ORIGINAL ARTICLE

Neurobehavioral Deficits at Adolescence in Children at Risk for Schizophrenia

The Jerusalem Infant Development Study

Sydney L. Hans, PhD; Joseph Marcus, MD; Keith H. Nuechterlein, PhD; Robert F. Asarnow, PhD; Benedict Styr, MD; Judith G. Auerbach, PhD

Background: The Jerusalem Infant Development Study is a prospective investigation comparing offspring of schizophrenic parents with offspring of parents who have no mental disorder or have nonschizophrenic mental disorders. During infancy and school age, a subgroup of offspring of schizophrenic parents showed global neurobehavioral deficits that were hypothesized to be indicators of vulnerability to schizophrenia. The purposes of the present investigation were to determine if neurobehavioral deficits were present in the offspring of schizophrenics at adolescence, to examine their stability over time, and to explore their relation to concurrent mental adjustment.

Methods: Sixty-five Israeli adolescents were assessed on a battery of neurologic and neuropsychological assessments. They were also administered psychiatric interviews from which best-estimate *DSM-III-R* diagnoses and scores of global adjustment were derived.

Results: Adolescents with poor neurobehavioral functioning were identified from composites of motor and cognitive-attentional variables. A disproportionate number of offspring of schizophrenic parents (42%; 10/24), and especially male offspring of schizophrenic parents (73%; 8/11), showed poor neurobehavioral functioning relative to offspring of nonschizophrenic parents (22%; 9/41). Adolescent offspring of schizophrenics with poor neurobehavioral functioning had been poorly functioning at earlier ages and had poor psychiatric adjustment at adolescence. All 4 offspring of schizophrenics receiving schizophrenia spectrum diagnoses by adolescence showed a pattern of poor neurobehavioral functioning across developmental periods.

Conclusions: Results are consistent with the hypothesis that individuals at genetic risk for schizophrenia may display lifelong neurobehavioral signs that are indicators of vulnerability to schizophrenia and that are associated with psychiatric adjustment generally and schizophrenic spectrum disorder specifically.

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SCHIZOPHRENIC patients show neurobehavioral deficits in a variety of motor, visual-motor, attentional, and cognitive tasks.[1-6] While some neurobehavioral signs may simply accompany symptoms of schizophrenic illness, family studies suggest that some may also be indicators of genetic vulnerability to schizophrenia. First-degree nonpsychotic relatives of schizophrenic patients are more likely than individuals with no schizophrenic relatives to have abnormalities in smooth-pursuit eye movements,[7-9] grip-induced muscle tension,[10] perceptual motor speed,[11,12] sustained attention,[13,14] and mental flexibility.[15-17] Offspring of schizophrenics show deficits on the Continuous Performance Test,[18-21] the Span of Apprehension Test,[22] eye-tracking tasks,[23,24] the visual backward masking procedure,[25] and fine motor coordination tasks.[26-29] Anomalous patterns of neurobehavioral development have been observed in offspring of schizophrenics as early as the first days of life.[30-39] Debate continues about which specific neurobehavioral signs show the greatest sensitivity and specificity to schizophrenia and whether specific or general deficits are better indicators of vulnerability to schizophrenia.[35-40]

Although studies of first-degree relatives of schizophrenics suggest that neurobehavioral signs are genetic vulnerability indicators, this view would be strengthened by evidence that neurobehavioral deficits are stable over time and are associated with psychopathology, particularly with disorders in the schizophrenia spectrum. The longitudinal high-risk studies of offspring of schizophrenics are uniquely well suited to examine these issues.

To date, high-risk studies have reported stability of neurobehavioral signs from infancy to middle childhood[29] and

From the Department of Psychiatry, The University of Chicago, Chicago, Ill (Drs Hans and Marcus); the Neuropsychiatric Institute, the University of California at Los Angeles (Drs Nuechterlein and Asarnow); Eitanim Psychiatric Hospital, Jerusalem, Israel (Dr Styr); and the Department of Behavioral Sciences, Ben-Gurion University, Beer Sheva, Israel (Dr Auerbach).

