Neurocognitive Profile in Adolescents with Early-Onset Schizophrenia: Clinical Correlates

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Background: *Neurocognitive impairments have been documented in adolescents with early-onset schizophrenia (EOS; onset by age 18) and are important treatment targets. Information concerning the severity, pattern, and clinical correlates of these deficits in EOS remains limited.*

Methods: *Tests assessing motor skills, attention, memory, visuospatial abilities and executive functioning were administered to 54 clinically stabilized adolescents with EOS and 52 age- and sex-matched healthy controls. Childhood-onset patients (onset by age 13) were compared to those with an adolescent onset of illness. Patients' neurocognitive profiles were compared to those of controls. Relationships between neurocognitive deficits and demographic and clinical characteristics were explored.*

Results: *Neurocognitive profiles did not differ between childhood- and adolescent-onset participants. Patients showed a generalized neurocognitive deficit of 2.0 SDs compared to controls, with relative deficit in executive functioning and relative sparing of language and visuospatial abilities. Degree of generalized neurocognitive impairment was associated with premorbid adjustment and negative symptom severity (Adjusted $R^2 = .39$).*

Conclusions: *Results document both a significant generalized deficit and a relative deficit of executive functioning in adolescents with EOS. The overall pattern is similar to that observed in severely ill first-episode adult patients. The impairments across multiple neurocognitive domains suggest widespread brain dysfunction in EOS.*

Key Words: Schizophrenia, adolescents, cognition, generalized deficit, neuropsychology, executive

The onset of schizophrenia prior to age 13 is exceedingly rare (Rapoport et al 1999), but an estimated 39% of males and 23% of females with schizophrenia develop the illness by age 19 (Loranger 1984). Patients with early-onset schizophrenia (EOS; onset by age 18) (Vourdas et al 2003), including childhood-onset schizophrenia (COS; onset by age 13) (Rapoport et al 1999) and adolescent-onset schizophrenia (AOS; onset by age 13 and before age 18) (Kravariti et al 2003; Vourdas et al 2003) have shown a number of the same neurobiological abnormalities observed in adult-onset schizophrenia, suggesting a common neurobiological substrate. However, compared to individuals with adult-onset schizophrenia, an early onset of schizophrenia appears to be associated with higher rates of premorbid abnormalities (Hollis 1995; Nicolson et al 2000; Vourdas et al 2003), worse cognitive performance (Hoff et al 1996) and worse functional outcome (Hollis 2000). Together, these data suggest that EOS may represent a more severe form of the disorder.

Previous studies of neurocognition in EOS have variously examined COS (Asarnow et al 1994; Kumra et al 2000), AOS (Kravariti et al 2003), and combined groups of both COS and AOS patients (Kenny et al 1997; McClellan et al 2004; Oie and Rund 1999). Although somewhat arbitrary, the division of EOS between COS and AOS reflects a concern in the field that there are differences in etiology, frequency of presentation in each sex, prognosis and natural course of the disease, and response to treatment between these groups (Rapoport et al 1999). To our knowledge, there have been no published studies that have examined whether the two groups perform differently on neuropsychological profiles.

Adults with first-episode schizophrenia (Bilder et al 2000; Hoff et al 1992; Mohamed et al 1999; Saykin et al 1994) have across studies consistently shown a generalized neurocognitive deficit of approximately 1 to 1.5 standard deviations compared to healthy controls. Similar findings of large generalized deficit across a broad range of neuropsychological tests have been reported in studies of adolescents with EOS (Kenny et al 1997; McClellan et al 2004; Oie and Rund 1999; Ueland et al 2004), including antipsychotic-naive patients, those who have been hospitalized for short periods of time (Oie and Rund 1999), and patients with COS (Asarnow et al 1994; Kumra et al 2000) and AOS (Kravariti et al 2003).

The size and clinical significance of the degree of differential impairment among the various neurocognitive domains in schizophrenia has been an issue of some controversy in the studies of adults with schizophrenia. As with the adult literature, studies of EOS have highlighted the generalized neurocognitive deficit as a more salient and meaningful finding given the relatively small differences among domain effect sizes (Oie and Rund 1999), and given methodological considerations pertaining to matching of reliability and difficulty level of neurocognitive tasks (Chapman and Chapman 1989).

With regard to correlates of the generalized neurocognitive deficit in schizophrenia, studies of adults with first-episode schizophrenia have consistently found an association with negative symptoms at time of testing (Bilder et al 2000; Heydebrand et al 2004; Mohamed et al 1999). In addition, deficits in premorbid function (Bilder et al 2000; DeQuardo et al 1994; Silverstein et al 2003), global functioning, and antipsychotic dose at time of testing (Bilder et al 2000) have been found to predict degree of neurocognitive impairment in adult samples.

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The present investigation employs the largest sample to date of studies investigating neurocognition in EOS, allowing an examination of differential deficits as well as exploration of related clinical correlates. The primary aim of this report is to provide a comprehensive neurocognitive characterization of clinically stabilized adolescents with EOS. This study examines: 1) whether COS and AOS differ in neurocognitive profile, 2) the magnitude and pattern of neurocognitive deficits in adolescents with EOS compared to healthy controls, and 3) the relationship of neurocognitive functioning to clinical symptoms and premorbid adjustment.

Methods and Materials

Participants

One hundred six participants, ages 10 to 18 years old, who completed the Early-Onset Schizophrenia Neuroimaging Studies at the Zucker-Hillside Hospital in Glen Oaks, New York by May 2004 were included from the ongoing study (Kumra et al 2004). The North Shore-Long Island Jewish Health System Institutional Review Board approved all procedures, including recruitment and consent. Written, informed consent/assent was obtained from participants and their legal guardians.

