# Neurocognitive Deficits in Adolescents With Schizophrenia: Longitudinal Stability and Predictive Utility for Short-Term Functional Outcome

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**ABSTRACT**

**Objective:** Previous cross-sectional studies in adolescents with early-onset schizophrenia (EOS; onset of psychotic symptoms by 18 years of age) have reported patterns of generalized neurocognitive deficits as compared to healthy comparison subjects (HCSs). Here, the authors examined the longitudinal stability of neuropsychological deficits in adolescents with EOS relative to HCS and the associations of these deficits with short-term functional outcome in patients. **Method:** Fifty-two subjects (26 EOS, 26 HCS) were evaluated using a comprehensive neuropsychological test battery a median of 13 months after baseline examination. The stability of scores and the relationship between baseline test performance and functional outcome in patients was explored. **Results:** Adolescents with EOS were impaired across neurocognitive domains at baseline and follow-up compared to HCSs; these deficits remained relatively stable over time. Follow-up social/communication, personal living, and community living skills were significantly related to attention/vigilance, working memory and verbal memory at baseline; individual cognitive domains were more strongly related to functional outcome than a global measure of intelligence. **Conclusions:** Neuropsychological impairment in patients with EOS appears to remain relatively stable over time regardless of changes in clinical state. In addition, this report offers preliminary support for a longitudinal relationship between neurocognitive performance in specific domains and functional outcome. *J. Am. Acad. Child Adolesc. Psychiatry,* 2007;46(7):867–878. **Key Words:** schizophrenia, cognition, functional outcome, attention.

Early-onset schizophrenia (EOS; onset of psychotic symptoms by age 18) is a relatively rare and severe form of the disorder characterized by a chronic illness course and severe impairments in social relationships and independent living (Hollis, 2000; McClellan et al., 1999). Adolescents with EOS have been found to have generalized neurocognitive deficits between 1.5 and 2.0 SDs relative to healthy comparison subjects (HCSs; Kravariti et al., 2003; McClellan et al., 1999, 2004; Rhinewine et al., 2005), similar to what has been described in adults (Heinrichs and Zakzanis, 1998) and first-episode patients (Bilder et al., 2000) with schizophrenia. Due to the cross-sectional nature of these studies, the data could not definitively address whether the observed neurocognitive deficits were static or progressive across the course of illness. Because the majority of these studies ascertained subjects who were acutely ill at the time of testing, the acute effects of illness (e.g., stress of hospitalization, psychopathology) could have confounded test performance. In this regard, studies incorporating a longitudinal design with a period of follow-up sufficient to ensure adequate

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stabilization on antipsychotic medication could be helpful in determining the stability of these deficits.

In adults with schizophrenia, the stability of neurocognitive deficits across different phases of illness has been well described (Heaton et al., 2001; Hoff et al., 1999; Savla et al., 2006). There has been a relative paucity of comparable longitudinal studies in children and adolescents with the disorder. To our knowledge, the only longitudinal study of cognitive function in EOS was conducted in a group of 31 treatment-refractory adolescents with childhood-onset schizophrenia (COS; Gochman et al., 2005). This study found an initial steep decline in overall intellectual ability around the time at onset of psychosis with subsequent stabilization of deficits 1 to 2 years postonset (Gochman et al., 2005). Thus, additional studies are needed to confirm whether these findings generalize to a broader group of adolescents with schizophrenia, including those who are not treatment resistant.

In terms of cognition and its relationship with functioning, robust relationships between global and specific cognitive deficits (i.e., verbal memory, attention, working memory, executive function) and functional outcome (i.e., social problem solving/skill acquisition and community/daily activities) at a later follow-up assessment have been consistently demonstrated in adults with schizophrenia (Green et al., 2000, 2004; Jaeger et al., 2006). These studies also suggest specific cognitive domains may predict functional outcome better than Full Scale IQ (Green et al., 2000).

In contrast to the adult literature, there have been limited data published in peer-reviewed journals examining the relationships between neurocognitive deficits and functional outcome in adolescents with schizophrenia. There are some data demonstrating an association between cognitive deficits as indicated by a low IQ (<80) and functional outcome in terms of poor peer relationships after a mean follow-up interval of approximately 5 years in psychotic youths with bipolar disorder or schizophrenia (Werry and McClellan, 1992). However, in these analyses, baseline functional adjustment was not considered, rendering it difficult to completely understand the impact of the results. Furthermore, when adolescents with schizophrenia were examined alone, poor premorbid social adjustment, but not low IQ, best predicted indices of functional outcome. Earlier studies examining predictors of functional outcome in adolescents with schizophrenia (e.g., Werry and McClellan, 1992) were limited in that reliable and well-validated scales of adaptive function that specifically address the issue of independent living in a number of domains (e.g., Scales of Independent Behavior-Revised [SIB-R]; Bruininks et al., 1996) were not available. Thus, it would be advantageous to further examine whether specific deficits of neurocognitive domains predict short-term functioning in specific areas of outcome using available measures of adaptive function that have good psychometric properties.

These considerations provided the impetus for our group to conduct a longitudinal study of neurocognitive test performance and short-term functional outcome in 26 adolescents with EOS (age range at baseline 11.9–18.8 years) and 26 demographically similar HCSs (age range at baseline 11.8–19.0 years) that examined a broader range of measures than what has been reported (Gochman et al., 2005; Werry and McClellan, 1992). Based on findings from the limited number of previously published studies in adult and pediatric schizophrenia samples, we hypothesized that neurocognitive impairments in adolescents with schizophrenia would remain relatively stable over time compared to their healthy counterparts, regardless of changes in clinical state (Gochman et al., 2005; Heaton et al., 2001; Hoff et al., 1999; Savla et al., 2006). In addition, we hypothesized that there would be significant associations between baseline neurocognitive deficits in attention, working memory, and verbal memory and measures of functional outcome at follow-up (Green et al., 2000, 2004; Jaeger et al., 2006). Furthermore, we expected correlations between the other cognitive domains (i.e., sensory motor and motor speed) and the functional outcome measures to be nonsignificant.

