Neuropsychological Risk Indicators for Schizophrenia: A Review of Family Studies

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Abstract

We reviewed potential neuropsychological risk indicators for schizophrenia by addressing two broad questions about neuropsychological performance in biological relatives of schizophrenia patients: (1) Is there evidence of deficits, and, if so, (2) are those deficits similar to deficits found in schizophrenia patients themselves? There has not yet been adequate validation of most neuropsychological risk indicators, but promising leads have emerged from studies of relatives of persons with schizophrenia. The strongest evidence of impairment in relatives was in sustained attention, perceptual-motor speed, and concept formation and abstraction; to a slightly lesser extent, mental control/encoding (primarily with distraction) was implicated as well. Impairments in verbal memory and verbal fluency were also found, although these have been less well studied. The pattern of deficits paralleled that found in schizophrenia patients, thus suggesting dysfunction in prefrontal, temporal-limbic, and attentional systems. Findings were similar for children and adult relatives of schizophrenia patients. It is suggested that future studies (1) emphasize comprehensive test batteries, (2) develop composite neuropsychological measures, (3) use profile and deviant-responder analyses, (4) include psychiatric comparison groups, and (5) integrate neuropsychological assessments with brain imaging techniques.

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Over the past 10 to 15 years the idea that schizophrenia is a neurobehavioral syndrome has clearly become the mainstream position (Seidman 1983; Seidman et al. 1992). A substantial increase in neuropsychological studies has been an integral part of this trend. The goal of these studies is to identify cognitive and neuropsychological strengths and deficits, and ultimately, in conjunction with cognitive neuroscientific and brain-imaging approaches, to uncover the underlying structural or functional brain abnormalities associated with schizophrenia.

Although there is now substantial evidence of both brain abnormalities (Bilder 1992; Seidman et al. 1992) and genetic involvement (Faraone and Tsuang 1985) in schizophrenia, little is known about genetic factors in brain dysfunction specifically. Identifying neuropsychological risk indicators for schizophrenia is an important step in bridging these two areas of study. To qualify as a risk indicator, the variable under study should be (1) present and relatively stable in schizophrenia patients, (2) less common in patients with other psychiatric illnesses, and (3) present (perhaps in milder form) in those thought to be at risk for schizophrenia. More detailed criteria for risk indicators can be found elsewhere (Erlenmeyer-Kimling 1987; Garver 1987; Kremen et al. 1992*c*). There is ample evidence of neuropsychological deficits in schizophrenia patients (Bilder 1992; Seidman et al. 1992), but far less is known about what deficits may differentiate schizophrenia from other psychiatric ill-

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nesses. In this review, we focus on the third criterion by reviewing neuropsychological findings in the most likely group of at-risk persons: the biological (first-degree) relatives of schizophrenia patients.

We address two broad questions about neuropsychological performance in the relatives of schizophrenia patients: (1) Is there evidence of neuropsychological deficits, and if so, (2) how similar are the observed deficits to those found in schizophrenia patients? Given the theme of risk indicators in this issue, we emphasize the genetic epidemiologic implications of neuropsychological performance. Consequently, our principal intent is to determine which neuropsychological measures might be good indicators of the schizophrenia genotype.

We have organized the domains of function according to those commonly used in neuropsychology (Lezak 1983; Mirsky et al. 1991; Seidman et al. 1992). Because there are already several reviews of the neuropsychology of schizophrenia patients, we provide a context for studies of the relatives of schizophrenia patients by introducing each domain with only a sentence or two summarizing major findings; these summaries are based on Levin et al. 1989, Bilder 1992, and Seidman et al. 1992.

Within each domain, the findings are subdivided into studies of (1) children of schizophrenia patients and (2) adult relatives of schizophrenia patients. We separate these two groups because several factors may differentially affect neuropsychological functioning in each of them:

- Normal changes in cognitive development could account for differences between children and adults. Weinberger (1987), for example, has suggested that frontal lobe dysfunction may be relatively "silent" in childhood because some prefrontal brain structures have not yet come "on line."
- Course-of-illness factors may differentially affect cognitive changes. Because they have not reached the peak age of risk for schizophrenia, children are probably a heterogeneous group of both unaffected and preschizophrenic cases. This variability may be reduced in adults because they are generally well into the age of risk.
- Different life experiences may have different effects on cognitive functioning. For example, having a parent with schizophrenia might interfere more with cognitive development than having a sibling with schizophrenia would.
- Because of developmental differences, the same kinds of tests may not always be appropriate for both adults and children.

Results of neuropsychological measures in children and adult relatives of schizophrenia patients are shown in table 1. Because most of the findings regarding children of schizophrenia patients have been reviewed elsewhere (Nuechterlein and Dawson 1984; Erlenmeyer-Kimling 1987), we treat those results only briefly. Much of the research on adult relatives is recent, and several reports are from summaries of presentations to scientific meetings. Although preliminary, these reports offer exciting findings regarding neuropsychological risk indicators for schizophrenia.