Patients with a history of mental retardation prior to onset of psychosis or neurological disorder were excluded. Patients who were missing more than 3 neurocognitive test data points ($n = 3$) were also excluded. Healthy controls were recruited from advertisements and fliers distributed in libraries, doctors' offices and community centers. Initially, they were screened by telephone; prior psychiatric illness/treatment, past substance abuse, and history of schizophrenia or bipolar disorder in first-degree relatives constituted exclusionary criteria. This was followed by an in-person screening for neurological impairments and DSM-IV (American Psychiatric Association 1994) psychiatric diagnoses, especially prior substance abuse/dependence, and/or a history of developmental delays, learning disabilities or special education placement using portions of the Schedule for Affective Disorders and Schizophrenia for School-Age Children – Present and Lifetime Version (K-SADS-PL; Kaufman et al 1997). Healthy controls were matched to patients on the basis of age, sex, ethnicity and handedness but not on factors thought to be related to effects of illness such as IQ (Meehl 1970).

A research psychiatrist (SK, SB) or a psychologist (JPR) interviewed participants. Since the Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition (DSM-III; American Psychiatric Association 1980), the diagnosis of schizophrenia in childhood has been made using unmodified criteria for adults. Although misdiagnosis remains a significant problem (McKenna et al 1994), recent research has validated this approach (Rapoport et al 1999). The diagnostic procedures for the present study were similar to those used by the National Institute of Mental Health (NIMH) group (McKenna et al 1994) and consisted of a clinical examination, a screening questionnaire for autistic symptoms (Lord et al 1994) and a structured interview (Kaufman et al 1997). For younger children who had difficulty sitting through the entire interview and for some adolescents who had limited insight into their condition, a significant portion of the diagnostic information was obtained from the parent and the medical record. More cooperative, older adolescents were able to provide much more of their own diagnostic information. The K-SADS-PL has been used for establishing reliable and valid research diagnoses for childhood psychosis (McKenna et al 1994). Based on 71 consecutive screenings, good interrater reliability has been established for childhood-onset schizophrenia using this instrument (McKenna et al 1994). Following similar procedures established by the NIMH group (McKenna et al 1994), semi-structured interviews were conducted separately with the child and parent. A best-estimate diagnosis was made from all available information collected during the structured interview, information from prior hospitalizations and outpatient treatment, and a review of the medical record. The senior (SK) and primary (JPR) authors agreed on a diagnosis of a schizophrenia-spectrum versus non-schizophrenia-spectrum disorder in 88% (22/25) of cases that were co-rated by these authors.

All of the patients had been treated with antipsychotic medications in the past. Standing medications received by patients at time of testing are summarized in Table 1. Information regarding past antipsychotic trials was obtained and drug doses were converted into chlorpromazine equivalents for atypical (Woods 2003) and typical (Hales and Yudofsky 2003) antipsychotics to estimate lifetime and current antipsychotic exposure.

Measures and Procedures

The design of this study was modeled after a neurocognitive study in adults with first-episode schizophrenia (Bilder et al 2000). However, to enhance enrollment and increase the representativeness of the study, test sessions were conducted toward the end of hospitalization and at least two weeks after initiation of antipsychotic medications for subjects who were inpatients. Testing was initiated upon advice from hospital staff that the patient was clinically stabilized. Prior to testing subjects, a clinical judgment was made by the examiner that each subject could cooperate with testing in terms of his/her level of consciousness, concentration and affective state based on information gathered during the structured interview and clinical ratings. Patients who did not meet these criteria for symptom stability were tested as soon as possible after discharge from hospital.

Measures of symptomatology that were obtained concurrently with neuropsychological assessment included: the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1961), the Schedule for the Assessment of Negative Symptoms (SANS; Andreasen 1982), and the Premorbid Adjustment Scale, social, academic, and total scores (PAS; Cannon-Spoor et al 1982).

The total time for test administration for the neurocognitive test battery was approximately 4 hours including breaks; administration was generally broken into two 2-hour sessions as tolerated. Full-scale IQ scores were estimated from the Vocabulary, Similarities, Picture Completion, Block Design, Arithmetic and Coding subscales (Donders 1997) of the Wechsler Intelligence Scale for Children – Third Edition (WISC-III; Wechsler 1991; $n = 43$), or the Similarities, Picture Completion, Block Design, Arithmetic, Coding, Information and Digit Span subscales (Axelrod et al 2001) of the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler 1997) for subjects over the age of 16 ($n = 63$). In addition to the intelligence scales, the test battery included (in order of administration) the California Verbal Learning Test, Child Version or Adult Version (≥ 17 years) (Delis et al 1987), Judgment of Line Orientation (Benton et al 1983), Trailmaking parts A and B (Reitan 1979), Fingertapping (Reitan 1979), Grooved Pegboard (Matthews and Klove 1964), the Controlled Oral Word Association Test (COWAT; Benton et al 1983), the Wide Range Achievement Test (WRAT-3) Reading subtest (Wilkinson 1993), the Wisconsin Card Sorting Test, Computer Version 2 (WCST; Heaton et al 1993), and the Continuous Performance Test, Identical Pairs Version (CPT-IP; Cornblatt et al 1997).

Table 1. Characteristics of Adolescent Patients With Schizophrenia-Spectrum Disorders and Healthy Control Subjects

Characteristic	Patient Group ($n = 54$)		Healthy Control Group ($n = 52$)		Analysis		
	n	%	*n*	%	Statistic	*df*	*p*
Sex, male	34	63	27	52	$\chi^2 = 1.32$	1	.25
Handedness, right	50	93	48	92	$\chi^2 = .00$	2	1.00
Ethnicity, Caucasian	19	35	18	35	$\chi^2 = .00$	1	.95
Parental SES, low[a]	12	22	4	8	$\chi^2 = 4.36$	1	.04
Medication Status at Time of Testing							
Antipsychotic	50	93					
Traditional neuroleptic	4	7					
Atypical agent	50	93					
Anticonvulsant	8	15					
Antidepressant	16	30					
Lithium	11	20					
Benzodiazepine	7	13					
Stimulant	3	6					
Anticholinergic	10	19					
	Mean	(SD)	Mean	(SD)	Statistic	*df*	*p*
Age at Testing	16.0	(2.2)	15.6	(2.2)	$t = .78$	104	.44
Patient Characteristics							
Age of onset, yrs.	13.4	(3.1)					
Duration of psychosis, yrs.	2.6	(2.1)					
BPRS[b] total score	35.1	(7.6)					
BPRS psychosis score[c]	9.5	(4.2)					
SANS[d] total score	38.0	(17.6)					
Lifetime CPZ exposure[e]	97.4	(139.0)					
Current CPZ dosage[f]	269.9	(240.9)					