## METHOD

### Subjects

Subjects included 26 patients with EOS and 26 HCSs who completed two comprehensive neurocognitive evaluations a median of 13 months apart. Diagnoses were made using portions of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS; Kaufman et al., 1997); children and parents were interviewed separately. All of the diagnoses were made by a psychologist or psychiatrist using *DSM-IV* (American Psychiatric Association, 1994) criteria based on clinical interviews, available medical records, and information from treating clinicians; all of the diagnoses were reviewed by a board-certified child and adolescent psychiatrist (S.K.). The interrater

agreement of two of the study's principal diagnosticians for the primary classification of a schizophrenia-spectrum disorder (i.e., schizophrenia, schizoaffective disorder, or schizophreniform disorder; $n = 15$) versus other psychiatric disorders (i.e., bipolar disorder, psychosis not otherwise specified, substance-induced psychosis; $n = 10$) was strong ($\kappa = .83$) for 25 cases that were

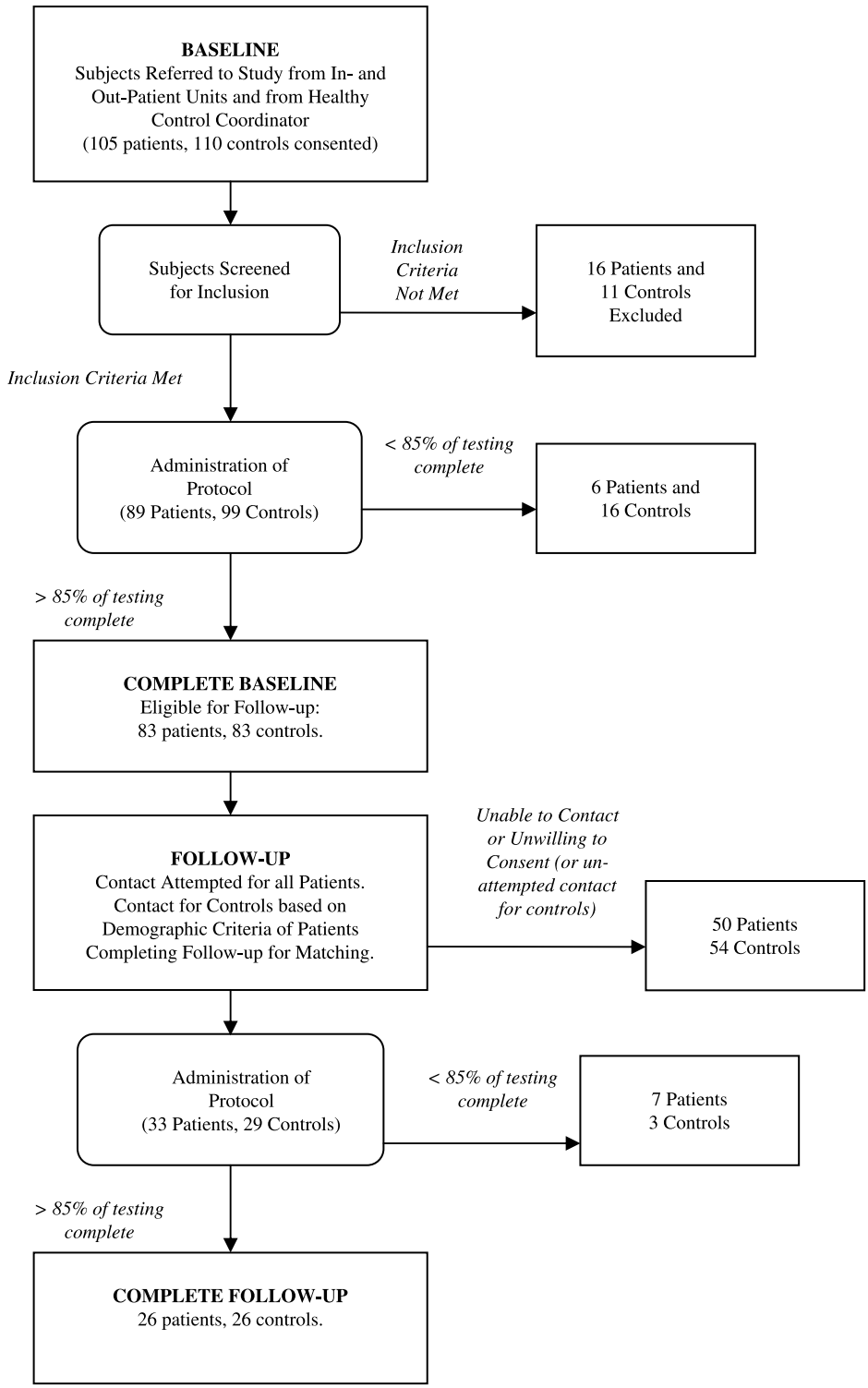


**Fig. 1** Subject recruitment and retention from baseline screening through completion of follow-up.

corated. HCSs were recruited from the surrounding community and adolescent medical clinics. Exclusion criteria for all of the participants included mental retardation, recent substance use, and neurological disorders that could potentially affect cognitive development. In addition, HCSs were excluded if they had a history of any major psychiatric disorder, a first-degree relative with bipolar disorder or schizophrenia, or a physical illness requiring medication that could potentially affect cognition (Kumra et al., 2005). The North Shore-Long Island Jewish Health System Institutional Review Board approved all of the procedures, including recruitment and consent. Written informed consent/assent was obtained from participants and their legal guardians (subjects younger than 18 years) at baseline and follow-up.