Neuropsychological Studies of Relatives of Schizophrenia Patients

Attention. Attentional dysfunction has been observed in schizophrenia patients on a variety of neuropsychological measures, including tests of immediate attention span, sustained attention, visual search and tracking, selective attention, and executive control of attention. In general, attentional deficits become more pronounced as task demands increase or processing load is enhanced. From a neuropsychological perspective, we have organized subsets of attention-related tests into domains of function derived from previous factor-analytic work. In factor-analytic studies by Mirsky et al. (1991) and Kremen et al. (1992*b*), the Wechsler Adult Intelligence Scale–Revised (WAIS–R; Wechsler 1981) digit-symbol subtest, cancellation tests (Talland 1965; Weintraub and Mesulam 1985), the Stroop Color-Word Test (Stroop 1935; Golden 1978), and the Trail Making Test (A and B) (The Adjutant General's Office 1944) all loaded on a single factor we call "perceptual-motor speed." Digit span, arithmetic (WAIS–R or Wide Range Achievement Test–Revised; Jastak and Wilkinson 1984), and mental control (a subtest of the Wechsler Memory Scale–Revised [WMS–R; Wechsler 1987]) loaded on another factor we call "mental control/encoding." Sustained attention, which may be the strongest neuropsychological risk indicator (Garver 1987), is addressed in a review of continuous performance tests elsewhere in this issue (Cornblatt and Keilp 1994, this issue).

Perceptual-Motor Speed.

Children of schizophrenia patients. These measures involve visual search combined with motor speed. Many of them, referred to as tests of selective attention in the information-processing paradigm, have already been reviewed

Table 1. Neuropsychological findings in children and adult relatives of schizophrenia patients versus normal controls

Domain of function	Test	Reference	Result	Comment
Attention				
Perceptual-Motor Speed				
Children	Spokes test	Asarnow et al. (1978)	±	Spokes B only
	Stroop test	Asarnow et al. (1978)	+	
	Visual search	Winters et al. (1981)	+	
	Visual cancellation	Lifshitz et al. (1985)	±	More omissions; time predicts schizophrenia spectrum disorders
	Digit symbol/coding	Landau et al. (1972)	+	
		Mednick and Schulsinger (1968)	+	
		Asarnow et al. (1978)	−	
		Worland and Hesselbrock (1980)	−	
Adult relatives	Trail Making Test	Condray and Steinhauer (1992)	±	Trails B suggests differences, but α set at 0.009
		Goldberg et al. (1990)[1]	±	Trails A (p = 0.03)
		Keefe et al. (1992)	+	Trails B only
		Pogue-Geile et al. (1989)	+	Trails B only
		Pogue-Geile et al. (1991)	+	Trails B only
	Composite (Trails, digit symbol, Stroop, visual cancellations)	HBNFS	±	(p = 0.06)
		Mirsky et al. (1992)[2] [Irish sample]	+	
		Mirsky et al. (1992)[2] [Israeli sample]	+	Adult children (age 32)
Mental Control/Encoding				
Children	Arithmetic	Landau et al. (1972)	+	
		Mednick and Schulsinger (1968)	+	
		Sohlberg (1985)	+	
		Worland and Hesselbrock (1980)	−	
	Attention-span task	Erlenmeyer-Kimling and Cornblatt (1978)	+	No difference in distraction condition
	Auditory and visual digit span	Cornblatt and Erlenmeyer-Kimling (1984)	+	
	Digit span	Cornblatt and Erlenmeyer-Kimling (1985)	+	
		Lifshitz et al. (1985)	−	Less vocal rehearsal
		Mednick and Schulsinger (1968)	−	
		Worland and Hesselbrock (1980)	−	

Table 1. Neuropsychological findings in children and adult relatives of schizophrenia patients versus normal controls—*Continued*

Domain of function	Test	Reference	Result	Comment
	Digit span (distraction)	Harvey et al. (1981)	+	Reduced primacy
		Winters et al. (1981)	+	
	Dichotic listening	Asarnow et al. (1978)	±	Trend, deviant responder subgroup
		Hallett et al. (1986)	−	Left-ear *advantage*
		Orvaschel et al. (1979)	−	
	Information overload	Cornblatt and Erlenmeyer-Kimling (1984)	+	Distraction conditions
Adult relatives	Arithmetic	Goldberg et al. (1990)[1]	−	
		Mirsky (1988)	+	Adult children (age 25)
	Digit span	Goldberg et al. (1990)[1]	−	
		Mirsky (1988)	+	Adult children (age 25)
	Composite (arithmetic, digit span, WMS-R mental control)[3]	HBNFS	+	
		Mirsky et al. (1992)[2] [Irish sample]	−	
		Mirsky et al. (1992)[2] [Israeli sample]	−	
	Dichotic listening (shadowing)	Spring (1985) [Study 1]	+	More intrusion of distractors
		Spring (1985) [Study 2]	+	More intrusions for paranoid patients and their relatives
Concept formation and abstraction				
Children	Concept attainment	Asarnow et al. (1978)	+	
	Object-sorting test	Winters et al. (1981); Neale (1982)	±	Trend for deviant subgroup (Neale 1982)
Adult relatives	Object-sorting test	McConaghy (1959)	+	
		Phillips et al. (1965)	+	
	Wisconsin Card Sorting Test (WCST)	Condray and Steinhauer (1992)	−	
		Goldberg et al. (1990)[1]	−	Trend? (p = 0.10)
		Keefe et al. (1992)	−	
		Mirsky et al. (1992)[2] [Irish sample]	+	
		Mirsky et al. (1992)[2] [Israeli sample]	+	Adult children (age 32)
		Pogue-Geile et al. (1989)	+	
		Pogue-Geile et al. (1991)	+	Difference based on time to complete task
	Composite (WCST, Visual-Verbal Test [VVT])	HBNFS	+	WCST (p = 0.07), VVT (p = 0.05); more deviant responders on composite