[a]Socioeconomic status, Hollingshead system (Hollingshead and Redlich 1958), where 1–3 = "high" and 4–5 = "low".
[b]Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1961); $n = 52$.
[c]The BPRS psychosis cluster consists of items 4, 11, 12 and 15.
[d]Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1982); $n = 51$.
[e]Chlorpromazine (CPZ) equivalent dosages (Woods 2003; Hales and Yudofsky 2003), 1,000s of milligrams.
[f]Chlorpromazine equivalent dosages (Woods 2003; Hales and Yudofsky 2003), milligrams per day.

Data Analysis

Individual test scores were combined into the following six cognitive domain summary scores: language, memory, attention, executive, motor, and visuospatial. Domains' test variable composites were based on a priori assessments of content validity.

Prior to encoding the domain variables, *Z*-scores for the entire sample were calculated using the mean and standard deviation of the healthy control group. All *Z*-scores were computed so that higher values indicated better performance. Following *Z*-score standardization, tests for normality in the control group were explored to identify nonnormally distributed test variables. As a result, data for the Trail Making Test A and WCST were log transformed for patient and control data. Scores were truncated at $\pm$ 4 standard deviations to prevent rarely occurring, extremely deviant scores from distorting profile shape (Saykin et al 1994).

The domain variables were then calculated by averaging each participant's z-scores (which are based on the distributions of the healthy control scores) on tests assessing the same functional domain according to Bilder and colleagues (2000) (see Table 2). If a participant was missing a test score, the mean of the available tests was used. Z-scores for each domain were then restandardized using the mean and standard deviation of the domain scores of the healthy control group. A global neurocognitive scale that represented the mean of the six scales was constructed. For those participants who had no tests in a given domain ($n = 2$), the global scale was not computed. WRAT-3 reading scores as well as WISC/WAIS-III vocabulary, information, and full-scale IQ are provided in order to further characterize the sample and provide estimates of premorbid and general intellectual functioning.

Analyses were conducted using SPSS 11.0 (SPSS Inc., Chicago, Illinois) and SAS 8.02 (SAS Institute Inc., Cary, North Carolina). To examine whether patients with childhood-onset schizophrenia (COS; onset before age 13) have different neuropsychological test profiles as compared to patients with adolescent-onset schizophrenia (AOS; onset between ages 13 and 18), the 6 summary neuropsychological domains were used as dependent variables in a Multivariate Analysis of Covariance (MANCOVA) where group (COS, AOS) was the between-subjects factor and age at time of testing, duration of psychosis (calculated by subtracting the age at first onset of psychotic symptoms from age at testing), and premorbid adjustment scales (childhood total and childhood social adjustment) were included as covariates. Age at time of testing, duration of psychosis, and premorbid adjustment were included in this model because the groups (COS, AOS) differed significantly on these factors when tested in a univariate screen. Multivariate Analysis of Variance (MANOVA) was used to evaluate profile level and shape with diagnostic group (Schizophrenia, Control) as a between-subjects factor and neuropsychological domain as a within-subject factor. MANCOVA was used to assess effects of possible moderating variables such as parental socioeconomic status and premorbid intellectual ability as assessed by WRAT-3 reading scores, since the diagnostic groups

Table 2. Scores on Neurocognitive Domains and Individual Test Variables among Adolescents with Schizophrenia-Spectrum Disorders and Healthy Controls

	Patient Group ($n = 54$)		Healthy Control Group ($n = 52$)		Analysis		
Domain and Individual Test Variables[a]	Mean	SD	Mean	SD	Difference in *Z* Scores	*n*	*df*
Language	−1.34	1.51	.00	1.00	−1.34	106	104
Verbal fluency							
Controlled Word Association Test (letter)	29.66	10.80	38.12	10.33		105	103
WISC/WAIS-III similarities (scaled)	8.56	2.81	11.85	2.53		106	104
Memory	−1.79	1.37	.00	1.00	−1.79	105	103
Verbal learning							
California Verbal Learning Test, Child/Adult Edition (CVLT), total trials 1–5	37.77	14.27	55.52	9.96		105	103
Verbal delayed recall							
CVLT, delay free recall	8.02	3.46	12.10	2.53		105	103
Attention	−2.33	1.31	.00	1.00	−2.33	106	104
WISC/WAIS-III							
Digit span (scaled)	7.76	2.87	10.19	2.53		106	104
Arithmetic (scaled)	7.34	3.58	12.59	2.82		104	102
Digit symbol (scaled)	6.13	2.62	12.00	3.41		106	104
Trail Making Test, part A[b]	40.24	28.57	22.88	10.07		105	103
Continuous Performance Test, Identical Pairs version (CPT-IP), d-prime	.75	.74	1.74	.86		95	93
Executive	−2.55	1.97	.00	1.00	−2.55	105	103
Wisconsin Card Sorting Test, perseverative responses[b]	23.00	18.87	9.08	7.00		97	95
Trail Making Test, part B	94.41	58.06	47.04	20.52		104	102
Motor	−2.33	1.63	.00	1.00	−2.33	106	104
Right							
Finger Tapping Test	41.83	9.97	47.57	6.66		106	104
Grooved Pegboard	110.62	44.63	65.94	8.11		106	104
Left							
Finger Tapping Test	39.70	9.61	43.71	6.15		106	104
Grooved Pegboard	122.71	50.42	71.96	12.09		106	104
Visuospatial	−1.65	1.25	.00	1.00	−1.65	106	104
WISC/WAIS-III, block design (scaled)	7.50	3.07	12.21	3.44		106	104
Judgment of Line Orientation (Form H)	18.32	6.56	24.52	3.90		105	103
Global	−2.02	1.09	.00	.58	−2.02	104	102
Premorbid Functioning	−1.43	1.13	.00	.74	−1.43	106	104
WRAT-3 reading score (scaled)	93.29	16.61	108.47	9.84		103	101
WISC/WAIS - III							
Full-scale IQ (scaled)	83.45	14.36	113.02	12.76		104	102
Information (scaled)	8.85	3.13	12.48	2.60		106	104
Vocabulary (scaled)	8.06	3.07	12.00	2.81		106	104

WISC-III, Wechsler Intelligence Scale For Children-Third Edition; WAIS-III, Wechsler Adult Intelligence Scale, Third Edition.