The sample reported herein represents the first 52 adolescents (26 EOS, 26 HCSs) from our baseline study (Rhinewine et al., 2005) who were recontacted and completed follow-up. Up to four attempts were made to contact all of the patients who completed the baseline protocol (Fig. 1). Patients who had not consented to follow-up were either unable to be contacted, withdrew consent, or were unable to consent due to clinical condition. Final sample size was not based on power calculations, but rather an attempt was made to reassess as many patients as possible. HCSs were contacted strategically to best match the sample of patients who completed follow-up. Not all controls were contacted to participate in the follow-up protocol.

The sample of patients with complete baseline data who did not undergo a second testing ($n$ = 57) was not significantly different ($p < .05$) from those who did participate ($n$ = 26) in terms of age, gender, ethnicity, age at onset of psychosis, duration of illness, severity of psychiatric symptoms (Brief Psychiatric Rating Scale [BPRS]; Overall and Gorham, 1962), severity of negative symptoms (Scale for the Assessment of Negative Symptoms [SANS]; Andreasen, 1982), premorbid adjustment (Premorbid Adjustment Scale; Cannon-Spoor et al., 1982), global functioning (Children's Global Assessment Scale [CGAS]; Bird, 1999) or premorbid intelligence (Wide Range Achievement Test [WRAT]) reading subtest (Wilkinson, 1993). Patients and controls included in this follow-up report were similar on factors that could potentially affect neuropsychological test performance such as age, parental socioeconomic status (Hollingshead and Redlich, 1958), and time elapsed between assessments (Table 1). Complete clinical characteristics of patients at baseline and follow-up are presented in Table 2.

**TABLE 1**
Characteristics of Adolescent Patients With Schizophrenia and Healthy Control Subjects

| | Patients ($n$ = 26) | Controls ($n$ = 26) | Test Statistic | $p$ |
|---|---|---|---|---|
| Mean age at baseline (SD), y | 16.0 (2.2) | 15.6 (2.1) | $t$ = 0.60 | .55 |
| Mean age at follow-up (SD), y | 17.2 (2.1) | 16.8 (2.3) | $t$ = 0.69 | .50 |
| Mean follow-up observation period (SD), mo | 14.2 (9.8) | 15.5 (10.5) | $t$ = −0.49 | .62 |
| Gender | | | | |
| Male | 15 | 13 | | |
| Female | 11 | 13 | $\chi^2$ = 0.31 | .58 |
| Ethnicity | | | | |
| White | 11 | 9 | | |
| Nonwhite | 15 | 17 | $\chi^2$ = 0.33 | .57 |
| Handedness | | | | |
| Dextral | 24 | 24 | | |
| Nondextral | 2 | 2 | $\chi^2$ = 0.00 | 1.00 |
| Socioeconomic status[a] | | | | |
| High | 23 | 25 | | |
| Low | 3 | 1 | $\chi^2$ = 1.08 | .30 |
| Mean WRAT at baseline (SD) | 92.2 (18.4) | 109.9 (6.8) | $t$ = −4.03 | <.005 |

*Note:* WRAT = Wide Range Achievement Test, Reading Subtest.
[a] Hollingshead system (Hollingshead and Redlich, 1958), 1–3 = high and 4–5 = low.

## Neuropsychological Examinations

An extensive neurocognitive battery was administered to each subject at baseline, at which point the majority of patients were inpatients in an acute setting and were exhibiting clinically significant psychotic symptoms (Rhinewine et al., 2005). The second assessment for patients was at least 6 months after baseline to allow for clinical stabilization from the acute episode of psychosis (i.e., clinically significant reduction in positive symptoms assessed with the BPRS and/or clinically significant increase in functioning assessed with the CGAS, determined by study staff based on interviews with patients, parents, and clinicians). Furthermore, no subjects were currently being hospitalized in an acute setting at follow-up. Variability in the actual time of follow-up (range 6–36 months) was due to when the patient achieved significant clinical stabilization as well as the patient's availability.

The neurocognitive battery consisted of the following tests (in order of administration at baseline): WISC-III (age <16), WAIS-III (age ≥16), California Verbal Learning Test, Judgment of Line Orientation, Grooved Pegboard, Trail Making Test parts A and B, Finger Tapping Test, the Controlled Oral Word Association Test, the WRAT-3 Reading subtest, the Wisconsin Card Sorting Test, and the Continuous Performance Test, Identical Pairs Version (Spreen and Strauss, 1998; complete test information, procedures, and test-retest reliabilities are available on the *Journal's* Web site at www.jaacap.com via the ArticlePlus feature). A psychologist or trained psychometrician (J.R., J.C., K.C.) with at least a master's degree in clinical psychology administered all of the neurocognitive tests; a neuropsychologist (K.B.) supervised all of the examiners to ensure fidelity and to protect against examiner "drift." It was not practical to keep the testers blind to the subject's diagnostic group due to the patients' overt and residual symptoms. For the purpose of valid comparison, all of the subjects received the same neurocognitive battery as was administered at baseline, although it was administered in reverse order at follow-up. Subjects were given the alternate version of the Controlled Oral Word Association Test (CFL, PRW) and the WRAT (tan, blue) at follow-up to help reduce practice effects. The WRAT was used as an estimate of premorbid intelligence as it is particularly resilient to the effects of deterioration associated with brain disease (Nelson and O'Connell, 1978).

