the functioning of the remaining 22 elderly subjects (Faraone et al., 1996). Nearly all relatives were tested at the hospital sites, but a few who were unable to go to the hospital were tested at home.

In a previous paper, we reported on 35 relatives (Faraone et al., 1995b). In the full sample reported here we studied 54 relatives who were related to 38 schizophrenic probands and included 36 siblings, 8 parents, and 10 adult children of these probands. The mean age of probands was 40.7 years (SD = 9.9) and 33 of these probands were male. The ethnicity of one proband was unknown, but of the remaining 37, 32 were Caucasian. Of the 36 patients with available illness information, the mean age at first hospitalization was 21.0 years (SD = 7.3) and 50% were inpatients. Of the 32 probands for whom we had information on education level, 41% had less than a high-school education, 47% had a high-school degree, and 12% had more than a high-school education.

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). The interviews were carried out by BA- and MA-level research assistants who had received extensive training in diagnostic interviewing. Teams of at least two clinicians (clinical psychologists or psychiatrists) reviewed the structured interview results and the subject's entire medical record to determine the final lifetime diagnoses. These diagnoses were consensus diagnoses using the DSM-III-R criteria for Axis I disorders and DSM-III criteria for Axis II disorders (because the latter were derived from the SIDP, a DSM-III instrument). Within our larger research program the interviewers, diagnosticians and testers were working on neuropsychological and family studies of both schizophrenia and mood disorders. Thus, it was possible to maintain blindness between neuropsychological and diagnostic interview data and between data from probands and relatives. Additional methodological details are provided by Faraone et al. (1995b).

We recruited 72 normal controls through advertisements in the catchment areas of the hospitals from which the probands had been ascertained. Our goal was to obtain controls from the same geographic area, economic background and ethnicity as the relatives. Potential controls went through the same screening process as the relatives. In addition, controls were screened for psychopathology by using the short form of the Minnesota Multiphasic Personality Inventory (MMPI-168; Vincent et al., 1984) and by inquiring about history of psychosis or psychiatric hospitalization in their biological relatives. Potential control subjects were excluded if any clinical or validity scale, except Masculinity–Femininity, was above 70. We gathered information on the following, but did not exclude controls for a lifetime history of psychopathology or substance abuse or for neuropsychological dysfunction. Further description of our control group is reported elsewhere (Faraone et al., 1995b).

We used the reading test of the Wide Range Achievement Test-Revised (WRAT-R) in order to match groups on expected ability (Jastak and Wilkinson, 1984). In previous work, we found some support for the 'matching fallacy' in schizophrenic patients and their biological relatives (Kremen et al., 1995, 1996). This notion suggests

that matching on education or IQ may systematically mismatch on theoretically expected ability, i.e., the ability persons would be expected to achieve without the genetic or other biological risk for schizophrenia. Procedures below pertain to controls and relatives of the schizophrenic probands.

2.2. Measures

For the present work, we focussed on the tests comprising the functions that met criteria for risk indicators in our initial sample: abstraction, verbal memory and auditory attention. Measures of abstraction included the Wisconsin Card Sorting Test (WCST; Grant and Berg, 1948; Heaton, 1981) and the Visual Verbal Test (VVT; Feldman and Drasgow, 1981). WCST scores included number of categories achieved and number of perseverations. The VVT score used was the total number of errors. To measure verbal memory, we used the immediate (LMI) and delayed (LMII) recall conditions of the Wechsler Memory Scale-Revised (WMS-R) Logical Memories Subtest (Wechsler, 1987). To measure auditory attention, we used the Auditory Continuous Performance Test (A-CPT; Weintraub and Mesulam, 1985) and the Dichotic Listening Test (DLT; Kimura, 1967). The auditory CPT consisted of 300 audiotaped letters presented at the rate of 1 per second; 30 of these were the target letter 'A'. Our measure was the total number of errors including omission, commission, and late responses. The dichotic listening measure was the total number of digits apprehended (regardless of ear of report accuracy) in both ears over 24 trials, following four practice trials. Each trial consisted of strings of three digits presented simultaneously to each ear. Right and left digits were of equal intensity (80 dB). Hearing loss or other sensory deficits were screened by interview. We assessed hearing by presenting five trials of three digits to each ear individually, for a total of 15 digits per ear (Seidman et al., 1993). Subjects had to get at least 14 of 15 correct to be administered the tests.