[a]Test variable scores are raw test scores except where noted as scaled. Domain scores are averages of *Z* scores calculated from data available test scores, and that were truncated at $-4.0 < Z < 4.0$.

[b]Two test variables (Trailmaking A and WCST perseverative responses) were log transformed prior to creating domain scores.

differed on both these variables. Deviations from flatness in the patient profiles, if suggested by significant effects of the interactions of group and domain, were assessed by pairwise comparisons of the domains. This analysis was conducted to determine areas of selective deficit, as opposed to generalized impairment affecting all neuropsychological domains.

Regression analysis was used to study the relative contributions of various predictors to the global generalized deficit. Selection of variables for the regression model was based on correlation analyses (see Table 3). Variables were included in the model if they were significantly correlated at the $p < .01$ level with the global generalized deficit or if they were considered to be possible confounders (e.g., duration of psychosis, parameters related to medication exposure and parental socioeconomic status). For those factors measured as total scales and subscales (negative symptoms, premorbid function), if both were significantly correlated with global generalized deficit, only the total scale was included in the regression model due to considerations of parsimony and multicollinearity.

Results

Fifty-four patients completing neuropsychological exams satisfied DSM-IV criteria for schizophrenia ($n = 31$), schizoaffective disorder ($n = 21$), and schizophreniform disorder ($n = 2$). Twenty-three (43%) of 54 patients were classified as having COS. To determine if these 23 patients were representative of the larger group (EOS), we compared the 23 patients with COS to the

Table 3. Correlations Between Clinical Variables and Neurocognitive Domain Scores Among 45 Adolescent Patients with Schizophrenia-Spectrum Disorders

Variable	Correlation with Neurocognitive Domain Score (*r*, 2-tailed)						
	Language	Memory	Attention	Executive	Motor	Visuospatial	Global
Duration of Psychosis	−.09	−.02	−.14	−.05	.08	−.12	−.08
Age at Onset of Psychosis	.30	−.06	.13	−.05	.14	.11	.11
Antipsychotic Dosage[a]	.04	.04	.05	.00	−.13	.13	.02
Lifetime CPZ Dosage[b]	−.27	−.08	−.27	−.27	−.19	−.14	−.28
Positive Symptoms (BPRS[c])							
Total score	−.08	−.13	−.15	−.22	−.17	−.29	−.25
Psychosis	−.02	−.05	−.08	.00	−.17	−.14	−.11
Negative Symptoms (SANS[d])							
Total score	−.22	−.16	−.27	−.53[f]	−.27	−.40[g]	−.45[g]
Affective Flattening	−.19	.07	−.19	−.30	−.32	−.41[g]	−.32
Alogia	−.28	−.17	−.20	−.39[g]	−.12	−.21	−.32
Apathy	−.06	−.20	−.16	−.44[g]	−.15	−.31	−.35
Anhedonia	−.07	−.20	−.26	−.40[g]	−.15	−.24	−.33
Premorbid Adjustment (PAS[e])							
Total score	−.57[f]	−.30	−.42[g]	−.22	−.27	−.25	−.43[g]
Social	−.44[g]	−.14	−.26	−.07	−.19	−.11	−.26
Academic	−.52[f]	−.37[g]	−.45[f]	−.30	−.26	−.32	−.48[f]

[a]Chlorpromazine (CPZ) equivalent dosages at time of testing (Hales and Yudofsky 2003; Woods 2003).
[b]Estimate of lifetime exposure to antipsychotic medications in chlorpromazine equivalent dosages (Hales and Yudofsky 2003; Woods 2003).
[c]Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1961) administered at time of testing.
[d]Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1982) administered at time of testing.
[e]Premorbid Adjustment Scale (Cannon-Spoor et al 1982).
[f]$p < .001$
[g]$p < .01$

31 patients with AOS. The two groups were similar in terms of sex, parental socioeconomic status, handedness, ethnicity, lifetime chlorpromazine equivalents, chlorpromazine equivalents at time of testing, WRAT-3 scaled reading scores, and measures of clinical symptoms (all p values $> .05$). Compared to patients with AOS (mean age = 17.1 years, SD = 1.0), patients with COS (mean age = 14.4 years, SD = 2.5) were younger at time of testing ($t = -5.45$, $df = 52$, $p < .0001$). Also, compared to patients with AOS (mean duration = 1.5 years, SD = 1.2), patients with COS (mean duration = 4.0 years, SD = 2.3) had a longer duration of psychosis ($t = 5.37$, $df = 52$, $p < .0001$). Patients with AOS had lower scores on both PAS total (mean PAS total = 7.5, SD = 4.8) and PAS social items (mean PAS social items = 3.7, SD = 2.7) than did patients with COS (mean PAS total = 11.5, SD = 4.6, mean PAS social items = 6.2, SD = 3.0) ($t = 3.05$, $p < .01$, $t = 3.05$, $p < .01$, respectively).

MANCOVA was used to test the association between performance pattern and onset (AOS, COS). Since age at time of testing, duration of psychosis, PAS total score and PAS social items were possible confounders, these were included as covariates in the model. There was no significant difference in the performance pattern on the neuropsychological profiles across groups (COS, AOS), with the overall MANCOVA being nonsignificant (Wilks' lambda = .89, $F = .75$, $df = 6, 38$, $p = .61$, $n = 49$). Neither the main effect (group status) nor the covariates were statistically significant in the model. As there was no significant association between performance pattern and onset, we did not divide the patient group based on age of onset for subsequent analyses.