Table 1. Neuropsychological findings in children and adult relatives of schizophrenia patients versus normal controls—*Continued*

Domain of function	Test	Reference	Result	Comment
	Luria-Nebraska relational concepts	Condray and Steinhauer (1992)	+	
		Pogue-Geile et al. (1989)	+	
Verbal ability and language				
Children	Speech-Sounds Perception (modified)	Hallett and Green (1983)	+	
Adult relatives	Verbal fluency	Goldberg et al. (1990)[1]	−	
		Keefe et al. (1992)	+	
		Pogue-Geile et al. (1991)	+	
Learning and memory				
Children	Memory-for-Designs	Orvaschel et al. (1979)	−	
	Short-term memory lag	Rutschmann et al. (1980)	+	Subject determined if items were previously seen
	Intentional and incidental learning	Driscoll (1984)	±	Worse intentional learning with distraction
Adult relatives	Wechsler Memory:	Goldberg et al. (1990)[1]	−	(p = 0.02)
	Logical memories	HBNFS	+	Also more deviant responders
	Visual reproductions	Goldberg et al. (1990)[1]	−	
		HBNFS	−	
	Paired associates	Goldberg et al. (1990)[1]	−	
		HBNFS	±	More deviant responders (verbal)
Visual spatial ability				
Children	Embedded Figures test	Nuechterlein and Dawson (1984) (review)	±	Inconsistent results
Adult relatives	Block design, road map	Goldberg et al. (1990)[1]	−	
	Composite (block design, Benton Line Orientation, Hooper Visual Organization, WMS-R visual reproduction copy)	HBNFS	−	
Motor function				
Children[4]	Individual rhythm	Lifshitz et al. (1985)	−	
	Mirror drawing	Lifshitz et al. (1985)	+	Slower, less efficient
Adult relatives	Composite (Purdue Pegboard, Dynamometer, Manual	HBNFS	−	

Table 1. Neuropsychological findings in children and adult relatives of schizophrenia patients versus normal controls—*Continued*

Domain of function	Test	Reference	Result	Comment
	position and Graphic sequencing			
	Go/No/Go	Goldberg et al. (1990)[1]	–	
	Dynamometer (maintenance of grip tension)	Rosen et al. (1991)	+	
Cerebral asymmetry				
Children	Story comprehension and recall	Hallett and Green (1983)	+	Impaired binaural relative to monaural
		Hallett et al. (1986)	+	
	Verbal dichotic listening	Hallett et al. (1986)	–	Left-ear *advantage*
	Handedness	Hallett and Green (1983); Hallett et al. (1986)	+	More left-handers in combined sample
Adult relatives	Handedness	HBNFS	–	

Note.—Portions of this table regarding children of schizophrenia patients were adapted from Erlenmeyer-Kimling (1987) and Nuechterlein and Dawson (1984) HBNFS = Harvard–Brockton VA Neuropsychology Family Study (based on Kremen et al. 1992*a* and work in preparation); WMS–R = Wechsler Memory Scale–Revised (Wechsler 1987); + = significant difference from controls (unless indicated, relatives perform more poorly than controls), – = nonsignificant results; ± = mixed results or trend

[1] Relatives in this study were unaffected monozygotic twins of schizophrenia patients.

[2] Significance values for relatives versus controls in the Mirsky et al. (1992) samples were provided by A.F. Mirsky, Ph.D (personal communication, October 1992).

[3] Mirsky et al. (1992) includes arithmetic and digit span only.

[4] Neuromotor deficits have been a consistent finding in children of schizophrenia patients, but those results are based primarily on neurologic, rather than neuropsychological, findings (Asarnow and Goldstein 1986).

extensively for children of schizophrenia patients (Nuechterlein and Dawson 1984; Erlenmeyer-Kimling 1987). Evidence for poorer performance on tests of perceptual-motor speed among such children than among children of normal parents is fairly strong (see table 1).

Adult relatives of schizophrenia patients. Five studies found significant deficits on perceptual-motor speed tests among relatives of schizophrenia patients; results suggested differences in three other studies. Thus, the evidence is fairly strong for perceptual-motor speed deficits in adult relatives as well. Nonpsychotic relatives were significantly slower on the Trail Making Test (part B) in the studies of Pogue-Geile et al. (1989, 1991) and Keefe et al. (1992). Using the perceptual-motor speed function described above, Mirsky et al. (1992) found significant deficits in both samples studied. (Significance values for relatives vs. controls in the Mirsky et al. 1992 samples were provided by A.F. Mirsky, Ph.D., personal communication, October 1992.)

Our group (Kremen et al. 1992*a*) created composite scores in each of 10 domains of function: (1) abstraction/executive, (2) general verbal ability, (3) general visual spatial ability, (4) verbal memory, (5) visual memory, (6) learning, (7) perceptual-motor speed, (8) mental control/encoding, (9) auditory attention/vigilance, and (10) motor ability. These scores were derived from a linear combination of standardized scores for variables within each domain, after adjusting for demographic variables. We refer to this study below as the

"Harvard–Brockton VA Neuropsychology Family Study" (HBNFS); all results reported herein are based on neuropsychological function scores adjusted for age, sex, and parental socioeconomic status. Nonpsychotic adult relatives in the HBNFS were marginally significantly worse than controls (p = 0.06) on the perceptual-motor speed function.