## Psychiatric Symptom Measures

The BPRS, SANS, and CGAS were administered to patients at the time of each neuropsychological assessment; the Premorbid

**TABLE 2**
Characteristics of Patients with Early-Onset Schizophrenia at Baseline and Follow-up ($n$ = 26)

| | Baseline | Follow-up | Test Statistic | $p$ |
|---|---|---|---|---|
| Clinical symptoms | | | | |
| Mean age at onset of psychosis (SD), y | 13.1 (3.8) | — | | |
| Mean duration of psychosis (SD), mo | 33.7 (31.3) | 47.8 (33.5) | | |
| Mean BPRS total (SD) | 36.7 (6.9) | 31.4 (9.0) | $t = -2.08$ | .05 |
| Mean BPRS psychosis cluster (SD) | 10.7 (4.8) | 6.4 (3.2) | $t = -4.04$ | <.01 |
| Mean SANS total (SD) | 36.5 (18.0) | 27.0 (18.1) | $t = -2.04$ | .05 |
| Functional measures | | | | |
| Mean CGAS (SD) | 40.0 (8.4) | 49.1 (13.1) | $t = 2.81$ | .01 |
| Mean SIB-R[a] (SD), social/ communication | — | 88.6 (13.0) | | |
| Mean SIB-R[a] (SD), personal living | — | 87.7 (16.0) | | |
| Mean SIB-R[a] (SD), community living | — | 84.7 (14.0) | | |
| Mean SIB-R[a] (SD), motor skills | — | 91.5 (18.7) | | |
| Medication | | | | |
| No. of patients on antipsychotic medication(s)[c,d] | 23[b] | 21 | | .63 |
| Atypical | 23 | 21 | | .63 |
| Typical | 1 | 1 | | 1.00 |
| Concomitant medications[d] | | | | |
| Anticonvulsant | 4 | 1 | | .38 |
| Antidepressant | 7 | 5 | | .50 |
| Lithium | 3 | 3 | | 1.00 |
| Antianxiety | 4 | 2 | | .63 |
| Stimulant | 2 | 4 | | .50 |
| Anticholinergic | 5 | 6 | | 1.00 |
| Mood stabilizer | 4 | 6 | | .63 |
| Mean CPZE[e] (SD) | 324.3 (224.6) | 266.2 (185.4) | $t = -1.30$ | .20 |

*Note:* BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms; CGAS = Children's Global Assessment Scale; SIB-R = Scales of Independent Behavior-Revised.

[a] SIB-R standard score.

[b] One patient was taking study medication at baseline (either low-dose or high-dose risperidone or placebo).

[c] Four patients at baseline and seven patients at follow-up were taking more than one antipsychotic medication. Three subjects were not receiving antipsychotic medication at follow-up.

[d] McNemar test with binomial distribution.

[e] Chlorpromazine (CPZE) equivalent for current antipsychotic medication (Hales and Yudofsky, 2003; Woods, 2003).

Assessment Scale was collected at baseline. A trained psychologist (J.P.R.) and psychometrician (K.L.C.) conducted consensus ratings during the course of the study to help ensure reliability ($\alpha$ >.80 for all of the scales). Clinical measures were collected primarily to assess the patient's improvement over time. Additional psychometric information regarding the clinical scales