2.3. Analyses

Several t tests and χ^2 analyses were conducted to assess comparability between groups on demographic variables. We conducted t tests to compare the performance of relatives and controls on the neuropsychological tests. When the variances differed significantly between groups, the t value for separate variances was used rather than the t value for pooled variances. Similar analyses were reported on for our initial sample with the first 35 relatives (Faraone et al., 1995b). Spearman rank order correlations were used to examine the relationship between neuropsychological measures within each group separately. Rank order correlations were used because of the varying distributions between groups. Fisher's z tests were calculated to compare correlation values between relatives and controls. We also used a logistic regression model using neuropsychological variables as predictor variables in attempting to discriminate relatives from controls.

3. Results

Table 1 presents demographic characteristics of the relatives of schizophrenic patients and the normal comparison group. The two groups were similar in age, reading level, parental education, sex and handedness. There was a trend for a higher percentage of Caucasians in the control group.

Table 2 presents the findings from t tests comparing the groups on all neuropsychological measures. With the exception of the VVT and a trend for the A-CPT, relatives performed significantly worse on all measures when compared to controls. Relatives also displayed significantly greater variability than controls on the WCST categories and perseverations, the A-CPT errors, and the DLT number of digits detected.

Table 3 reports the pattern of intercorrelations among neuropsychological measures within each group. For ease of presentation, the signs of correlations were changed so that, in all cases, a positive correlation indicates that better performance on one test is associated with better performance on another test. The four significant intercorrelations within the control group were between WCST categories and perseverations, WCST perseverations and the VVT errors, LMI and LMII, and A-CPT and VVT. Within the relative group, there

Table 1
Demographic characteristics of relatives of schizophrenic patients vs controls

Variable	Relatives ($n=54$) Mean	(SD)	Controls ($n=72$) Mean	(SD)	p
Age	39.1	(11.3)	36.0	(10.1)	0.11
WRAT-R reading	100.0	(10.6)	101.7	(12.3)	0.41
Parental education	11.4	(**3.0**)	11.5	(1.9)	0.94
	n	(%)	n	(%)	χ^2
Sex (% female)	39	(72)	44	(61)	0.19
Handedness (% RH)	49	(91)	65	(90)	0.97
Ethnicity (% Caucasian)	45	(83)	64	(96)	0.09

Bold type indicates SD with significantly greater variance.

Table 2
Neuropsychological test scores in relatives of schizophrenic patients vs controls

Test	Relatives Mean	(SD)	Controls Mean	(SD)	p
WCST					
No. of categories	5.0	(**1.8**)	5.6	(1.1)	0.04
Perseverations	12.8	(**16.4**)	6.9	(8.0)	0.02
Visual–Verbal					
Total misses	15.0	(7.0)	13.2	(6.5)	0.15
WMS-R Logical					
Memories—Immediate	26.1	(6.5)	30.8	(5.2)	0.0001
Memories—Delayed	23.1	(7.3)	27.1	(6.1)	0.001
Auditory CPT					
No. of errors	1.6	(**2.4**)	1.0	(1.3)	0.09
Dichotic Listening					
No. of digits detected	108.3	(**17.9**)	118.0	(12.9)	0.003

Bold type indicates SDs with significantly greater variance.

were nine significant intercorrelations. These were between A-CPT and all of the following: DLT, VVT, LMI and LMII; between DLT and WCST perseverations, LMI and LMII; between WCST categories and perseverations; between WCST perseverations and the VVT; and between LMI and LMII.