Condray and Steinhauer (1992) examined six persons with schizotypal personality disorder who were siblings of schizophrenia patients; they reported no deficit on the Trail Making Test (on the basis of a modified Bonferroni corrected alpha of 0.009). However, the means and standard deviations (SDs) for Trails B times of the schizotypal relatives and controls (99.2 [±68.1] and 60.1 [±16.6], respectively) do suggest slower, more variable performance among the relatives. In the National Institute of Mental Health (NIMH) twin study, Goldberg et al. (1990) found that unaffected monozygotic cotwins were not significantly worse than normal control twins on the Trail Making or Stroop Test. Trails A was worse in the unaffected cotwins, but the p value of 0.03 was nonsignificant with a Bonferroni correction.

Mental Control/Encoding.

Children of schizophrenia patients. Many tests in this section have been referred to as measures of short-term memory or selective attention in the information-processing paradigm (Nuechterlein and Dawson 1984; Erlenmeyer-Kimling 1987). Three of four studies reporting on Wechsler subtests showed significantly lower arithmetic subtest scores in children of schizophrenia patients than in children of normal parents, even though verbal IQ was not necessarily lower (positive findings: Mednick and Schulsinger 1968; Landau et al. 1972; Sohlberg 1985; negative finding: Worland and Hesselbrock 1980).

Results have been inconsistent for simple attention-span tasks. However, deficits among children of schizophrenia patients have been present when these tasks include a distraction component (Harvey et al. 1981; Winters et al. 1981). Harvey et al. (1981) also noted that such children showed reduced primacy; that is, they had difficulty recalling the first digits presented in the lists. Reduced primacy showed some specificity for schizophrenia in that it was worse in children whose parents had schizophrenia than in those whose parents had affective disorders.

Dichotic listening tests have had mixed results (Asarnow et al. 1978; Orvaschel et al. 1979; Hallett et al. 1986), but significant deficits among children of schizophrenia patients were found in the information-overload test, in which a matching task was performed with auditory distraction (Cornblatt and Erlenmeyer-Kimling 1984). In addition, such children showed deficits in recalling the story in one of the distraction conditions.

Adult relatives of schizophrenia patients. At age 25, children of schizophrenia patients in the Israeli high-risk study had significantly worse performance on WAIS–R digit span and arithmetic tests than adult children of normal controls (Mirsky 1988). Goldberg et al. (1990) found no difference in digit span or WAIS–R arithmetic between unaffected monozygotic cotwins and controls. Relatives in the HBNFS had significantly lower scores than controls on the composite mental control/encoding function; however, Mirsky et al. (1992) found no differences in two samples using a similar composite function.

Spring (1985) reported two studies in which subjects hearing competing verbal messages presented to each ear were required to repeat back (shadow) stimuli presented in one ear while ignoring stimuli presented to the other (distractor) ear. Schizophrenia patients and their siblings had significantly more intrusion of distractors at the phoneme level than controls or affective patients. In the second study, the effect was found for paranoid schizophrenia patients and their relatives. The increased intrusions were present even though their shadowing performance was unimpaired. Because shadowing accuracy in the distraction condition was not different from the controls, it seems unlikely that the apparently lower resistance to interference was caused by reduced overall processing capacity.

Overall, there is some evidence that both children and adult relatives of schizophrenia patients perform more poorly on mental/control encoding tasks, but the effect is seen primarily under auditory-distraction conditions. Although several explanations are possible, we suggest that disruption of working memory is a common factor underlying these deficits because these tests necessitate performing two tasks simultaneously, which, according to Baddeley et al. (1991), requires working memory.

Concept Formation and Abstraction. This section primarily covers sorting tests, which have been widely used in the neuropsychological paradigm to study abstrac-

tion, concept formation, and executive control. Deficits in sorting have long been considered characteristic of schizophrenia. In the past, sorting tests were intended to assess thought disorder, but more recently emphasis has shifted to the putative ability of such tests (particularly the Wisconsin Card Sorting Test [WCST; Heaton 1981]) to tap prefrontal lobe function in schizophrenia patients.

Children of schizophrenia patients. Concept formation and abstraction have not been examined in many studies of children of schizophrenia patients. Asarnow et al. (1978) found deficits in such children, but Winters et al. (1981), using more narrow criteria for schizophrenia, did not. However, a deviant subgroup of children showed a trend toward poorer performance compared with children of normal parents (Neale 1982).

Adult relatives of schizophrenia patients. Several studies have found concept-formation and abstraction deficits in adult relatives of schizophrenia patients. In two older studies, impairment on sorting tests was found in parents and siblings of schizophrenia patients (McConaghy 1959; Phillips et al. 1965). In the more recent studies using contemporary methods and criteria for diagnosis, there has been an emphasis on the WCST as a measure of concept formation, abstraction, and cognitive flexibility.

In two samples, Pogue-Geile et al. (1989, 1991) found that siblings of schizophrenia patients did worse on the WCST than controls. It appears that the variable measured in the second study was time to complete the task, which is not a standard measure of WCST performance. Mirsky et al. (1992) found significant WCST deficits in two samples as well. In the HBNFS, there was a trend ($p = 0.07$) toward worse WCST performance in relatives of schizophrenia patients than in controls. However, Condray and Steinhauer (1992) and Keefe et al. (1992) did not find evidence of impaired WCST performance among adult relatives of schizophrenia patients, nor did Goldberg et al. (1990) among unaffected monozygotic cotwins of schizophrenia patients compared with controls.