The demographic characteristics for the study sample are summarized in Table 1. As shown in Table 1, the healthy comparison group and the patient group did not differ significantly on sex, age, ethnicity, or handedness; however, the groups differed significantly on parental socioeconomic status ($\chi^2 = 4.36$, $p < .04$).

Complete neurocognitive test data were available for 89 (84%) of 106 participants (42 of 54 patients and 47 of 52 controls). No participant had more than 3 missing test data points. With the exception of the two computer tests that the patients experienced as more difficult, there were only 2 missing data points from any test. To determine if the 42 patients with complete test data were representative of the larger group, we compared the 42 patients with complete test data to the 12 patients with incomplete test data. There were no significant differences between the two groups with respect to age, sex, racial/ethnic group composition, parental socioeconomic class, duration of psychosis, lifetime chlorpromazine equivalents of medications and severity of clinical symptoms at testing (all p values $> .05$). Available data for patient and control participants for each test is presented in Table 2. Estimated full-scale IQ scores were 83.5 (SD = 14.4, $n = 53$) for patients and 113.0 (SD = 12.8, $n = 51$) for controls, which were significantly different ($t[102] = -11.087$, $p < .0001$). Mean WRAT-3 reading scaled scores were 93.3 (SD = 16.6, $n = 52$) for patients and 108.5 (SD = 9.9, $n = 51$) for controls; this difference was also significant ($t[101] = -5.6$, $p < .0001$).

Independent sample t-tests demonstrated that the neurocognitive test performance of the patient group was more impaired than the comparison group on all neurocognitive tests ($p < .01$).

The patient profile deviated significantly from flatness (group-by-scale interaction: Wilks' lambda = .78; $F = 5.48$, $df = 5, 98$, $p < .0002$). Pairwise comparisons, using a Bonferroni adjustment, were carried out within the MANOVA model. The language and visuospatial domains were significantly less impaired than attention, motor, or executive functioning. Although memory was also significantly less impaired than executive functioning, it was not significantly different from attention or motor.

MANCOVA was used to examine the effects of parental social class and premorbid intellectual ability using WRAT-3 reading

Table 4. Backwards Elimination Linear Regression of Global Neurocognitive Scores in 45 Adolescent Patients With Schizophrenia-Spectrum Disorders Controlling for Negative Symptoms[a] and Premorbid Adjustment[b]

Variable	B	SE	*F*	*p*
Intercept	−.135	.375	.13	.721
SANS total[a]	−.027	.007	13.69	.000
PAS total[b]	−.092	.025	13.57	.000

Negative symptoms[a], premorbid adjustment[b], lifetime chlorpromazine equivalents, current chlorpromazine equivalents, parental socioeconomic status, and duration of illness were all entered into a backward elimination regression. The final model is presented above, where F [2, 44] = 13.93, $p < .0001$, $R^2 = .39$.

[a]Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1982).

[b]Premorbid Adjustment Scale (PAS; Cannon-Spoor et al 1983).

scores on the relationship between patient profile and group (SZ, NC). Neither covariate (parental social class or WRAT-3 reading score) was significant; conducting the analyses covarying for parent SES and WRAT-3 reading scores minimally diminished the generalized deficit between groups to 1.64 SDs. Therefore, the model remained as patient profile = diagnostic group (SZ, NC).

Correlations among neurocognitive domain scores and demographic and clinical variables were explored, including: duration of psychosis, age at onset of psychosis, positive and negative symptoms at the time of testing, premorbid adjustment, chlorpromazine equivalent dosage at time of testing and lifetime chlorpromazine equivalents (see Table 3). Since a large number of correlations were examined in this analysis, the threshold for significance was set at $p < .01$ to limit the possibility of a Type I error. All correlations are shown in Table 3.

The set of variables entered into the regression model as predictors of global neurocognitive scores included: premorbid adjustment, SANS total score, chlorpromazine equivalent dose at time of testing, lifetime chlorpromazine equivalents, duration of psychosis, and parental socioeconomic status. Backwards elimination was used, and the results were confirmed using forward selection. Only negative symptoms as measured by the SANS and premorbid adjustment scores were significant. These factors accounted for 39% of the variance of global neurocognitive scores (see Table 4).

Discussion

In this study of adolescents with EOS, we found a generalized deficit of 2.0 standard deviations relative to healthy controls, with a subtle relative deficit in executive functioning and subtle relative sparing of language and visuospatial skills. This overall pattern is similar to that observed in previous studies of adolescents with EOS (Asarnow et al 1994; Kenny et al 1997; Kumra et al 2000; Oie and Rund 1999; Ueland et al 2004) and severely affected first-episode adult patients (Bilder et al 2000; Mohamed et al 1999). We did not find a statistically significant difference in the neuropsychological profiles of adolescents with COS and AOS. Thus, the present investigation does not provide any evidence that patients with a childhood onset are more cognitively impaired than patients with an adolescent onset of illness. In a model that included premorbid adjustment, severity of negative symptoms, duration of psychosis, antipsychotic dose at time of testing, cumulative antipsychotic exposure, and parental socioeconomic status entered together, severity of generalized cognitive deficit was predicted by severity of negative symptoms and premorbid adjustment.

These results are mostly consistent with data from adults with first-episode schizophrenia (Bilder et al 2000). Both samples showed evidence of a large generalized deficit, with a subtle relative deficit in executive functioning and subtle relative sparing of language function. In particular, adults with low levels of general ability (median split on the global neuropsychological scale) were more impaired in terms of executive function compared to their counterparts with high levels of general ability. Thus, these data are compatible with a hypothesis that early-onset schizophrenia represents a more severe form of the disorder. In contrast, memory function did not emerge as a relative deficit in EOS as seen in adults with first-episode schizophrenia. This could reflect the smaller sample size of the current study and/or differences in the psychometric properties of the neuropsychological tests that make interpreting profiles of performance across groups less reliable than interpreting global differences (Mojtabai et al 2000). Similar to adults with first-episode schizophrenia (Bilder et al 2000; Mohamed et al 1999), we also found that neuropsychological test scores tended to correlate more strongly with negative symptoms than with positive symptoms or overall psychopathology.