SUBJECTS AND METHODS

ORIGINAL STUDY SAMPLE: INFANCY AND SCHOOL AGE

The original JIDS sample was recruited from 1973 through 1977 by identifying pregnant women from Jerusalem's maternal and child care centers and mental health clinics.[32] Research Diagnostic Criteria diagnoses[54] were made for all biological mothers and fathers based on a Hebrew-language version of the Current and Past Psychopathology Scales[55] and/or psychiatric and social work records for individuals who had received treatment. Based on these diagnoses, families were assigned to 3 groups: schizophrenic parent, parent with nonschizophrenic mental disorder, and parent with no mental illness.

A follow-up of the JIDS children was conducted when the children were a mean age of 10.3 years. Siblings of the original children who had not been part of the infant cohort were added to the school-age sample if they were between the ages of 8 and 13 years.

At the school-age follow-up, more than 80% of biological parents were interviewed using the Schedule for Affective Disorders and Schizophrenia–Lifetime Version.[56] Hospital and clinic records were assembled for all parents receiving mental health treatment. If parents were deceased or unavailable, spouses provided mental health history updates. Based on all available information, revised lifetime parent diagnoses were made using *DSM-III-R*[57] criteria and, where necessary, changes made in group assignment. All but 7 parents were available for research psychiatric interviewing at the infant and/or school-age assessments, and those 7 (3 schizophrenics, 1 mentally ill spouse of a schizophrenic, 2 nonschizophrenics with mental disorders) had sufficiently complete psychiatric or social worker records to make group assignment.

ADOLESCENT FOLLOW-UP

Beginning in 1992, a follow-up of the JIDS sample was conducted when the offspring were between the ages of 14 and 21 years (mean, 17.56; SD, 1.75). Sixty-five adolescents participated in the follow-up: 29 females, 36 males; 24 from the schizophrenic group, 25 from the other mental illness group, and 16 from the no mental illness group (**Table 1**). The parent diagnosis groups did not differ significantly in terms of mean age of adolescents (17.8 years for schizophrenia, 17.5 years for other mental illness, and 17.3 years for no mental illness) or proportion of males (46% [11/24] for schizophrenia, 56% [14/25] for other mental illness, and 69% [11/16] for no mental illness). Seven families (8 offspring) chose not to participate in the adolescent follow-up and 1 youth was excluded from participation because of a head injury that impacted neuropsychological functioning.

During the adolescent follow-up, parents were rediagnosed only if additional treatment records were available. These records required some revised diagnoses and eliminated some previously "questionable" diagnoses, but did not necessitate changes in group assignment.

Written informed consent was obtained from youth participants older than 18 years and from parents of those younger than 18 years.

Offspring Neurobehavioral Assessments

Adolescents were administered a neurobehavioral battery during two 2½-hour sessions at the Hebrew University, Jerusalem, Israel. Examiners were a psychiatrist (for neurologic examination) and master's degree–level psychologists (for all other instruments) trained to reliability and unaware of parents' diagnoses. The battery included assessments used in the National Institute of Mental Health Israeli High-Risk Study[28,58] and the school-age JIDS, with additional tests found in other studies to be sensitive to schizophrenic diathesis.[38,59,60] The battery included neurologic tasks scored on 4-point clinical scales (indicating no, mild, moderate, or severe impairment)[61-63] and averaged across multiple presentations of items as well as standard administered neuropsychological tests and procedures.[58-60,64-81] For analyses in this article, 20 summary variables were selected from these instruments (**Table 2**).

from childhood through adolescence.[27,41] They have also shown correlations between childhood measures of neurobehavioral functioning, particularly attentional functioning, and later indicators of general adjustment[19,41-48] and schizophrenia spectrum disorders.[49-51] The anomalous neurodevelopmental pattern of infancy termed *pandysmaturation* has also been related to adult schizophrenia spectrum disorder.[52,53]