**TABLE 3**
Neurocognitive Scores for Patients and Controls at Baseline and Follow-up

| Domain and Individual Test Variables[a] | Controls | | | | | Patients | | | | | Internal Consistency α for Domains[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline | | Follow-up | | | Baseline | | Follow-up | | |
| | $n^b$ | Mean | SD | Mean | SD | $n^b$ | Mean | SD | Mean | SD | |
| Working memory/ problem solving | 26 | −0.01 | 0.54 | 0.30 | 0.56 | 26 | −1.46 | 1.08 | −1.32 | 1.14 | 0.87/0.89 |
| Similarities | | | | | | | | | | | |
| WISC | 14/14 | 23.86 | 3.66 | 26.64 | 4.11 | 10/10 | 17.00 | 5.31 | 18.20 | 3.29 | |
| WAIS | 12/12 | 24.08 | 3.73 | 26.67 | 3.96 | 16/16 | 15.31 | 6.06 | 16.88 | 7.02 | |
| Arithmetic | | | | | | | | | | | |
| WISC | 14/14 | 22.64 | 2.73 | 21.29 | 3.75 | 10/10 | 17.30 | 3.59 | 18.60 | 7.17 | |
| WAIS | 12/12 | 16.42 | 3.29 | 16.75 | 4.09 | 16/16 | 9.38 | 4.06 | 10.31 | 4.35 | |
| Block design | | | | | | | | | | | |
| WISC | 14/14 | 51.93 | 13.68 | 54.86 | 12.33 | 10/10 | 42.00 | 11.35 | 42.80 | 12.59 | |
| WAIS | 12/12 | 53.67 | 10.17 | 58.92 | 6.30 | 16/16 | 30.13 | 18.14 | 30.25 | 16.04 | |
| WCST % perseverative errors[c] | 24/23 | 9.38 | 5.64 | 7.39 | 2.13 | 24/24 | 15.13 | 6.48 | 14.30 | 7.88 | |
| COWAT | 26/26 | 38.00 | 10.96 | 41.15 | 8.59 | 26/26 | 31.52 | 12.48 | 30.81 | 11.36 | |
| Line orientation | 25/26 | 25.12 | 4.02 | 26.04 | 4.59 | 24/25 | 18.21 | 7.89 | 19.72 | 5.18 | |
| Attention/vigilance | 26 | −0.01 | 0.59 | 0.26 | 0.68 | 26 | −1.33 | 0.92 | −1.14 | 0.90 | 0.84/0.85 |
| Digit span | | | | | | | | | | | |
| WISC | 14/14 | 15.14 | 3.18 | 16.78 | 2.61 | 10/10 | 11.90 | 3.35 | 13.33 | 4.83 | |
| WAIS | 12/12 | 19.58 | 4.35 | 17.58 | 3.73 | 16/16 | 14.19 | 4.56 | 13.50 | 3.78 | |
| Digit symbol | | | | | | | | | | | |
| WISC | 14/14 | 71.86 | 17.39 | 81.21 | 16.64 | 10/10 | 50.20 | 17.02 | 59.40 | 17.57 | |
| WAIS | 12/12 | 91.42 | 17.22 | 100.83 | 12.36 | 16/16 | 53.31 | 14.87 | 61.50 | 11.89 | |
| CPT 2fn d-prime | 23/25 | 3.50 | 0.39 | 3.41 | 0.57 | 23/25 | 2.30 | 0.98 | 2.50 | 1.07 | |
| Trail Making Test A[c] | 26/26 | 22.00 | 10.93 | 20.15 | 7.74 | 26/26 | 36.65 | 21.43 | 34.69 | 18.14 | |
| Trail Making Test B[c] | 26/26 | 46.27 | 19.96 | 45.81 | 27.99 | 25/26 | 83.99 | 48.09 | 92.17 | 61.00 | |
| Sensory motor | 25 | 0.00 | 1.00 | −0.05 | 1.42 | 25 | −2.24 | 1.55 | −2.26 | 1.38 | 0.94/0.91 |
| Grooved Pegboard[c] | | | | | | | | | | | |
| Dominant | 25/26 | 66.00 | 6.28 | 66.30 | 11.92 | 25/25 | 97.76 | 44.01 | 94.03 | 29.44 | |
| Nondominant | 25/26 | 73.36 | 12.57 | 75.23 | 18.04 | 25/25 | 116.48 | 48.01 | 107.29 | 38.06 | |
| Verbal learning/memory | 25 | 0.00 | 0.94 | 0.14 | 0.83 | 25 | −1.83 | 1.31 | −1.44 | 1.69 | 0.89/0.94 |
| CVLT verbal learning | 25/25 | 56.88 | 9.38 | 59.88 | 7.10 | 25/26 | 38.57 | 13.46 | 43.08 | 17.10 | |
| CVLT delayed recall | 25/25 | 12.40 | 2.29 | 12.32 | 2.36 | 25/26 | 8.04 | 3.80 | 9.00 | 4.04 | |
| Motor speed | 25 | 0.00 | 0.95 | 0.07 | 0.76 | 26 | −0.65 | 1.00 | −0.65 | 0.75 | 0.91/0.84 |
| Finger Tapping Test | | | | | | | | | | | |
| Dominant | 25/26 | 47.66 | 8.20 | 47.78 | 7.39 | 25/26 | 42.59 | 8.45 | 42.18 | 6.76 | |
| Nondominant | 25/26 | 44.02 | 7.48 | 44.95 | 5.72 | 25/26 | 38.96 | 8.37 | 39.23 | 5.95 | |
| Premorbid | | | | | | | | | | | |
| WRAT-3 Reading Subtest Scaled | 26/26 | 109.92 | 6.80 | 111.00 | 8.12 | 26/26 | 92.22 | 18.42 | 89.73 | 17.22 | |

*Note:* COWAT = Controlled Oral Word Association Test; CPT 2fn d-prime = Continuous Performance Test-Identical Pairs Version; CVLT = California Verbal Learning Test; WCST = Wisconsin Card Sort Test; WRAT-3 = Wide Range Achievement Test.

[a] Individual test scores are presented as raw scores; Grooved Pegboard, Trail Making, and Finger Tapping Test scores presented in seconds. Domain scores presented as *z* scores.

[b] Time 1/time 2.

[c] Lower score indicates better performance.

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### Outcome Measures

At follow-up patients were administered the SIB-R. This measure was not collected at baseline. All of the outcome measures were administered by a psychologist (J.P.R., J.G.C.) or trained psychometrician (K.L.C.) using standardized test instructions. Examiners made consensus ratings to ensure reliable administration. To permit comparison with adult studies, we focused on functional outcome data from three SIB-R scales that most closely mapped onto the constructs that have been used in the adult literature (Green et al., 2000), namely, social interaction/communication skills, community living skills, and personal living skills. The global functioning scale was not used because it is a composite measure of the three included subscales and a fourth, motor functioning subscale. The fourth subscale (motor functioning) was not included as an outcome measure because it was not hypothesized to be of value for these analyses. Although, to our knowledge, the SIB-R has not been previously used as a measure of functional outcome in adolescents with schizophrenia, it has been shown to have high reliability in both healthy pediatric samples and pediatric samples with mental retardation (Winters et al., 2005; more complete psychometric information is available on the *Journal's* Web site at www.jaacap.com via the ArticlePlus feature). The SIB-R interview was conducted with the patient's parents and/or clinicians. The same examiner who rated the SIB-R often also administered the neurocognitive test battery at follow-up. This was done to enhance feasibility because many subjects were tested on weekends and holidays when there was limited staff availability.

### Data Analysis

All of the analyses were performed using SPSS 11.0 (SPSS Inc., Chicago, IL). Independent sample *t* tests and $\chi 2$ tests were used to compare the demographic characteristics of patients versus controls at each time point. Paired samples *t* tests were used to assess changes in patient's symptoms over time.

### Neurocognitive Domain Construction

Domains were created by deriving factors using the data from our baseline sample (83 EOS, 83 HCSs). These domains were then used in the analyses conducted in the subset of subjects in this report with longitudinal data. Detailed technical information regarding domain construction can be found on the *Journal's* Web site at *www.jaacap.com* via the ArticlePlus feature. The final domains and their neurocognitive test components are presented in Table 3.

