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Course of Neurocognitive Deficits in the Prodrome and First Episode of Schizophrenia

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Understanding the trajectory of cognitive changes in the development of schizophrenia may shed light on the neurodevelopmental processes in the beginning stage of illness. Subjects at risk for psychosis (AR, $n = 48$), patients in their first episode of schizophrenia (FE, $n = 20$), and normal comparison subjects ($n = 29$) were assessed on a neurocognitive battery at baseline and at a 6-month follow-up. There were significant group differences across all cognitive domains as well as a significant group by time interaction in the verbal learning domain. After statistically controlling for practice effects and regression to the mean, a high proportion of FE subjects showed an improvement in verbal learning, and a significant number of AR subjects improved in general intelligence. Moreover, a higher than expected percentage of FE subjects, as well as AR subjects who later converted to psychosis, showed a deterioration in working memory and processing speed. These inconsistent trajectories suggest that some domains may improve with stabilization in the early stages of psychosis, whereas others may decline with progression of the illness, indicating possible targets for cognitive remediation strategies and candidate vulnerability markers for future psychosis.

Keywords: neuropsychological, longitudinal, schizophrenia, at risk, prodromal

The schizophrenia prodrome is a period of rapid developmental change that precedes illness onset and is characterized by a substantial functional decline together with the emergence of subthreshold psychotic symptoms (Yung & McGorry, 1996). Longitudinal studies have shown that the population that meets the "prodromal" definition, based on carefully defined criteria combining subsyndromal psychotic symptoms, family history, and functional decline (Miller et al., 2003), has a 20% to 30% chance of converting to psychosis within 1 year of ascertainment (e.g., Cannon et al., 2008; Olsen & Rosenbaum, 2006; Yung, Phillips, Yuen, & McGorry, 2004).

The early identification of individuals in the prodromal phase and first episode of schizophrenia, using brain-based vulnerability markers, may add important insights into the neurodevelopmental processes and dynamic changes in this beginning stage of the illness. The present study is among the first to examine the magnitude and longitudinal course of neurocognitive dysfunction prior to and following the onset of psychosis. We use the term *at risk* throughout this article to refer to those individuals who are putatively "prodromal" for psychosis given that the latter state can only be truly diagnosed retrospectively. Neurocognitive vulnerability markers were selected because of established deficits across schizophrenia spectrum groups (Cadenhead, Perry, Shafer, & Braff, 1999; Cannon et al., 1994; Hawkins et al., 2004; Heinrichs & Zakanis, 1998), high reliability in repeated testing (Faraone et al., 1999; Heaton, et al., 2001a; Rund, Landro, & Orbeck, 1997), and evidence of heritability (Ando, Ono, & Wright, 2001; Greenwood et al., 2007; Posthuma, Mulder, Boomsma, & de Geus, 2002). Unlike other endophenotypic markers that require special equipment and extensive training to be collected and analyzed, neurocognitive tests are relatively easy to administer in the office setting. Neurocognitive deficits may be important in understanding the pathogenesis of early psychosis, and could help define individuals at greatest risk for the full-blown illness (Cadenhead, 2002). Moreover, assessing neurocognitive performance over time may reveal a decline in certain domains, which might indicate a greater risk for disability and a need for earlier or more aggressive treatment. Therefore, neurocognitive change over time could be another potential marker for vulnerability to disease that may shed light on both the pathological changes in brain structure and function that occur early in the illness, as well as abnormal variants of the normal brain changes that take place during adolescence and early adulthood.

Substantial cognitive deficits in people who go on to develop schizophrenia are apparent in childhood (Woodberry, Giuliano, & Seidman, 2008), tend to exacerbate before the onset of overt

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psychotic symptoms, and worsen even more with the initial episode of the illness (Bilder et al., 2006). However, widespread cognitive impairment should not be assumed in all people with schizophrenia, as cognitive heterogeneity is likely to be present at onset as well as throughout the illness. Joyce, Hutton, Mutsatsa, and Barnes (2005) found that although only half of their subjects with first-episode schizophrenia had a low premorbid IQ or a general cognitive decline from normal levels, all of them (including those with preserved high or average IQ) had a specific impairment in working memory. At a group level, however, it has been demonstrated that when compared with healthy normal comparison subjects, subjects at risk for psychosis have neurocognitive deficits across multiple domains that are intermediate to those observed in first-episode schizophrenia patients (e.g., Eastvold, Heaton, & Cadenhead, 2007; Keefe et al., 2006).