The present article reports on the development of adolescents at risk for schizophrenia from the Jerusalem Infant Development Study (JIDS). Within this longitudinal sample, more global neurobehavioral signs were previously identified in infant and school-aged offspring of schizophrenic parents than in children whose parents had no mental disorder or nonschizophrenic disorders. Assuming that neurobehavioral signs are indicators of genetic vulnerability to schizophrenia, in this article we will examine hypotheses that (1) during adolescence neurobehavioral signs will be more prevalent in adolescent offspring of schizophrenics than in other young people, (2) adolescent offspring of schizophrenics with neurobehavioral signs will have shown signs at earlier developmental stages, and (3) neurobehavioral signs will be associated with psychiatric adjustment at adolescence, as well as with adolescent-onset schizophrenia spectrum disorder.

RESULTS

DIAGNOSTIC GROUP DIFFERENCES

Forty-two percent (n = 10) of the offspring of schizophrenic parents showed poor neurobehavioral functioning compared with 22% (n = 9; 5 from the other mental illness and 4 from the no mental illness group) of the offspring of nonschizophrenic parents.

The logistic regression model predicting poor neurobehavioral functioning was significant ($\chi^2_3 = 8.05$,

Offspring Psychiatric Assessment

During home visits, each adolescent and 1 parent were administered 2 diagnostic interviews: the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Epidemiologic Version (K-SADS-E)[82] and the Semi-Structured Kiddie Interview for Personality Syndromes (K-SKIPS),[83,84] which, modeled after the Structured Clinical Interview for *DSM-III-R* Disorders,[85] was designed to assess personality syndromes falling within the schizophrenia spectrum. Parental information was used primarily to corroborate or add to the information provided by the adolescent. Where available, additional information from school records and mental health providers was obtained. All available information was used to make best-estimate *DSM-III-R* diagnoses[57] and Children's Global Assessment Scale ratings.[86] The interviewers included a senior psychiatrist and 2 other experienced clinicians who had received specialized training on administration of the K-SADS-E and K-SKIPS. Twenty randomly selected cases were blindly reviewed and independently diagnosed by 2 psychiatrists. Interrater agreement was high, although this random sample did not contain cases within the schizophrenia spectrum. All 7 cases diagnosed within the schizophrenia spectrum were independently reviewed by one of the senior investigators (J.M.), who agreed that all belonged within the spectrum. Disagreement on the specific schizophrenia spectrum diagnosis occurred for 1 case and was resolved by further discussion among all authors.

DATA ANALYSIS

In the infancy and school-age phases of this project, global measures of neurobehavioral functioning derived from 2-dimensional data structures were more effective than specific items or tests at discriminating a subgroup of poorly functioning offspring of schizophrenic parents from other children.[29] To produce a 2-dimensional data structure, the 20 adolescent neurobehavioral variables were subjected to a 2-factor principal components analysis with varimax rotation. Three of the variables (abnormal arm movements, tendon reflexes, and eye movements) had loadings less than 0.35. The principal components analysis was recomputed without these 3 variables. The rotated components in this analysis explained 20.3% and 18.9% of the total variance. Variables with loadings of at least 0.35 on the first component were primarily cognitive-attentional; variables with loadings of at least 0.35 on the second component were primarily motoric (Table 2). The 17 variables were standardized, and cognitive-attentional and motor component scores were computed by averaging items with unit weights. Bender scores were entered into both the motor and cognitive-attentional averages. All variables were scaled before averaging so that positive scores indicated more problematic behavior.