To examine the stability of neurocognitive deficits over time, all of the neurocognitive data were transformed into *z* scores using the means and SDs of our HCSs at baseline as a standardization group (Bilder et al., 2000; Rhinewine et al., 2005). Raw scores (i.e., not age normed) for all of the tests were used to create *z* scores to accurately assess change over time within subjects (Table 3). The domain *z* scores represent the average of the *z* scores for the tests included in that domain. If a subject was missing data for one of the tests in a particular domain, then the average of the remaining tests was used to determine the domain score. If the subject did not have data available for all of the tests in a particular domain, then a domain score was not calculated for that subject. The HCSs had, by definition, baseline *z* scores with a mean of 0 and SD of 1 for each test (± a small amount of error variance). *z* Scores were calculated using these methods for a number of reasons including some subjects aged out of the test they were administered at baseline (i.e., WISC to WAIS or California Verbal Learning Test-C to California Verbal Learning Test-A) but were readministered the same test at follow-up, rendering it impossible to norm the follow-up scores using published procedures; and compared to available normative data, our HCSs more closely resembled our ethnically diverse patient population.

### Stability of Neurocognition Over Time and Association With Future Functioning

The effects of time point (baseline, follow-up) and diagnostic grouping (patient, control) on *z* scores for the five neurocognitive domains were examined using repeated-measures analysis of variance, with time elapsed between test sessions (to help account for the variability in follow-up periods) and an estimate of premorbid intellectual function (to help to correct for the significant differences in estimated premorbid intelligence between groups) included in the model as covariates. Relationships between changes in symptom severity (i.e., BPRS total, BPRS psychosis cluster, SANS total) and changes in neurocognitive functioning over time, controlling for amount of time elapsed and baseline score on the clinical measure, were explored using partial correlations, with $\alpha < .05$ considered significant.

To analyze the associations between neurocognitive deficits and future functioning in patients, correlative analyses were conducted between the baseline neurocognitive domain scores and functional outcome scores controlling for baseline functional adjustment using the CGAS. As described earlier, we hypothesized that there would be significant positive correlations between the attention/vigilance, working memory, and verbal memory domains and the three functional outcome measures (i.e., community living skills, social and communication skills, and personal living skills). We hypothesized that there would not be a significant correlation between the other two neurocognitive domains (i.e., gross motor and sensory motor) and the functional outcome measures. In addition, exploratory correlations between Full Scale IQ at baseline (WISC/WAIS) and premorbid adjustment and functional outcome scores were conducted. A priori hypotheses were tested at $\alpha < .05$ and exploratory analyses were tested at $\alpha < .01$.

## RESULTS

### Clinical Measures

Between baseline and follow-up, the patients did not significantly differ on class (typical/atypical) or dose of antipsychotic medications (using chlorpromazine equivalents) or the types of concomitant medications they were receiving. As expected, due to the criteria for follow-up eligibility, there was a significant improvement in the severity of clinical symptoms and global functioning (Table 2). Partial correlations between changes in neurocognitive performances in each domain over time and changes in clinical symptoms

**TABLE 4**
Partial Correlations Between Neurocognition or Premorbid Adjustment and Outcome in Adolescents With Early-Onset Schizophrenia ($n$ = 26)[a]

| | Time 2 Social and Communication Skills[b] | Time 2 Personal Living Skills[b] | Time 2 Community Living[b] |
|---|---|---|---|
| Hypothesized to be significant relationships | | | |
| Attention/vigilance | | | |
| Time 1 ($n$ = 22) | 0.37 | 0.56** | 0.51* |
| Time 2 ($n$ = 22) | 0.33 | 0.59** | 0.43* |
| Working memory | | | |
| Time 1 ($n$ = 22) | 0.20 | 0.48* | 0.40 |
| Time 2 ($n$ = 22) | 0.32 | 0.49* | 0.55** |
| Verbal learning and memory | | | |
| Time 1 ($n$ = 22) | 0.52* | 0.48* | 0.51* |
| Time 2 ($n$ = 19) | 0.28 | 0.29 | 0.44* |
| Hypothesized not to be significant relationships | | | |
| Sensory motor | | | |
| Time 1 ($n$ = 21) | −0.01 | −0.02 | 0.10 |
| Time 2 ($n$ = 22) | 0.14 | 0.24 | 0.16 |
| Motor speed | | | |
| Time 1 ($n$ = 21) | 0.12 | −0.25 | −0.03 |
| Time 2 ($n$ = 22) | 0.00 | −0.24 | −0.16 |
| Exploratory relationships | | | |
| Time 1 Full Scale IQ[c] ($n$ = 22) | 0.30 | 0.39 | 0.48 |
| Premorbid adjustment[d] | | | |
| Social isolation ($n$ = 22) | −0.48 | −0.13 | −0.26 |
| Total ($n$ = 22) | −0.53** | −0.24 | −0.41 |

*Note:* SIB-R = Scales of Independent Behavior-Revised; PAS = Premorbid Adjustment Scale.

[a] After correcting for baseline functioning as measured by the Children's Global Assessment Scale.

[b] As measured by the Scales of Independent Behavior-Revised.

[c] As measured by the WISC/WAIS.

[d] As measured by the Premorbid Adjustment Scale at time 1. Social isolation = sum items 1 and 2; total = sum items 1–4. Lower score indicates better adjustment. Correlations not adjusted for baseline global functioning.

* $p < .05$.

** $p < .01$.

(i.e., BPRS total, BPRS psychosis cluster, SANS total) over time, after accounting for time elapsed and baseline clinical symptoms, revealed no significant associations ($p < 0.05$).