Concept-formation and abstraction deficits have been found on other tests as well. In the HBNFS, mean performance levels on the Visual-Verbal Test (Feldman and Drasgow 1959) and a composite measure comprising the Visual-Verbal Test and the WCST were significantly worse in relatives than in controls. Moreover, a significantly greater proportion of relatives than of controls was impaired (2 SDs below control mean). Two studies using the Luria-Nebraska relational concepts test (Golden et al. 1978) also found significant impairments among adult relatives of schizophrenia patients (Pogue-Geile et al. 1989; Condray and Steinhauer 1992). Although the latter test was designed primarily as a language measure, we have included it in the concept formation/abstraction domain because it appears to place fairly substantial demands on reasoning ability and working memory.

Verbal Ability and Language. Schizophrenia patients generally show mild language disturbances characterized by relative intactness of elemental language functions (e.g., naming, comprehension, repetition) and impairment of more complex language and communication functions, including verbal fluency.

Children of schizophrenia patients. Aside from vocabulary, there has been little neuropsychological evaluation of language in children of schizophrenia patients, perhaps because the related areas of concept formation and thought disorder have received greater emphasis. Hallett and Green (1983) found that such children made significantly more errors than children of normal parents on a test of perception of speech sounds. Impairment on this test of phoneme discrimination could be secondary to attentional deficits. On the other hand, their results suggest that some deficits observed in relatives of schizophrenia patients (e.g., dichotic listening) could be confounded by subtle speech-processing impairments.

Adult relatives of schizophrenia patients. Although most studies have found no differences in general verbal ability, two studies using verbal fluency tests (Benton 1968) found significant impairments in adult relatives of schizophrenia patients (Pogue-Geile et al. 1991; Keefe et al. 1992). The NIMH twin study did not find verbal-fluency deficits in unaffected cotwins. Verbal fluency fits within the domain of language function, thus implicating left temporal lobe structures. However, there is also strong evidence that verbal fluency is associated with left frontal lobe function (Lezak 1983). The frontal component of verbal-fluency deficits may be significant, given that adult relatives of schizophrenia patients do not tend to have deficient vocabulary scores, particularly if one accounts for education.

Learning and Memory. Impairments in short-term verbal and

visual memory have been shown consistently in schizophrenia patients (e.g., Saykin et al. 1991). That these deficits are generally greater for recall than for recognition has suggested impairment in encoding processes owing to slowed processing and ineffective mnemonic organization. However, deficits in recall persist in some chronic patients, even after effective encoding and organization have been established (Levin et al. 1989).

Children of schizophrenia patients. Although the attention-related tests referred to above include recognition and recall components, there has been little study of direct memory assessment in children of schizophrenia patients. Orvaschel et al. (1979) found no impairment on the Memory-For-Designs Test (Graham and Kendall 1960), a measure of visual memory. Rutschmann et al. (1980) found deficits among such children on a task that required subjects to tell whether items were new or had been presented previously. The researchers concluded that the difficulties on this recognition task were not caused by memory decay. Driscoll (1984) found no intentional or incidental learning differences between children of schizophrenia patients and comparison groups under nondistraction conditions. However, with auditory distraction such children had significantly worse intentional learning than children of normal or psychiatric comparison parents. These findings are largely consistent with the results of the mental control/encoding tasks.

Adult relatives of schizophrenia patients. Two studies examined learning and memory in adult relatives of schizophrenia patients. In the NIMH twin study, neither logical memories (verbal recall), nor visual reproductions (visual recall), nor verbal paired-associate learning on the WMS–R was considered worse in unaffected cotwins than in controls (Goldberg et al. 1990). Logical memories were worse at the 0.02 level, but Goldberg and colleagues set significance at 0.002 with a Bonferroni correction. Thus, the conclusion of no difference may be overly conservative, particularly because previous work with patients would reasonably suggest the a priori hypothesis of impaired memory in the relatives of schizophrenia patients.

In the HBNFS, we found that adult relatives of schizophrenia patients were significantly impaired on WMS–R logical memories but not visual reproductions. In addition, a significantly higher proportion of relatives than of controls was impaired (2 SDs below control mean) on the verbal-recall measure. Our learning measure was composed of the WMS–R verbal and visual paired associates. Mean differences were not found, but a significantly higher proportion of relatives than of control subjects was impaired. Again, the deficit was accounted for primarily by the verbal subtest. These results are consistent with neuropsychological and morphological studies showing temporal-lobe and limbic (hippocampal) abnormalities (stronger in the left hemisphere) in schizophrenia patients (Seidman et al. 1992). Verbal memory deficit may thus be a promising risk indicator.

Visual Spatial Ability. Schizophrenia patients tend to have essentially intact performance on simple visual perceptual tasks. Relative to other functions, visual spatial ability appears to be less impaired in schizophrenia, particularly after accounting for confounding influences such as IQ or attentional dysfunction.

Children of schizophrenia patients. Visual spatial ability has not been studied much in high-risk samples. There have been inconsistent results for the Embedded Figures Test (Witkin et al. 1962) in very young children (original reports cited in Nuechterlein and Dawson 1984).

Adult relatives of schizophrenia patients. Consistent with the literature on schizophrenia patients, no studies found deficits among relatives on measures of visual spatial ability. These include WAIS–R block design as well as other visual spatial tasks (Goldberg et al. 1990 [road map]; HBNFS [Benton Line Orientation Test, Benton et al. 1983; Hooper Visual Organization Test, Hooper 1958; WMS–R visual reproductions copy]).