To divide the sample into subjects with good and poor neurobehavioral functioning, the contours of an Epanechnikov kernel[87-89] were superimposed on a plot of subjects' 2 principal components scores (**Figure**). This nonparametric procedure identifies the most concentrated region of data points in an empirical bivariate distribution. Because we wanted an empirical basis for identifying a region of normality, we used only the subjects with mentally healthy parents as a basis for computing the kernel and set program defaults so that approximately 68% of subjects fell within the kernel. Subjects from all 3 groups whose data points fell within the kernel, as well as any whose data points fell outside the boundary of the kernel but in the direction of better than average performance, were considered to be functioning well. All others outside the boundaries of the kernel were considered functioning poorly.

The relation of parent diagnosis to offspring neurobehavioral functioning was examined using contingency tables and logistic regressions predicting to the dichotomous neurobehavioral outcome from dummy variables for parental diagnosis, sex, and age. The stability of good and poor neurobehavioral outcomes over time was examined using contingency tables and κ statistics as a measure of association appropriate for dichotomous variables. The relation of neurobehavioral functioning to offspring psychopathology was examined using an analysis of variance with Children's Global Assessment Scale scores as the dependent variable and neurobehavioral functioning (2 levels) and parental diagnosis (3 levels) as independent variables.

All statistical tests are 2-tailed. For testing primary hypotheses, α levels were set at $P = .05$.

$P < .05$). Male children were nearly 4 times more likely to be poorly functioning (odds ratio, 3.99; 95% confidence interval, 1.12-14.20) than females. Trends suggested that offspring of schizophrenics were more than 3 times as likely to be poorly functioning as offspring of parents with other mental illness (odds ratio, 3.64; 95% confidence interval, 0.93-14.24; $P = .06$) and no mental illness (odds ratio, 3.15; 95% confidence interval, 0.70-14.15; $P = .13$). Since the odds ratios for the 2 comparison groups were similar, they were combined to provide greater statistical power and regressions recomputed. In this analysis, offspring of schizophrenic parents were more than 3 times as likely to be poorly functioning as offspring of nonschizophrenic parents (odds ratio, 3.43; 95% confidence interval, 1.03-11.42; $P < .05$).

Because inclusion of siblings in the sample violates the statistical assumption of independent sampling, we explored whether a few sibships were unduly contributing to the finding of poor functioning in offspring of schizophrenics. This was not the case. In the 9 schizophrenic sibships, there were only 2 in which both siblings were poorly functioning and 2 in which both were well functioning.

Sex differences moderated the relation of parent diagnosis to poor neurobehavioral functioning. Seventy-three percent of the male offspring of schizophrenics (8 of 11) were poorly functioning, compared with 24% of the male offspring of nonschizophrenic parents (6 of 25; $\chi^2_1 = 7.63$, $P = .006$), 15% of the female offspring of schizophrenics (2 of 13; $\chi^2_1 = 8.06$, $P = .005$), and 19% of the female offspring of nonschizophrenic parents (3 of 16; $\chi^2_1 = 7.87$, $P = .005$).

Because in the JIDS school-age follow-up, pregnancy and birth complications (PBCs) were related to poor motoric functioning in the offspring of schizophrenic parents, we explored the role of PBCs for the 36 adolescent subjects with Research Obstetric Scale[90] data. Within the group of male offspring of schizophrenics, there was a

Table 1. Sample Size at Infancy, School Age, and Adolescent Assessments (Based on Parental Diagnoses Confirmed at School Age)

	Infancy		School Age			Adolescence			
Parental Diagnosis	Families	Infants	Families	School-aged Children Observed From Infancy	School-aged Siblings	Families	Adolescents Observed From Infancy	Adolescent Siblings Observed From School Age	Total Adolescence Sample
Schizophrenia	17	19	14	15	10	14*	15	9	24
Other mental illness	19	20	17	19	11	14	15	10	25
No mental illness	18	19	11	11	7	9	10	6	16
Total	**54**	**58**	**42**	**45**	**28**	**37**	**40**	**25**	**65**

Eleven with schizophrenic mother, 2 with schizophrenic father, 1 with 2 schizophrenic parents.