### Longitudinal Course of Neurocognitive Test Performance

Neurocognitive data are presented in Table 3. Patients at baseline showed generalized neurocognitive impairment (i.e., >1 SD below controls), with relative sparing of motor speed (0.65 SD below controls). The results of the repeated-measures analysis of covariance showed no group x time point (Wilks $\lambda$ = 0.99, $F$ = 0.35, $df$ = 5, 44; $p$ = .56) or group x time point x domain interaction (Wilks $\lambda$ = .94, $F$ = 0.57, $df$ = 2, 47; $p$ = .68), indicating that the slopes of improvement in test performance in different domains across groups were essentially parallel lines. The covariate WRAT was significant in this model ($F$ = 12.85, $df$ = 1; $p < .01$), but time elapsed was not ($F$ = 0.12, $df$ = 1; $p$ = .73). When the repeated-measures analysis of covariance was repeated with the covariates omitted, the group × time point (Wilks $\lambda$ = 1.00, $F$ = .007, $df$ = 1,51; $p$ = .93) and group × time point × domain (Wilks $\lambda$ = 0.95, $F$ = 0.48, $df$ = 4, 46; $p$ = .98) interactions remained nonsignificant.

### Relationship Between Baseline Neurocognitive Test Performance and Outcome Measures

As illustrated in Table 4, all of the significant ($p < .05$) partial correlations between neurocognition and functional outcome controlling for baseline CGAS were positive, indicating that better test performance at baseline was associated with better functional outcome. Although we did not correct for multiple correlations, all of the significant correlations between neurocognitive domains at baseline and functional domains at follow-up were associations predicted a priori. Similar significant correlations existed between follow-up neurocognitive performance and outcome, which was expected because neuropsychological test performance was relatively stable over time. One exploratory correlation (overall premorbid adjustment with social/communication at follow-up) was significant at $p < .01$.

## DISCUSSION

In this study we found that at baseline the range of neuropsychological test $z$ scores for the patient group was 0.6 to 2.2 SDs below those of the HCSs, which is relatively consistent with the range of generalized cognitive deficits observed in studies of adults (Heinrichs and Zakzanis, 1998) and adolescents with schizophrenia (McClellan et al., 2004; Rhinewine et al., 2005). These results should be interpreted cautiously because they may be an overestimate, given the higher

than average intelligence of our control sample. The stability of neurocognitive deficits over time in patients with EOS despite improvement in psychiatric symptoms implies that the two are at least somewhat distinct targets for treatment and that neurocognitive deficits represent a stable, traitlike feature of the disorder even with fluctuation of symptoms. Although this finding needs to be taken in the context of a relatively short follow-up period, especially given the chronic nature of the disorder, the result is consistent with findings from a number of adult studies describing stable deficits after illness onset despite changes in clinical state (Heaton et al., 2001; Hoff et al., 1999).

In terms of the relationship between baseline neurocognitive functioning and functional outcome, our hypotheses were confirmed because our data indicated that after controlling for baseline functional adjustment using partial correlations, verbal learning was significantly associated with all three hypothesized areas of functional outcome; attention/vigilance was significantly associated with personal living and community living skills; and working memory was associated with personal living skills. Of interest, the amount of time elapsed between first and second testing was not a significant covariate in our models, but given the small sample size and the relatively short follow-up period, this finding must be analyzed cautiously. In addition, the areas of neurocognitive functioning at baseline that were hypothesized not to be significantly related to functional outcome (i.e., sensory motor, motor speed, and working memory) were found to be nonsignificant. Overall, these outcome data are in agreement with those of adult studies of patients with schizophrenia that have shown attention and verbal memory function as predictors of personal living skills (Milev et al., 2005) and social interaction/communication skills (Addington and Addington, 2000; Green et al., 2000).

In addition to the associations between time 1 neurocognition and time 2 functioning, we also found that time 2 attention/vigilance, working memory, and verbal learning/memory were correlated with some functional outcome measures. These findings leave open the possibility that poor level of adaptive function may be driving neuropsychological test performance or vice versa. Furthermore, the two are probably intercorrelated to some degree and may represent a bidirectional relationship. However, data from genetic high-risk samples suggest that deficits in cognition are present early in childhood well before functional deterioration becomes evident in adolescence and early adulthood (Erlenmeyer-Kimling et al., 2000). It is important to note that associations rather than causality were assessed in this study.

In addition to the main findings of the study, we found that lower overall premorbid adjustment was associated with poorer social/communication skills, indicating a continuity of skill deficits from the premorbid to postpsychotic phases of illness that has been noted previously in adolescents with schizophrenia (Werry and McClellan, 1992). Because it is impossible to improve premorbid adjustment after the onset of illness, we believe that the most interesting and useful findings of the present study are those relating cognition to outcome since interventions after illness onset are possible to explore. The lack of significant correlations ($p < .01$) between Full Scale IQ at baseline and functional outcome measures suggest that tests assessing specific neurocognitive abilities may be more highly associated with outcome than measures of global intelligence.

### Limitations

A number of methodological limitations should be taken into consideration when interpreting the present findings. We recognize that type II error is a serious concern in this study in light of covariance of estimated premorbid intelligence, small sample size, and conservative α values (although we believe that the α values chosen were appropriate to prevent type I error because of the large number of measures). To mitigate type II error, we repeated our analyses without the use of a covariance strategy and the null findings of a group × time and a group × domain × time interaction remained. In addition, we had to rely on an estimate of premorbid intelligence for analyses (i.e., WRAT-3 Reading), which has been shown to have some validity in patients with schizophrenia (Bilder et al., 2000). To help address issues of type I error, we split our correlation analyses into three groups: hypothesized significant relationships, hypothesized nonsignificant relationships, and exploratory analyses. As can be deduced from Table 4, the hypothesized positive relationships were more consistently significant than the other two sets of analyses.