Table 4 lists the p values of the Fisher's z tests and the difference between the correlations within relatives and the correlations within controls. Correlations that were significantly greater among relatives than among controls were those between two attention measures (A-CPT and DLT), between attention and verbal memory (A-CPT and LMII; DLT and LMI; DLT and LMII) and between attention and abstraction (A-CPT and WCST perseverations; A-CPT and VVT).

For the logistic regression, we used a summary variable for each neuropsychological function. Scores on each test were standardized and summed within function, creating three predictor variables for verbal memory, abstraction and auditory attention. Verbal memory was the only statistically significant predictor variable in discriminating relatives from controls, χ^2 (1, $n=107$) $=8.3$, $p=0.004$.

In order to determine whether the pattern of intercorrelations within each group and the difference in these patterns between groups was

Table 3
Spearman correlation coefficients among auditory attention, abstraction and verbal memory within relatives and within controls[a]

	A-CPT	DLT	WCSTCAT	WCSTPV	VVT	LMI	LMII
A-CPT		0.36 $p=0.02$ $n=44$	0.16 $p=0.26$ $n=52$	0.27 $p=0.05$ $n=52$	0.31 $p=0.03$ $n=52$	0.33 $p=0.02$ $n=50$	0.37 $p=0.01$ $n=50$
DLT	−0.08 $p=0.53$ $n=67$		0.24 $p=0.12$ $n=43$	0.42 $p=0.005$ $n=43$	0.21 $p=0.17$ $n=44$	0.48 $p=0.001$ $n=41$	0.48 $p=0.002$ $n=41$
WCSTCAT	−0.02 $p=0.84$ $n=70$	0.01 $p=0.91$ $n=67$		0.74 $p=0.0001$ $n=53$	0.20 $p=0.17$ $n=51$	−0.04 $p=0.80$ $n=50$	0.07 $p=0.65$ $n=50$
WCSTPV	−0.12 $p=0.33$ $n=70$	0.13 $p=0.29$ $n=67$	0.58 $p=0.0001$ $n=71$		0.29 $p=0.04$ $n=51$	0.06 $p=0.66$ $n=50$	0.20 $p=0.16$ $n=50$
VVT	−0.28 $p=0.02$ $n=70$	0.23 $p=0.06$ $n=67$	−0.04 $p=0.72$ $n=71$	0.27 $p=0.02$ $n=71$		0.26 $p=0.07$ $n=49$	0.32 $p=0.02$ $n=49$
LMI	0.03 $p=0.81$ $n=70$	0.01 $p=0.91$ $n=67$	−0.13 $p=0.27$ $n=71$	−0.06 $p=0.63$ $n=71$	0.14 $p=0.24$ $n=72$		0.88 $p=0.0001$ $n=51$
LMII	0.01 $p=0.92$ $n=70$	0.06 $p=0.64$ $n=67$	−0.17 $p=0.14$ $n=71$	−0.10 $p=0.43$ $n=71$	0.14 $p=0.25$ $n=72$	0.83 $p=0.0001$ $n=72$	

[a]Correlations within relatives are above the diagonal and those within controls are below the diagonal. Some of the correlation signs were changed such that, in this table, a positive correlation always indicates that a better performance on one test is associated with a better performance on the other test. Due to some subjects missing data on some tests, the sample size for these analyses ranges as noted.