The results of the current study are also generally consistent with prior studies of COS and EOS in that evidence has been found of a large generalized deficit, with a subtle deficit in executive function (Ueland et al 2004) and a subtle relative sparing of language (Kenny et al 1997; Kumra et al 2000) and visuospatial function (Asarnow et al 1994; Oie and Rund 1999). Together, these data suggest that children with schizophrenia tend to perform most poorly on tasks that make extensive demands on information-processing resources, reflective of a disruption of fronto-striatal networks and working memory capacity (Asarnow et al 1994).

In contrast to prior studies of EOS that have found measures of sustained attention to be the least impaired in EOS patients (Kravariti et al 2003; Oie and Rund 1999), we found deficits in sustained attention in this sample of EOS patients consistent with data from adults with first-episode schizophrenia (Bilder et al 2000), as well as adolescents at genetic risk for schizophrenia (Erlenmeyer-Kimling et al 2000). This discrepancy across EOS studies may reflect differences in the measure of sustained attention used and the lower full-scale IQ of the present sample. A prior study (Oie and Rund 1999) measured sustained attention using the Degraded Stimulus Continuous Performance Task (DSCPT; Nuechterlein 1983), which emphasizes the visual and vigilance components of attention. In contrast, the present study assessed attention with the CPT-IP (Cornblatt et al 1997), a task that additionally demands a working-memory component, in combination with several other tasks that are more demanding of working memory than the DSCPT. Also, the full-scale IQ of Kravariti and colleagues' (2003) patient sample (mean = 93) and that of Oie and Rund (1999) (mean = 98) were .5 to 1 normative standard deviations higher than ours (mean = 84). Thus, this New York community-based EOS sample may be more cognitively impaired than were previously studied EOS samples.

Although our sample showed substantial range of both age of onset of psychosis and duration of psychosis, we did not find that either factor was significantly associated with neurocognitive test performance. Our sample showed a median duration of 2.6 years, reflecting both inclusion of adolescents in the sample who had multiple episodes of psychosis, as well as participants who had a long duration of untreated psychosis. A delay of approximately 2 years between age at which symptoms are first recognized and first presentation for treatment of schizophrenia

is typically found, even in childhood-onset schizophrenia (e.g., Schaeffer and Ross 2002). Further, it should be noted that previous neuropsychological studies have also found no progression in the severity of neurocognitive deficits in adults with schizophrenia within the first few years of illness (Heaton et al 2001; Heydebrand et al 2004; Hoff et al 1996).

In this study we found that premorbid adjustment, particularly premorbid academic adjustment, and severity of negative symptoms at time of testing emerged as the strongest correlates of the global neurocognitive deficits. Both severity of negative symptoms (Bilder et al 2000; Heydebrand et al 2004; Mohamed et al 1999) and premorbid function (DeQuardo et al 1994; Levitt et al 1996; Silverstein et al 2003) have been found to be significantly correlated with generalized neurocognitive impairments in adults with schizophrenia. The consistency in the neuropsychological profile across studies of COS (Asarnow et al 1994; Kumra et al 2000) and EOS (Kenny et al 1997; Kravariti et al 2003; Oie and Rund 1999), as well as the pattern of associations, suggest that neurocognitive deficits in EOS represent a stable, trait-like characteristic evident early in the course of illness. These data also suggest a common neurobiological substrate (involvement of heteromodal association cortex) for deficits in motivation, socialization and neurocognition observed in adolescents with EOS (Mojtabai et al 2000).

A number of methodological limitations of the present investigation should be highlighted. First, we elected to test EOS patients while they were receiving stable medication regimens to enhance compliance and optimize performance. It is difficult to estimate the confounding influence of medication exposure on our test results due to the naturalistic design of this study. Although it is possible that some of the variance of the neuropsychological deficit in patients could be secondary to sedation, or to adjusting to a newly prescribed or recently increased dose of antipsychotic medication, we did not find any significant associations between medication dose at time of testing and neuropsychological test performance. There is increasing evidence that atypical antipsychotics improve some aspects of neurocognitive function such as fine motor functions, verbal fluency, executive functions and visual/motor/attentional coordination (Keefe et al 1999), as well as overall neurocognitive functioning (Keefe et al 2004). Thus the bias of exposure to antipsychotic medication use would have been to diminish group (patient/controls) differences and possibly alter the profile of relative strengths and weaknesses. However, a similar pattern of impairments in global neurocognition and motor function have been reported in other populations of schizophrenic adolescents who had limited medication exposure and were early in the course of their illness (Oie and Rund 1999) and individuals at genetic high risk for schizophrenia (Erlenmeyer-Kimling et al 2000). Furthermore, we did not find any significant correlations between lifetime antipsychotic medication exposure with performance on any of the summary scores that we used. Although anticonvulsants may adversely affect memory (Loring and Meador 2004), these medications were prescribed to relatively few (15%) of our patients. Together, these data suggest that it is unlikely that the group differences we observed could be significantly attributed to medication effects.

We chose to test patients once they were clinically stabilized on their antipsychotic medication during their inpatient stay, and once they appeared able to cooperate with testing based on the judgment of the primary clinician and our own examination. An alternative approach would have been to wait for 6 months after an adolescent had been stabilized on antipsychotic medication and had achieved remission or a stable level of residual symptoms (Bilder et al 2000). We rejected this latter approach due to concerns regarding patient attrition after discharge from hospital. We did not find an association between level of psychopathology at time of testing (as measured by Brief Psychiatric Rating Scale scores) and neuropsychological test performance, suggesting little evidence that acute effects of illness affected neuropsychological test scores.