Another limitation of the study was the inconsistent length of the follow-up period (i.e., 6–36 months), which reflected the variability in the time to clinical stabilization in our patients. We addressed this issue by including time elapsed between assessments in our statistical models and found that there was no statistically significant effect for this variable on test performance. Thus, we felt confident that the differences in length of follow-up did not measurably affect the results. Given the chronic nature of the illness, the length of follow-up in this study was relatively short and limits the scope of the findings; further research in this population using longer follow-up periods are needed to verify these results.

Having the same examiner administer and rate the SIB-R and administer the neurocognitive assessment at follow-up provides a number of benefits and drawbacks. In addition to facilitating recruitment by allowing for weekend and holiday visits, when staff availability was limited, this strategy also helped the examiner build a stronger rapport with the subjects to reduce anxiety and improve reliability of test results. Unfortunately, this approach also introduces a significant confound to the study by increasing the likelihood of bias and potentially inflating the association between measures. We believe that in this preliminary study the benefits outweigh any potential bias that may have occurred due to the use of a single examiner.

A more minor limitation has to do with reversing the order of tests at follow-up. Although this is common practice in studies using multiple scales/tests to reduce potential bias due to order of administration, it may also represent a confound because the longitudinal test session was not identical in administration to the baseline test session (e.g., differences in fatigue based on test order changes).

Last, the small sample size of this study limited the interpretability of results. Small sample size is a problem inherent in longitudinal neuropsychological studies in adolescents with schizophrenia (Gochman et al., 2005) and reflects both the relative rarity of EOS (Cannon et al., 2003) and the challenges associated with repeat assessments. However, this study design represents the most robust method for an investigation of this nature. Even given these limitations, the research presented here is important in extending previous findings in adult schizophrenia patient populations that have linked neurocognition and later levels of functional impairment. Future research using larger samples of children and adolescents and a more structured follow-up schedule is needed to replicate these initial results. In addition, study designs that include separate, blinded raters for the neurocognitive and functional measures are needed to validate the results presented here.

### Clinical Implications

These data have a number of implications for future clinical research. First, they suggest that the neurocognitive deficits that adolescents with schizophrenia display during an acute episode of psychosis are relatively stable over time, even with continued antipsychotic medication regimens that achieve a reduction in traditional psychiatric symptoms. The data imply that neurocognitive deficits and psychiatric symptoms in schizophrenia represent discrete dimensions of the illness and that each should be considered separate targets for therapeutic intervention (Gold, 2004; Klingberg et al., 2005).

Determining whether cognitive enhancement can influence functional outcome in individuals with schizophrenia has begun to be investigated in the literature and continues to develop as an area of great interest to researchers and clinicians (e.g., NIMH MATRICS initiative; Green et al., 2004). A recent review of the published longitudinal data in adults linking functional status with cognitive impairment in schizophrenia (Matza et al., 2006) concluded that there is initial support validating the relationship; the authors point out, however, that the small number of studies provides inconsistent findings, a variety of methodologies, and numerous unanswered questions.

Among the cognitive enhancement interventions that have been explored, cognitive remediation therapy (Kurtz, 2003; Penades et al., 2006) and neurocognitive enhancement therapy (Bell et al., 2005) have shown some promise for improving functioning in adult patients with schizophrenia, especially when paired with other forms of therapy (i.e., work therapy). The long-term effectiveness of these types of interventions is not yet known.

Recent literature has also suggested that a number of pharmacological interventions may be useful for achieving cognitive enhancement. Galantamine as an add-on to risperidone in stabilized patients may

improve attention and memory (Schubert et al., 2006). Monotherapy treatment with ziprasidone (Harvey et al., 2004; Malhotra et al., 2006), aripiprazole, or olanzapine (Kern et al., 2006) has also been found to be beneficial for improving cognition in these patients. Amphetamines (Barch and Carter, 2005) may also be viable options when added to a regimen of typical antipsychotic agents. In general, the drawback of preliminary pharmacotherapy studies aimed at studying cognitive enhancement is that they have not addressed the overarching question of whether changes in cognitive enhancement due to pharmacotherapy are linked to changes in functional measures. Furthermore, most cognitive enhancement studies have focused on adult patient populations; the use of these treatment options in children and adolescents, when they may have greater impact due to more brain plasticity and an earlier phase of illness, should be targets of future research.

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**Infection in the First 2 Years of Life and Autism Spectrum Disorders** Nila J. Rosen, MPH, Cathleen K. Yoshida, MS, Lisa A. Croen, PhD

*Objective:* The purpose of this work was to investigate the association between infections in the first 2 years and subsequent diagnosis of autism spectrum disorders. *Methods:* We conducted a case-control study among children born at Kaiser Permanente Northern California from 1995 to 1999. Case subjects ($n$ = 403) were children with an autism diagnosis recorded in Kaiser Permanente databases. Control subjects ($n$ = 2,100) were randomly sampled from the remaining children without autism and frequency matched to case subjects on gender, birth year, and birth hospital. Information on infections and covariates were obtained from Kaiser Permanente and birth certificate databases. *Results:* Overall, infection diagnoses in the first 2 years of life were recorded slightly less often for children with autism than control children (95.0% vs 97.5%). Among specific diagnoses, upper respiratory infections were significantly less frequently diagnosed and genitourinary infections more frequently diagnosed in children with autism. In the first 30 days of life, the frequency of having an infection was slightly higher among children with autism (22.6% vs 18.7%). *Conclusions:* Children with subsequent diagnoses of autism do not have more overall infections in the first 2 years of life than children without autism. Data suggest that children with autism may have modestly elevated rates of infection in the first 30 days and that, during the first 2 years, children with autism may be at higher risk for certain types of infections and lower risk for others. Additional studies that explore the associations between prenatal and early childhood infections and autism may help clarify the role of infection and the immune system in the etiology of autism spectrum disorder. **Pediatrics** 2007;119:e61–e69.