Motor Function. One of the most consistent findings in schizophrenia is the slowing of response speed and reaction time. Although neuroleptics are associated with motor impairments, especially on fine motor tasks, motor abnormalities were noted in schizophrenia long before the introduction of neuroleptics.

Children of schizophrenia patients. Neuromotor deficits have been found consistently in children of schizophrenia patients, but these deficits have been assessed primarily within the neurological, rather than the neuropsychological, paradigm (Asarnow and Goldstein 1986). However, Lifshitz et al. (1985) reported on two motor tests: individual rhythm (tapping tasks) and mirror drawing. For the

most part, they found no deficits among children of schizophrenia patients on individual rhythm, but these children were significantly slower, were less efficient, and had more disorganized responses on mirror drawing tasks. Although we have included it in this section, mirror drawing does share features of some of the perceptual-motor speed tasks.

Adult relatives of schizophrenia patients. Adult relatives of schizophrenia patients in the HBNFS were unimpaired on a composite motor-function measure. Goldberg et al. (1990) found no impairment on the Go/No/Go Test (Benson and Stuss 1982) in unaffected monozygotic cotwins. Even ill twins were unimpaired on this test.

In an interesting variation of the Hand Dynamometer Test (Reitan and Wolfson 1985), Rosen et al. (1991) demonstrated a deficit in the ability to maintain a constant level of grip-induced muscle tension among schizophrenia patients and their parents and siblings. Some specificity for this apparent deficit in monitoring ongoing behavior was shown as well, because performance was worse in schizophrenia patients than in affective patients. The difficulty was thought to be associated with deficits in corollary discharge (cited in Rosen et al. 1991). Corollary discharge deficits may, in turn, be related to subtle dysfunction in frontal (executive) systems. One question arising from this work is whether early neuromotor abnormalities would predict later impairment in maintaining grip tension.

Cerebral Asymmetry. Anomalies in cerebral laterality are found in at least some subgroups of schizophrenia patients. Reaction-time studies implicate greater left- than right-hemisphere dysfunction, although such anomalies tend to be superimposed on bilateral impairments. Dichotic listening studies also tend to show bilateral impairment in schizophrenia patients; despite considerable variability, schizophrenia patients do tend to have the expected right- and left-ear advantages on verbal and nonverbal tasks, respectively. However left-hemisphere overactivation (especially among paranoid patients) has also been inferred on the basis of subtly increased rates of left-handedness and findings of an exaggerated right-ear advantage on verbal dichotic tasks (see reviews by Goldberg and Seidman 1991 and Seidman et al. 1992).

Children of schizophrenia patients. Two studies by Hallett and colleagues (Hallett and Green 1983; Hallett et al. 1986) required subjects to answer questions about stories presented binaurally and monaurally to each ear. Children of schizophrenia patients were deficient in binaural, relative to monaural, comprehension and recall. Hallett and colleagues concluded that this pattern reflected abnormal interhemispheric integration. Hallett et al. (1986) also used a verbal dichotic listening task on which such children had equal performance with each ear and significantly higher left-ear scores than controls. These findings are unusual in that they indicate a performance *advantage* among children of schizophrenia patients; however, they are difficult to interpret because the left-ear advantage was accounted for primarily by the boys, 29 percent of whom were left-handed.

Information on handedness, another index of asymmetry, was provided in the two studies by Hallett and colleagues. In their combined samples (35 per group), there were 29 and 3 percent left-handers among children of schizophrenia patients and those of normal parents, respectively ($p < 0.05$).

Adult relatives of schizophrenia patients. In the HBNFS, there were no differences in handedness distributions between 60 controls (90% right, 7% mixed, 3% left) and 35 relatives (91% right, 9% mixed, 0% left). The distribution among relatives did not change appreciably even when those with psychotic symptoms were included. Given findings of increased incidence of left-handedness in schizophrenia patients, further assessment of handedness in relatives is of interest.

Discussion

Initially, neuropsychological measures were applied to children of schizophrenia patients in prospective, high-risk studies, most of which emphasized attention-related functions, as examined through the information-processing paradigm. In our view, the ability of brain imaging techniques to assess brain structure and function directly has made the neuropsychological approach, with its emphasis on brain-behavior relationships, increasingly more valuable. Some recent studies of adult relatives of schizophrenia patients have taken a more direct neuropsychological approach. Several of these studies have put additional emphasis on concept formation, abstraction, executive function, and learning and memory.

Possible Risk Indicators. Not only is there evidence of neuro-

psychological deficit in relatives of schizophrenia patients, but the areas of function in which deficits are most consistently observed are much the same as those in which prominent deficits have been found in schizophrenia patients themselves. The strongest evidence of impairment in relatives is in sustained attention (see Cornblatt and Keilp 1994, this issue), perceptual-motor speed, and concept formation and abstraction; to a slightly lesser extent, mental control/encoding (primarily with distraction) is implicated as well.

It is perhaps not surprising that the strongest evidence of dysfunction in relatives is found in the areas of functioning that have been most widely studied. However, other areas of functioning that have been less well studied bear promise. These include verbal learning and memory, and verbal fluency. These deficits have been observed even though evidence of impairment in general verbal or visual spatial function has been largely negative. These functions, along with the attention-related and concept formation/abstraction functions, provide the most promising leads for neuropsychological risk indicators for schizophrenia. Future studies will need to include more systematic work aimed at separating attentional, conceptual, linguistic, and memory components.