Table 2. Summary of Measures Used in Principal Components Analysis With Loadings >0.35 Indicated

Type of Functioning	Variable	Cognitive-Attentional Component	Motor Functioning Component
Concentration[66]	Wechsler Intelligence Scale for Children Digit Span scaled score	−0.72	. . .
Perceptual motor speed[67,68]	Total seconds on Reitan Trail-Making Test (A and B)	0.71	. . .
Responses to signal[63,69]	Total errors on opposing action, alternating movement to command, go-no-go tasks	0.64	. . .
Flexibility of cognitive set[60,70]	Wisconsin Card Sorting Test, perseverative errors	0.61	. . .
Vigilance[71-73]	Continuous Performance Test (sensitivity score, A[1], during degraded stimulus condition)	−0.59	. . .
Span of apprehension[74-76]	Span of Apprehension Test (number detected, 12-item array)	−0.56	. . .
Motor synchrony[59]	Average of synchrony scores from 20, 40, 80, 120, and 200 beats-per-minute trials	−0.45	. . .
Interference with cognitive set[77,78]	Stroop Color-Word Test interference score	−0.39	. . .
Auditory visual integration[79]	Birch-Belmont Test total incorrect trials	0.38	. . .
Fine motor coordination[61]	Average of right- and left-hand scores from finger opposition, diadochokinesis, finger following, and match stick placement tasks	. . .	0.74
Associated movements[61]	Average of overflow scores during forcible tongue protrusion, walking on tiptoe, walking on heels, and hopping on 1 leg	. . .	0.71
Serial coordinated movements[62]	Average scores from fist-clap-cut test, fist-ring test, and Ozeretski test	. . .	0.69
Mirror movements[61]	Average of right- and left-hand overflow scores during finger opposition and diadochokinesis tasks	. . .	0.66
Visual-motor flexibility[58,64]	Mirror drawing—distance score	. . .	0.53
Fine motor speed[65]	No. of pegs placed on Purdue Pegboard (right and left hands)	. . .	−0.49
Abnormal postures[61]	Average of ratings of abnormalities in rotation, extension, and abduction of raised arms and finger spooning	. . .	0.46
Visual-motor-perceptual maturity[80,81]	Bender Motor Gestalt Test with Pascal-Suttell scoring	0.39	0.44
Abnormal arm movements[61]	Average of scores from distal choreiform movements, proximal choreiform movements, nonspecific gross movements, nonspecific small movements, and tremors	. . .	. . .
Tendon reflexes[61]	Average of knee jerk and ankle jerk scores	. . .	. . .
Abnormal eye movements[61]	Average of scores assessing convergence and fixation on objects, jerks during horizontal following and fixation, and strabismus	. . .	. . .

strong trend for PBCs to be related to poor motoric functioning (component 2) ($r = 0.64$, $P < .09$, 2-tailed; n = 8). The 3 male offspring of schizophrenics with more than 4 PBCs (numbers 45, 58, 61 in the Figure) all showed poor motoric functioning. Exploratory analyses suggested no relation between PBCs and poor motoric behavior in female offspring of schizophrenics or offspring without a schizophrenic parent. Pregnancy and birth complications were also unrelated to poor cognitive-attentional functioning.

STABILITY OF POOR FUNCTIONING FROM EARLIER AGES TO ADOLESCENCE

Offspring of schizophrenic parents showed greater stability in neurobehavioral functioning over age (Cohen $\kappa = 0.92$) than offspring of nonschizophrenic parents ($\kappa = 0.48$). More offspring of schizophrenics (42%; n = 10) were poorly functioning at both ages than offspring of mentally healthy parents (12.5%, n = 2; $\chi^2_1 = 3.89$, $P < .05$) or than offspring of parents with other mental disorders (12%, n = 3; $\chi^2_1 = 5.53$, $P < .05$) (**Table 3**). In contrast, stable good functioning across 2 age periods occurred for a high proportion of the offspring of schizophrenics (54%; n = 13) and the offspring of nonschizophrenics (71%; n = 29).