Test abbreviations: A-CPT = Auditory Continuous Performance Test; DLT = Dichotic Listening Test; WCSTCAT = Wisconsin Card Sorting Test—Categories; WCSTPV = Wisconsin Card Sorting Test–Perseverations; VVT = Visual Verbal Test; LMI = WMS-Revised Logical Memories Immediate Memory; LMII = WMS-Revised Logical Memories Delayed Memory.

restricted to those functions hypothesized to be core vulnerability indicators, we conducted similar analyses on two functions not hypothesized to be vulnerability indicators: motor ability and visual spatial ability. The tests of motor ability included the purdue pegboard, a measure of fine motor skill, and the dynamometer, a measure of grip strength. The tests of visual spatial ability included the visual reproductions subtest of the WMS-R (copy condition), the age-scaled score of the Block Design subtest of the Wechsler Adult Intelligence Scale-Revised, and the Hooper Visual Organization Test. Within each group, visual spatial tests were significantly correlated with each other, while the two motor tasks were not significantly correlated with each other. Within both groups, there were limited relationships between motor functioning and visual spatial ability. Fisher's z tests were non-significant for the comparison of these correlations within controls and within relatives.

4. Discussion

This study investigated the association of verbal memory, abstraction, and auditory attention

Table 4
Differences between correlations among auditory attention, abstraction and verbal memory in relatives vs controls[a]

	DLT	WCSTCAT	WCSTPV	VVT	LMI	LMII
A-CPT	0.44 $p=0.02$	0.18 $p=0.34$	0.39 $p=0.03$	0.59 $p=0.001$	0.30 $p=0.10$	0.36 $p=0.05$
DLT		0.23 $p=0.24$	0.29 $p=0.12$	−0.02 $p=0.92$	0.47 $p=0.01$	0.42 $p=0.02$
WCSTCAT			0.16 $p=0.12$	0.24 $p=0.20$	0.09 $p=0.63$	0.24 $p=0.20$
WCSTPV				0.02 $p=0.91$	0.12 $p=0.53$	0.30 $p=0.11$
VVT					0.12 $p=0.51$	0.18 $p=0.32$
LMI						0.05 $p=0.32$

[a]The actual correlation within controls was subtracted from the correlation within relatives to yield the values in the table. The p values correspond to the Fisher's z test that measured the significance of the difference between the actual correlations within each group.
Test abbreviations: A-CPT = Auditory Continuous Performance Test; DLT = Dichotic Listening Test; WCSTCAT = Wisconsin Card Sorting Test—Categories; WCSTPV = Wisconsin Card Sorting Test—Perseverations; VVT = Visual Verbal Test; LMI = WMS-Revised Logical Memories Immediate Memory; LMII = WMS-Revised Logical Memories Delayed Memory.

among relatives of schizophrenic patients. Compared to controls, the relatives were more impaired in these neuropsychological domains and displayed significantly greater variance in abstraction and auditory attention. Moreover, there were significant intercorrelations among the three functions within the relative group, whereas within the control group, the significant correlations were primarily within different tests of the same function. The significant correlations among relatives between attention and verbal memory and between attention and abstraction differed significantly from these correlations in the control group. Thus, neuropsychological functions that are putative risk indicators for schizophrenia co-occur to a greater degree within relatives than within controls. The increased correlations within relatives are specific to the putative risk indicators, as this pattern was not observed with the functions of motor and visual spatial ability.

Neuropsychological deficits found in this sample are consistent with those described in our earlier report from the first 35 relatives (Faraone et al., 1995b). Notably, in that sample, as well as in the complete sample reported here, relatives were significantly impaired on these tests with the exception of the VVT and A-CPT. Overall, our results are consistent with previous research on the relatives of schizophrenic patients (Kremen et al., 1994) and support the hypothesis that neuropsychological dysfunction among relatives is an indicator of the familial predisposition to schizophrenia (Faraone et al., 1995a). The fact that the risk indicator deficits found in relatives of schizophrenic patients, albeit mild, parallel those observed among schizophrenic patients, suggests to us that we are identifying meaningful deficits (Goldberg and Seidman, 1991; Hoff et al., 1992; Levin et al., 1989; Saykin et al., 1991; Seidman, 1983, 1990; Seidman et al., 1992).