This clustering of impaired functions implicates prefrontal (e.g., WCST, Trails B, verbal fluency tests) and temporal-limbic (e.g., logical memories, dichotic listening) brain regions (Lezak 1983; Bilder 1992; Seidman et al. 1992). The consistent attentional deficits suggest the involvement of prefrontal-subcortical (anterior limbic and reticular) systems; however, attentional deficits may involve parietal and temporal areas as well (Mirsky et al. 1991; Seidman et al. 1992). Thus, the brain regions or systems most strongly implicated by the deficits found in relatives of people with schizophrenia closely parallel the neuropsychological as well as structural and functional brain imaging data for schizophrenia patients (Bilder 1992; Seidman et al. 1992). The deficits observed in relatives are less consistent and more subtle than those found in schizophrenia patients, but that is expected, since not all patients manifest these impairments either. On the other hand, the obvious parallels between the two sets of findings strengthen the view that some of these neuropsychological deficits may indeed constitute risk indicators for schizophrenia.

Results were inconsistent for motor function in relatives of schizophrenia patients, but we believe this domain warrants further study. Neurologic findings in children of schizophrenia patients have consistently indicated neuromotor abnormalities, but only a few such studies have been conducted using neuropsychological measures of motor function in adult relatives. Traditional neuropsychological tests did not show impairment (Goldberg et al. 1990; HBNFS). The lack of consistent motor abnormalities in adult relatives could also be attributable, in part, to developmental factors. That is, many early neuromotor abnormalities are relatively nonspecific and may not necessarily predict later abnormalities in the same functional domain. For example, Rinaldi et al. (1991) found that neuromotor deficits in children of schizophrenia patients predicted affective flattening in adolescence. In contrast, the difficulty in maintaining grip tension found by Rosen et al. (1991) appears promising as a risk indicator for schizophrenia.

Disturbance in cerebral asymmetries of function has been a prominent neuropsychological theory of schizophrenia (Goldberg and Seidman 1991), yet few studies of relatives have addressed it directly. Thus, further study is warranted in this area as well. Moreover, deficits observed among relatives in verbal, as opposed to visual spatial, functioning provide indirect evidence consistent with the hypothesis of greater left- than right-hemisphere dysfunction.

Children Versus Adult Relatives of Schizophrenia Patients. With the possible exception of motor function, in cases for which there are relatively comparable data, there appears to be general consistency between children and adult relatives of schizophrenia patients. Evidence of impairment in the attentional domains noted above is about equally strong in children and adult relatives. There is limited evidence regarding concept formation and abstraction in children because most work assessing these functions has been conducted with adults. To some extent, developmental factors may account for the focus on adults. For example, normal persons do not consistently perform well on the WCST—the most widely used neuropsychological measure in this domain—until ages 10 to 12 (Chelune and Baer 1986).

Genetic and Environmental Factors. There has been some evidence of significant heritability for a few neuropsychological measures (Cornblatt et al. 1988; Kendler et al. 1991), but much more system-

atic work is needed to determine the heritability of neuropsychological deficits that may be indicators of risk for schizophrenia. These potential risk indicators may, in turn, be valuable for genetic linkage analyses. Heritability data are also useful for elucidating the extent of environmental influences that contribute to neuropsychological deficits. Environmental differences between children and adult relatives (e.g., being raised by a parent with schizophrenia) might lead to neuropsychological differences, but the general consistency between the two groups reduces the likelihood that such environmental factors play a significant role in these deficits. Nevertheless, the impact of familial environmental factors in relatives versus controls cannot be ruled out on the basis of these data.

An advantage in assessing relatives is that confounding nongenetic factors, such as the effects of medication or hospitalization, are reduced or eliminated. On the other hand, power to detect deficits in relatives is reduced because schizophrenia itself may be genetically heterogeneous, and all relatives are not expected to carry the schizophrenia genotype. Profile analysis and deviant responder analysis represent potential solutions to these problems.

Profile and Deviant Responder Analyses. In the neuropsychological approach, the presence of a deficit is determined by deviation from an individual's own mean or some estimate of his or her "true" potential (Lezak 1983; Seidman 1990). An average score on a single test may still represent a deficit if it appears against a background of superior scores. Thus, profile analysis (i.e., evaluation of within-subject variability based on a comprehensive test battery) is at the heart of the neuropsychological approach (cf. Seidman 1990; Saykin et al. 1991) and distinguishes clinical neuropsychology from the cognitive information-processing paradigm. Generating profiles of relative strengths and weaknesses may be an effective way to discern subgroups with qualitatively different types of deficits, that is, profiles of different shape. Some members of these subgroups may, in turn, be classified as deviant responders. Theoretically, these profiles might differentiate relatives who do or do not carry the schizophrenia genotype, or profiles of relatives might correspond to specific neuropsychological profiles or diagnostic subtypes in probands.

With so few comprehensive neuropsychological assessments of relatives, we know little about the extent to which, within individuals, impairments in one neuropsychological domain are associated with impairments in other domains. As with patients, determining whether separate functional systems or a single, unified system underlies the various deficits observed in relatives will require the use of comprehensive test batteries in concert with brain-imaging techniques.