Similar analyses comparing neurobehavioral functioning at infancy and adolescence suggest considerably less stability. The offspring of schizophrenic parents showed only very modest stability from infancy (Cohen $\kappa = 0.32$) and the offspring of nonschizophrenic parents showed no stability (Cohen $\kappa = 0.08$).

Although many children did show shifts in functioning across age periods, fully half of the 40 children tracked from birth showed consistent levels of functioning across infancy, school age, and adolescence. Twelve offspring of nonschizophrenics (48%) showed consistently good functioning at all 3 developmental periods, and none showed consistently poor functioning. Four offspring of schizophrenics (27%) showed consistently good functioning, and 6 (40%) showed consistently poor functioning.

RELATION OF NEUROBEHAVIORAL FUNCTIONING TO GLOBAL PSYCHIATRIC ADJUSTMENT

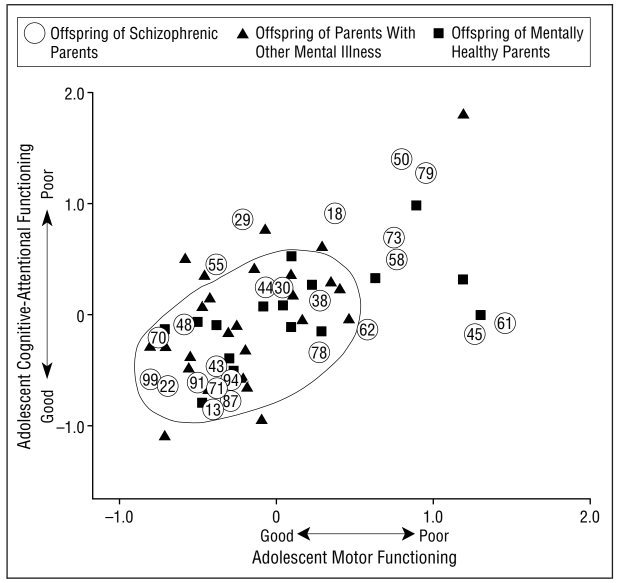
Analysis of variance computed on the Children's Global Assessment Scale scores using parent diagnosis (3 levels) and neurobehavioral functioning at adolescence (2 levels) as the independent variables showed a significant effect for neurobehavioral functioning ($F_{1,56} = 8.61$, $P < .001$) and no effects for parent diagnosis ($F_{2,56} = 2.25$) or the interaction between parent diagnosis and neurobehavioral functioning ($F_{2,56} = 2.25$). Post hoc Fisher least significant difference tests indicated that the offspring of schizophrenic parents with poor neurobehavioral functioning had poorer mean Children's Global Assessment Scale scores (n = 8; mean, 49.13; SD, 13.67) than the offspring of schizophrenic parents with good neurobehavioral scores (n = 13; mean, 71.08; SD, 12.06; $P < .001$), the offspring of parents with other mental illness who had poor (n = 5; mean, 64.80; SD, 14.84; $P < .05$) or good (n = 20; mean, 67.80; SD, 13.85; $P < .001$) neurobehavioral scores, and the offspring of parents with no mental illness who had good neurobehavioral scores (n = 12; mean, 72.42; SD, 14.47; $P < .001$). None of the other groups differed from one another.

RELATION OF NEUROBEHAVIORAL FUNCTIONING TO SCHIZOPHRENIC SPECTRUM ILLNESS

Although the JIDS offspring were early in the period of risk for schizophrenic breakdown at the time of follow-up, 4 youth with schizophrenic parents received diagnoses in the schizophrenia spectrum: 1 schizophrenia, 1 schizotypal personality disorder, and 2 paranoid personality disorder. All 4 showed a stable pattern of poor neurobehavioral functioning at school age and adolescence. Three also showed poor infant functioning as reported by Marcus et al[32]; the fourth was not in the sample during infancy. In an independent analysis of the infant behavior of these children, Fish et al[53] identified 2 of these infants as having probable pandysmaturation (developmental problems and growth retardation) and another as having a developmental pattern that was consistent with pandysmaturation but inconclusive because of missing physical growth data. An additional 3 male offspring without schizophrenic parents also received paranoid personality disorder diagnoses, but did not show consistently poor neurobehavioral functioning.