Our findings of a generalized neurocognitive deficit should be interpreted in the context of the psychometric limitations of currently available neurocognitive measures. The inability to remove the possible confounding factor of the differential discriminating power of the various tasks limits the interpretability of this and other studies of neurocognitive function in patients with schizophrenia (Chapman and Chapman 1989). Also, we administered different, albeit developmentally appropriate, versions of some tests based on the participant's age at the time of testing (e.g., CVLT, WISC/WAIS-III), which may raise questions about the comparability across the scales.

The lack of adequate matching on parental socioeconomic status is another limitation of this study. Healthy control participants were more likely to come from higher socioeconomic backgrounds and have higher premorbid intellectual ability, since we screened out subjects with a parental history of schizophrenia or bipolar disorder. Differences in parental socioeconomic status may also reflect an ascertainment bias between parents who presented their child for psychiatric treatment versus parents who brought their psychiatrically healthy children in for a research study. In addition, healthy controls, but not patients, were excluded based on presence of learning disabilities or substance abuse, conditions potentially associated with lower parental SES and education levels. Prior studies of EOS that excluded such subjects also found elevated levels of parental socioeconomic status and IQ scores among healthy controls (Rapoport et al 1999). Also, when we repeated the analysis covarying for these factors, results were essentially unchanged. The covariates explained only a small proportion of the variance in neurocognitive impairment, and thus were not significant confounds.

The present cross-sectional study could not definitively address the issue of changes in severity of neurocognitive deficits across time and different phases of illness. Consequently, findings may have been influenced to an unknown degree by the time at which neurocognition was assessed. Future investigations may elucidate whether the deficits observed progress or fluctuate across the course of illness in EOS or remain stable. Such studies may also explore longitudinally the associations between neurocognitive dysfunction, symptomatology, and functional capacities.

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American Psychiatric Association (1980): *Diagnostic and Statistical Manual of Mental Disorders,* 3rd ed. Washington, DC: American Psychiatric Press.

American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. Washington, DC: American Psychiatric Press.

Andreasen NC (1982): Scale For the Assessment of Negative Symptoms (SANS). Iowa City: University of Iowa.

Asarnow RF, Asamen J, Granholm E, Sherman T, Watkins JM, Williams ME (1994): Cognitive/ neuropsychological studies of children with schizophrenic disorder. *Schizophr Bull* 20:647–670.

Axelrod BN, Ryan JJ, Ward LC (2001): Evaluation of seven-subtest short forms of the Wechsler Adult Intelligence Scale-III in a referred sample. *Arch Clin Neuropsychol* 16:1–8.

Benton AL, Hamsher K, Varney NR, Spreen V (1983): Contributions to Neurocognitive Assessment. New York: Oxford University Press.

Bilder RM, Goldman RS, Robinson D, Reiter G, Bell L, Bates JA, et al (2000): Neuropsychology of first-episode schizophrenia: Initial characterization and clinical correlates. *Am J Psychiatry* 157:549–559.

Cannon-Spoor HE, Potkin SG, Wyatt RJ (1982): Measurement of premorbid adjustment in chronic schizophrenia. *Schizophr Bull* 8:470–484.

Chapman LJ, Chapman JP (1989): Strategies for resolving the heterogeneity of schizophrenics and their relatives using cognitive measures. *J Abnorm Psychol* 98:357–366.

Cornblatt B, Obuchowski M, Schnur D, O'Brien JD (1997): Attention and clinical symptoms in schizophrenia. *Psychiatr Q* 68:343–359.

Delis DC, Kramer JH, Kaplan E, Ober BA (1987): California Verbal Learning Test Manual. San Antonio, TX: The Psychological Corporation.

DeQuardo JR, Tandon R, Goldman R, Meador-Woodruff JH, McGrath-Giroux M, Brunberg JA, Kim L (1994): Ventricular enlargement, neuropsychological status, and premorbid function in schizophrenia. *Biol Psychiatry* 35: 517–524.

Donders J (1997): A short form of the WISC-III for clinical use. *Psychological Assessment* 9:15–20.

Erlenmeyer-Kimling L, Rock D, Roberts SA, Janal M, Kestenbaum C, Cornblatt B, et al (2000): Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: The New York high-risk project. *Am J Psychiatry* 157:1416–1422.

Hales RE, Yudofsky SC (2003): Textbook of Clinical Psychiatry, Fourth edition. Arlington, VA: American Psychiatric Publishing, Inc.

Heaton RK, Chelune GJ, Talley JL, Kay GG, Curtis G (1993): The Wisconsin Card Sorting Test Manual - Revised and Expanded. Odessa, FL: Psychological Assessment Resources, Inc.

Heaton RK, Gladsjo JA, Palmer BW, Kuck J, Marcotte TD, Jeste DV (2001): Stability and course of neuropsychological deficits in schizophrenia. *Arch Gen Psychiatry* 58:24–32.

Heydebrand G, Weiser M, Rabinowitz J, Hoff AL, Delisi LE, Csernansky JG (2004): Correlates of cognitive deficits in first episode schizophrenia. *Schizophr Res* 68:1–9.

Hoff AL, Harris D, Faustman WO, Beal M, DeVilliers D, Mone RD, et al (1996): A neuropsychological study of early onset schizophrenia. *Schizophr Res* 20:21–28.

Hoff AL, Riordan H, O'Donnell DW, Morris L, DeLisi LE (1992): Neuropsychological functioning of first-episode schizophreniform patients. *Am J Psychiatry* 149:898–903.

Hollingshead A, Redlich F (1958): *Social class and mental illness.* New York, NY: John Wiley and Sons.

Hollis C (1995): Child and adolescent (juvenile onset) schizophrenia: A case control study of premorbid developmental impairments. *Br J Psychiatry* 166:489–495.

Hollis C (2000): Adult outcomes of child- and adolescent-onset schizophrenia: Diagnostic stability and predictive validity. *Am J Psychiatry* 157:1652–1659.

Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al (1997): Schedule for affective disorders and schizophrenia for school-age children – present and lifetime version: Initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 36:980–988.

Keefe RS, Seidman LJ, Christensen BK, Hamer RM, Sharma T, Stiskoorn MM, et al (2004): Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. *Am J Psychiatry* 161:985–995.

Keefe RS, Silva SG, Perkins DO, Lieberman JA (1999): The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: A review and meta-analysis. *Schizophr Bull* 25:201–222.

Kenny JT, Friedman L, Finding RL, Swales TP, Strauss ME, Jesberger JA, et al (1997): Cognitive impairment in adolescents with schizophrenia. *Am J Psychiatry* 154:1613–1615.

Kravariti E, Morris RG, Rabe-Hesketh S, Murray RM, Frangou S (2003): The Maudsley early onset schizophrenia study: Cognitive function in adolescents with recent onset schizophrenia. *Schizophr Res* 61:137–148.

Kumra S, Ashtari M, McMeniman M, Vogel J, Augustin R, Becker DE, et al (2004): Reduced frontal white matter integrity in early-onset schizophrenia: a preliminary study. *Biol Psychiatry* 55:1138–1145.

Kumra S, Wiggs E, Bedwell J, Smith AK, Arling E, Albus K, et al (2000): Neurocognitive deficits in pediatric patients with childhood-onset schizophrenia and psychotic disorder not otherwise specified. *Schizophr Res* 42:135–144.

Levitt JJ, O'Donnell BF, McCarley RW, Nestor PG, Shenton ME (1996): Correlates of premorbid adjustment in schizophrenia with auditory event-related potential and neuropsychological abnormalities. *Am J Psychiatry* 153:1347–1349.

Loranger AW (1984): Sex difference in age of onset of schizophrenia. *Arch Gen Psychiatry* 41:157–161.

Lord C, Rutter M, LeCouteur A (1994): Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *J Autism Dev Disord* 24:659–685.

Loring DW, Meador KJ (2004): Cognitive side effects of antiepileptic drugs in children. *Neurology* 62:872–877.

Matthews CG, Klove H (1964): *Instruction manual for the Adult Neuropsychology Test Battery*. Madison, WI: University of Wisconsin Medical School.

McClellan J, Prezbindowski A, Breiger D, McCurry C (2004): Neurocognitive functioning in early onset psychotic disorders. *Schizophr Res* 68:21–26.

McKenna K, Gordon CT, Lenane M, Kaysen D, Fahey K, Rapoport JL (1994): Looking for childhood-onset schizophrenia: The first 71 cases screened. *J Am Acad Child Adolesc Psychiatry* 33:636–644.

Meehl PE (1970): Nuisance variables and the ex post facto design. In: Radner M, Winokur S, editors. *Minnesota Studies in the Philosophy of Science.* Minneapolis, ME: University of Minnesota Press, pp 373–402.

Mohamed S, Paulsen JS, O'Leary D, Arndt S, Andreasen N (1999): Generalized cognitive deficits in schizophrenia. *Arch Gen Psychiatry* 56:749–754.

Mojtabai R, Bromet EJ, Harvey PD, Carlson GA, Craig TJ, Fennig S (2000): Neuropsychological differences between first-admission schizophrenia and psychotic affective disorders. *Am JPsychiatry* 157:1453–1460.

Nicolson R, Lenane M, Singaracharlu S, Malaspina D, Giedd JN, Hamburger SD, et al (2000): Premorbid speech and language impairments in childhood-onset schizophrenia: Association with risk factors. *Am J Psychiatry* 157:794–800.

Nuechterlein KH (1983): Signal detection in vigilance tasks and behavioral attributes among offspring of schizophrenic mothers and among hyperactive children. *J Abnorm Psychol* 92:4–28.

Oie M, Rund BR (1999): Neurocognitive deficits in adolescent-onset schizophrenia compared with attention deficit hyperactivity disorder. *Am J Psychiatry* 156:1216–1222.

Overall J, Gorham D (1961): The brief psychiatric rating scale. *Psychiatry Res* 10:799–812.

Rapoport JL, Giedd JN, Blumenthal J, Hamburger S, Jeffries N, Fernandez T, et al (1999): Progressive cortical change during adolescence in childhood-onset schizophrenia: a longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry* 56:649–654.

Reitan RM (1979): *Manual for Administration of Neurocognitive Test Batteries for Adults and Children*. Tuscon, AZ: Reitan Neurocognitive Laboratory.

Saykin AJ, Shtasel DL, Gur RE, Kester BD, Mozley LH, Stafniak P, et al (1994): Neurocognitive deficits in neuroleptic naive patients with first-episode schizophrenia. *Arch Gen Psychiatry* 51:124–131.

Schaeffer JL, Ross RG (2002): Childhood onset schizophrenia: Premorbid and prodromal diagnostic and treatment histories. *J Am Acad Adolesc Psychiatry* 41:538–545.

Silverstein ML, Mavrolefteros G, Turnbull A (2003): Premorbid factors in relation to motor, memory, and executive functions deficits in adult schizophrenia. *Schizophr Res* 61:271–280.

Ueland T, Oie M, Landro NI, Rund BR (2004): Cognitive functioning in adolescents with schizophrenia spectrum disorders. *Psychiatry Res* 126:229–239.

Vourdas A, Pipe R, Corrigal R, Frangou S (2003): Increased developmental deviance and premorbid dysfunction in early onset schizophrenia. *Schizophr Res* 62:13–22.

Wechsler D (1991): *Wechsler Intelligence Scale for Children*, 3rd ed. San Antonio, TX: Psychological Corporation.

Wechsler D (1997): *Wechsler Adult Intelligence Scale*, 3rd ed. San Antonio, TX: Psychological Corporation.

Wilkinson GS (1993): *WRAT3: Wide Range Achievement Test Administration Manual*. Wilmington, DE: Wide Range, Inc.

Woods SW (2003): Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry* 64:663–667.