Given the notion of deviation from a measure of one's true potential, it is somewhat puzzling to have found weaker evidence for risk indicators in the unaffected monozygotic cotwins of schizophrenia patients (Goldberg et al. 1990) than in several of the studies of nontwin adult relatives. Still, the unaffected cotwins did fall somewhere between the controls and the ill twins on many neuropsychological measures. Monozygotic twins are, of course, at genetically higher risk than first-degree relatives, but selection factors in obtaining only discordant twin pairs could also affect results. One argument, for example, would be that discordant monozygotic twin pairs are the most likely place to find cases of schizophrenia in which nongenetic factors are rather strong (Lyons et al. 1989). On the other hand, a study finding similar rates of schizophrenia-like psychosis among the offspring of ill and unaffected monozygotic twins (Gottesman and Bertelsen 1989) is at odds with this argument. (See Lyons et al. 1989 for a more detailed discussion of this issue.)

Specificity and Sensitivity. There are as yet few data addressing whether neuropsychological deficits found in relatives are associated specifically with risk for schizophrenia. Measures described in this review for which some specificity was noted include (1) reduced primacy (Harvey et al. 1981), (2) impaired intentional learning with distraction (Driscoll 1984), (3) intrusion of distractors on dichotic listening (Spring 1985), and (4) impaired ability to maintain grip tension (Rosen et al. 1991). These deficits are consistent with dysfunction in one or more of the brain systems noted above as being implicated by the data on both schizophrenia patients and their relatives. Additional studies are needed that include both comprehensive test batteries and psychiatric comparison groups.

Stability. The more stable or traitlike a deficit is, the more likely it is to be a valid risk indicator (Rice et al. 1986). There has been little systematic research on the stability of neuropsychologi-

cal function in schizophrenia patients, let alone their relatives. Assessing stability may be more appropriate, or at least more clear, in adult samples. In children of schizophrenia patients, it will be more difficult to disentangle instability from developmental change. In some cases instability or uneven development has even been suggested as a risk indicator (Fish 1984). For children of schizophrenia patients, the more important issue is predictive validity, an issue that relates directly to the identification of deviant responders. For example, in the Israeli study, Lifshitz et al. (1985) found that children of schizophrenia patients made more omission errors on a cancellation task with distraction, but the mean time to complete the task was not different. However, Mirsky (1988) reported that time significantly predicted which subgroup of children in that sample developed schizophrenia-spectrum disorders by age 25.

Developing Better Risk Indicators. One can look for (1) lower (worse) group means, (2) larger variances (because the schizophrenia genotype contributes added variability), and (3) a higher proportion of deviant responders (subjects below an impairment cutoff) among relatives. Preliminary data in the HBNFS support the notion that neuropsychological functions are more likely to be useful risk indicators for schizophrenia as more of these three conditions are met. As noted above, profile analysis may be a more meaningful way to identify risk indicators for individual cases.

Another potentially effective way to develop more informative risk indicators is the use of composite measures. In the New York high-risk study, Cornblatt and Erlenmeyer-Kimling (1985) used a composite index of attentional dysfunction based on a continuous performance test, a digit-span task, and an attention-span task. Their index had very good specificity (0.91) and modest sensitivity (0.36), based on prediction of young adult behavioral abnormalities from testing at ages 7 to 12. Preliminary data from the HBNFS suggest that composite measures improve the ability to detect deviant responders compared with individual tests. Composite measures may combine tests from the same or different domains of function. If tests from different domains are effective in distinguishing high- and low-risk subjects, it would suggest that those different domains are functionally interrelated in at-risk individuals.

Conclusion

Although most neuropsychological risk indicators for schizophrenia have not yet been adequately validated, several promising leads have emerged from studies of the biological relatives of schizophrenia patients. The strongest evidence of impairment in relatives is in sustained attention, perceptual-motor speed, and concept formation and abstraction; to a slightly lesser extent, mental control/encoding (primarily with distraction) is implicated as well. Impairments in verbal memory and verbal fluency were also found, but these have been less well studied. The pattern of deficits parallels that found in schizophrenia patients themselves, thus suggesting dysfunction in prefrontal, temporal-limbic, and attentional systems. Findings were similar for children and adult relatives of schizophrenia patients. It is suggested that future studies (1) emphasize comprehensive test batteries, (2) develop composite measures of neuropsychological function, (3) use profile and deviant responder analyses, (4) include psychiatric comparison groups, and (5) integrate neuropsychological assessments of relatives with brain imaging techniques.

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Announcement of Increased Research Funds

The Theodore and Vada Stanley Foundation in collaboration with the National Alliance for the Mentally Ill welcomes applications for the **1994 Stanley Foundation Research Awards Program.** The purpose of the awards is to support research directly related to the causes or treatment of schizophrenia and bipolar disorder. The research awards are intended to attract established scientists from other areas of biology and medicine (e.g., biochemistry, immunology, virology, and neurology) into research on schizophrenia and bipolar disorder as well as to provide support for innovative research by scientists already in the field whose funding sources are limited. Applicants are invited from all stages of career development. Awards are for 1 or 2 years. They may be up to $75,000 per year for studies involving human subjects and up to $50,000 per year for other studies. The total funds to support research grants in 1994 is $3.5 million, twice as high as in 1993.

The deadline for receipt of applications is April 1, 1994. Notification of awards will be made in June and funding to award recipients will begin in August. Application forms may be requested from the address below. The four-page application form consists of a brief outline of the proposed project, a budget, and a list of current and pending sources of funding. Funds may be used for salaries, supplies, and equipment, but it is the policy of the Stanley Foundation not to pay indirect costs for administration of the award. The research applications are reviewed by a professional selection committee. Requests for applications and questions should be directed to:

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