Longitudinal studies of first-episode schizophrenia groups have shown high stability of neurocognitive functioning over the first few years of the illness (e.g., Addington, Saeedi, & Addington, 2005; Albus et al., 2006; Censits, Ragland, Gur, & Gur, 1997; Rund et al., 2007). There has been no evidence in group data of progressive cognitive deterioration after illness onset, as average performance either remained stable in most neurocognitive domains or improved slightly in some of them (e.g., Gold, Arndt, Nopoulos, O'Leary, & Andreasen, 1999; Nopoulos, Flashman, Flaum, Arndt, & Andreasen, 1994; Sweeney et al., 1991). The relatively fewer studies that examined the change in neuropsychological function in at-risk subjects found that a greater cognitive impairment at baseline is associated with subsequent conversion (Keefe et al., 2006; Lencz et al., 2006). Moreover, a decline in verbal abilities (memory in particular) and intellectual functions might predict conversion to psychosis (Brewer et al., 2005; Cosway et al., 2000; Eastvold et al., 2007; Pukrop et al., 2007; Whyte et al., 2006). It is interesting that Niendam et al. (2007) found that a subset of their high-risk subjects improved over an 8-month period on measures of speeded information processing, as well as visual and verbal learning and memory. However, the Niendam et al. study did not include a healthy comparison group to determine how much of the improvement observed was due to practice effects or decreased anxiety due to familiarity with the testing situation.

The primary aim of the current study was to examine and compare the stability or change in neurocognitive performance with repeated testing in the putative prodrome and first episode of schizophrenia. Although there is substantial evidence to support the stability of illness-related deficits even up to 10 years after the acute onset period (Hoff, Svetina, Shields, Stewart, & DeLisi, 2005), we do not know much about the evolution of those deficits in the early stages of psychosis. It is possible that some impaired functions are present before the onset of psychosis and remain stable throughout the prodrome and first episode of illness, whereas other abilities may decline with the onset of illness or may fluctuate with changes in clinical symptomatology and social functioning. Thus, our goal was to examine the pattern of change in neurocognitive performance over time at the group and individual levels. We hypothesized that the at-risk and first-episode groups would show significantly more changes in their performance over time relative to the normal comparison group.

Method

Participants

Our samples consisted of 48 subjects at risk for psychosis (AR), 20 first-episode schizophrenia patients (FE), and 29 normal comparison subjects (NC), who were compared at baseline and 6-month follow-up on a battery of neurocognitive tests. The majority of the AR subjects (70.9%) met criteria for at least one of the two most common prodromal syndromes (Miller et al., 2003; Seeber & Cadenhead, 2005; Yung et al., 2005): attenuated positive symptom (APS; new onset of subsyndromal psychotic symptoms) or genetic risk and deterioration (GRD; family history of schizophrenia in a first-degree relative or a diagnosis of schizotypal personality disorder that is associated with a recent decline in global functioning) per the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2003) and established Cognitive Assessment and Risk Evaluation (CARE) criteria (Ballon, Kaur, Marks, & Cadenhead, 2007). The APS category accounted for 28.2% of the at-risk sample, 6.3% met criteria for the GRD syndrome, 35.4% met both APS and GRD criteria, and 29.1% met criteria for the brief limited intermittent psychotic symptoms category. The total sample ($N = 97$) had a good representation of both genders (60.8% male), was ethnically diverse (60.8% non-Hispanic White), and had a mean of 11.4 years of education (high school). Ages ranged from 12 to 27 years in the NC group, 12 to 30 years in the AR group, and 13 to 34 years in the FE group. Adolescent subjects ages 16 years and younger ($n = 31$) were included in the analyses and represented 25% of the FE group, 33.3% of the AR group, and 34.5% of the NC group. In addition, 22.9% of the AR and 10% of the FE subjects had a first-degree relative with psychosis.