Our findings support other studies that have also found a relationship between different vulnerability indicators in high-risk groups. Grove et al. (1991) found that eye tracking and attentional abnormalities co-segregated in schizophrenia families. The correlations between functions in our

sample of relatives were not high, but are comparable to the range of correlations reported by Grove et al. (1991). Presumably, the size of the correlations reflects error variance and other factors' contribution to relatives' test scores in addition to the contribution of familial factors. Our findings are also consistent with the work of Roxborough et al. (1993), who reported that a subgroup of relatives with abnormal auditory event-related potentials also had other neuropsychological deficits.

In contrast, our results are not consistent with one report finding an inverse relationship between Trailmaking-A time (an attention related measure) and categories achieved in the Wisconsin Card Sorting Test (Yurgelun-Todd and Kinney, 1993) in 15 siblings of schizophrenic patients. We had data on the Trails test for this sample and computed this correlation for purpose of comparison. The correlation in our sample between Trails—A time and categories achieved in the complete Wisconsin was significant ($r=-0.34$, $p=0.02$). Since high scores on the Trails indicate poor performance and high scores on WCST indicate good performance, this correlation is consistent with our other data showing a positive relationship between attention and abstraction dysfunction in relatives.

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. Relatives of persons with milder cases of schizophrenia may not display the same deficits or the same pattern of intercorrelation of deficits.

The tests used in this study were relatively complex. It is not possible to determine whether the multiple deficits are due to one underlying cognitive deficit or to a number of deficits traceable to widely distributed neural systems. The greater degree of association of these neuropsychological functions within relatives provides support for a single underlying vulnerability dimension, rather than independent processes. However, our data do not shed light on the nature of that single underlying vulnerability. The single liability may affect different functions through some common mechanism. Alternatively, one function may be primary and the other functions may be secondary. Based on various models of attention that posit the fundamental importance of attention to other cognitive functions (Mesulam, 1990; Mirsky et al., 1991), we might expect primacy of the attentional function. If the attention deficits are primary, then beyond a certain threshold, attentional deficits may compromise the functions of abstraction and verbal memory.

An alternative cognitive explanation to that described above is that deficits in working memory, which have been proposed to be the core deficit in schizophrenia (Goldman-Rakic, 1991), could conceivably explain deficits in all three functions. Indeed, Park et al. (1995) found evidence of a working memory deficit in relatives of schizophrenic patients. Working memory is clearly dependent on the prefrontal cortex (Goldman-Rakic, 1991). Our Dichotic Listening task, which requires short-term recall and localization of perception of six digits, is very likely to depend heavily on working memory as the task requires holding information on-line while performing cognitive operations (Baddeley, 1986). The WCST, which requires ongoing monitoring of previously learned rule-based information, is also likely to depend on working memory, at least in part. Recall of the logical memory stories may also be influenced by working memory, because the length of the stories goes beyond the usual working memory span; thus, efficient recall requires cognitive operations such as strategies of encoding and organization of information. The relatives' performance, including reduced learning at immediate and delayed recall compared to controls, but without an abnormal rate of forgetting, is typical of memory disorders associated with frontal lobe dysfunction (Wheeler et al., 1995). Gold et al. (1992) found numerous memory deficits in schizophrenic subjects, despite varying levels of attentional demand in the memory tasks. They discussed how both frontal and temporal lobe structures are implicated in memory dysfunction in schizophrenia, and that the joint dysfunction may be responsible for impairments in abstraction and attention. Future research should explore further the role of working memory, and address the neural and cognitive mechanisms of vulnerability expressed through

these three functions. Clearly, brain imaging studies using structural and cognitive neuroscience paradigms are needed to test these hypotheses in relatives of schizophrenic patients (Seidman, 1997; Seidman et al., 1997, in pr; Strauss and Summerfelt, 1994). In the mean time, as discussed by Faraone et al. (1995a), the use of multiple risk indicators simultaneously may help us better identify those relatives with the greatest vulnerability.

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