COMMENT

Three types of evidence from the adolescent follow-up of JIDS converge to suggest that neurobehavioral signs may be markers of vulnerability to schizophrenia: (1) global neurobehavioral signs were more prevalent in offspring of schizophrenic parents than in other young people; (2) neurobehavioral signs were stable over development for a subgroup of offspring of schizophrenic parents, but not other young people; (3) for offspring of schizophrenic parents, neurobehavioral signs were associated with psychopathology and adolescent schizophrenia spectrum disorders.



Individual subjects plotted by cognitive-attentional and motor functioning components. Component 1 (on the y-axis) is the mean of concentration, perceptual motor speed, responses to signal, flexibility of cognitive set, vigilance, span of apprehension, motor synchrony, interference with cognitive set, auditory visual integration, and visual-motor-perceptual maturity standard scores. Component 2 (on the x-axis) is the mean of fine motor coordination, associated movements, serial coordinator movements, mirror movement, visual-motor flexibility, fine motor speed, postures, and visual-motor-perceptual maturity standard scores. An Epanechnikov kernel identifies the region of most concentrated data points for offspring of parents with no mental illness that is used to demarcate the offspring with good and poor neurobehavioral functioning. Identification numbers are noted for offsprings of schizophrenics only and are consistent with those reported in the school-age follow-up.

When the JIDS sample was assessed during the first year of life, more offspring of schizophrenics showed problems in motor and sensorimotor behavior than offspring of parents with no mental disorder or nonschizophrenic mental disorder. During school age (7-13 years) when the JIDS children and their similarly aged siblings were assessed, again a subgroup of offspring of schizophrenics showed poor motor and cognitive functioning. The present article, reporting on the adolescent follow-up of the original JIDS sample and their siblings, again identifies a subgroup of children of schizophrenics with poor neurobehavioral functioning. Overall, 42% (n = 10) of the offspring of schizophrenics were poorly functioning at adolescence compared with only 22% (n = 9) of the offspring of parents with other mental disorders or no mental disorder. During the school-age and infancy assessments, the proportion of poorly functioning offspring of schizophrenics had been 44% and 68%, respectively, compared with 20% and 23% for the children without schizophrenic parents. After controlling for age and sex in logistic regression analyses, offspring of schizo-

Table 3. Cross Tabulation of Well- and Poor-Functioning Subgroups at School Age and Adolescence Grouped by Parent Diagnosis

		Offspring of					
		Schizophrenic Parents		Parents With Other Mental Illness		Parents With No Mental Illness	
Adolescence	Poor	0	10	2	3	2	2
	Good	13	1	17	3	12	0
		Good	Poor	Good	Poor	Good	Poor
		School Age					

phrenics were more than 3 times as likely as other young people to have neurobehavioral signs.

Although we had not originally hypothesized sex differences, adolescents with neurobehavioral signs, particularly those with motoric signs, were predominantly male offspring of schizophrenics. The incidence of poor neurobehavioral functioning was 73% in the males with a schizophrenic parent compared with less than 25% in the female offspring of schizophrenics and male and female offspring of nonschizophrenics. Although the incidence of schizophrenia is similar between males and females, sex differences abound in the study of schizophrenia.[91-93] Castle and Murray[94] have even hypothesized that male schizophrenics typically suffer from a different type of schizophrenia than females, with schizophrenia in males characterized by more neurobehavioral and neuroanatomical signs and more closely associated with PBCs than genetic vulnerability. Data from the present study are consistent with this hypothesis in that at-risk males show poorer neurodevelopmental course prior to illness onset and their poor functioning, at least in the motoric domain, may be associated with a history of PBCs in the small number of subjects for whom PBC data were available. However, data from the present study also suggest that the role of genetics cannot be ignored in considering the course of neurodevelopmental problems in schizophrenia for males, since neurobehavioral signs were only increased in males with PBCs and a schizophrenic parent. We believe the most parsimonious explanation of the data is that males at genetic risk are especially vulnerable to the effects of prenatal hazards.

The global neurobehavioral measures used in this study showed stability across ages. This stability was strong between school age and adolescence, although only modest between infancy and adolescence. As reported in other high-risk studies,[41,95] the stability was greater for the offspring of schizophrenics than for the children with nonschizophrenic parents and most notably was anchored by a poorly functioning subgroup of offspring of schizophrenics. Fully 42% of the offspring of schizophrenics had been poorly functioning at both school age and adolescence, compared with only 12% of the offspring of nonschizophrenics. Six of the 40 children in the sample observed from birth through adolescence have shown consistently poor neurobehavioral functioning over time. All 6 of these children were the offspring of schizophrenics.

An association was found between the neurobehavioral measures and psychopathology. Other high-risk studies have found linkages between neurobehavioral signs (especially attentional deviance) and concurrent global psychopathology[19,41] and later schizophrenia spectrum disorders.[49,50,52,96] The present study determined that the adolescent offspring of schizophrenics showing neurobehavioral signs were at risk for poorer global psychiatric adjustment as well as specific schizophrenia spectrum disorders.

At the time JIDS began, virtually no empirical attention had been given to biobehavioral measures indicating enhanced vulnerability to schizophrenia. Fish[96] had described a pattern of anomalous early development she termed "pandysmaturation," which she proposed was "a 'marker' in infancy for the inherited neurointegrative defect in schizophrenia." We interpreted the JIDS infancy findings as suggesting "some kind of genetically determined vulnerability to schizophrenia."[32] Today, hosts of studies on first-degree relatives of schizophrenics have searched for behavioral, neurochemical, neuroanatomical, and genetic vulnerability indicators of schizophrenia,[97,98] and a number of theoretical conceptions of vulnerability indicators have evolved from these (see further Kremen et al[99]). The JIDS adolescent follow-up data, in showing associations between neurobehavioral signs and genetic risk for schizophrenia, stability in neurobehavioral signs over time, and correlation between these signs and psychopathology, continue to support the hypothesis that global neurodevelopmental deficits may be premorbid indicators of genetic vulnerability to schizophrenia. Because the measures we have used at adolescence, school age, and infancy are global, we do not claim that they are specific to schizophrenia. In fact, they occur, although with lower incidence and little stability, in offspring of parents with no mental illness and offspring of parents with other, nonschizophrenic mental disorders.

Researchers studying the brain basis of schizophrenia are suggesting that the types of neuroanatomical anomalies associated with schizophrenia do not result from degenerative processes, but from developmental processes that may begin early in life.[100,101] The JIDS longitudinal data, combined with the pioneering work of Fish,[96] the recent studies of Walker et al,[102,103] and an accumulation of other infancy data from the high-risk field,[33] add further support for the view that schizophrenia is a neurodevelopmental disorder with origins very early in life.

The primary limitation of the present study, and most high-risk studies, is its sample size. Results need to be interpreted with caution and in relation to findings from other studies. A second limitation is that, because of the long-term longitudinal design, measurement techniques are not always contemporary by the time of follow-up. Even in the most recent follow-up, limitations of budget and technology available in Israel did not allow for state-of-the-art measures such as neuroimaging or brain potentials. The greatest limitation of the present report is that none of the subjects in the sample have yet passed through the period of risk for schizophrenia and conclusions about actual schizophrenic illness must be treated cautiously.

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Reprints: Sydney L. Hans, PhD, Department of Psychiatry, MC3077, The University of Chicago, 5841 S Maryland Ave, Chicago, IL 60637.

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