Six (12.5%) of the 48 AR subjects transitioned to psychosis within the follow-up period or up to 18 months after entry into the study. Compared with the AR sample as a whole, the AR subjects who later converted to psychosis were more likely to have abused drugs and to have been treated with an antipsychotic medication prior to conversion to psychosis (Haroun, Dunn, Haroun, & Cadenhead, 2006). In fact, only 33.3% of them were not taking any psychiatric medications at baseline. Five of the 6 AR subjects who transitioned to psychosis did so after the follow-up neurocognitive testing, and 1 subject transitioned at 1 month in the study. The mean time to conversion of these subjects was 10.7 months. Two of them converted to schizophrenia, 2 to psychotic mania, 1 was diagnosed with schizoaffective disorder, and 1 with psychosis not otherwise specified. They were all males and had a mean age of 20.2 ± 2.9 years at follow-up.

Procedure

Details about sample ascertainment have been presented elsewhere (Eastvold et al., 2007). In brief, subjects were recruited through health services and public schools and colleges in the community of San Diego, California. To be included in the CARE program, subjects had to meet the inclusion and exclusion criteria summarized in Table 1. Subjects who met *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) criteria for lifetime substance abuse or dependence were not excluded from the sample unless they had abused substances in the month prior to baseline cognitive testing; 31.2% of the AR group and 45% of the FE group

Table 1
Inclusion and Exclusion Criteria

Group	Inclusion criteria	Exclusion criteria
At risk (AR)	Recent onset (<1 year) of subsyndromal psychotic symptoms per SIPS; first-degree relative with schizophrenia or diagnosis of schizotypal personality disorder plus recent deterioration in functioning	History of head injury (loss of consciousness >15 min or neurological sequelae); substance abuse within the past month; neurological disorder; IQ below 80
First episode (FE)	First psychotic episode within the past year; *DSM–IV* diagnosis of schizophrenia	Same as AR group
Normal controls (NC)	Comparable to AR and FE subjects with respect to age, ethnicity, and parental education	Same as AR and FE groups; personal history of mental illness or learning disability; Cluster A personality disorder or evidence of prodromal symptoms; family history of psychotic illness; history of taking psychotropic medications

Note. SIPS = Structured Interview for Prodromal Syndromes; *DSM–IV* = *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.).

had a lifetime history of alcohol or drug abuse. Subjects who fit the preliminary entry criteria on the basis of telephone screening underwent an extensive intake diagnostic interview and were followed up every month for clinical assessment. Qualifying participants also completed a battery of neurocognitive tests at baseline and then at 6-month intervals. The AR subjects, like the FE subjects, were ambulatory, treatment seeking, and were receiving treatment as usual (pharmacological or psychosocial) according to their presenting symptoms. Fourteen of the 20 FE subjects (70%) and 10 of the 48 AR subjects (20.8%) were on at least one antipsychotic with or without other psychotropic medications at baseline. The medicated AR subjects tended to have lower Global Assessment of Functioning scores than the unmedicated AR subjects, and the medicated FE subjects tended to be younger and less symptomatic than the unmedicated FE subjects. Five additional AR and 3 FE subjects were prescribed an antipsychotic between baseline and follow-up, and 4 AR subjects who were on medications initially discontinued them before the second testing. None of the patients were involved in cognitive remediation, although some were participating in group therapy or vocational rehabilitation but were at various stages of treatment during the course of the study.

Measures

Clinical measures. The SIPS (Miller et al., 2003) was used to assess prodromal symptoms. The at-risk subjects were identified according to the CARE prodromal criteria that slightly differ from the SIPS criteria in the required frequency and duration of symptoms (Ballon et al., 2007). Axis I and Axis II diagnoses were assessed with the Structured Clinical Interview for *DSM–IV* Axis I Disorders (First, Gibbon, Spitzer, & Williams, 1996) and the Structured Interview for *DSM–IV* Personality Disorders (SIDP; Pfohl, Blum, & Zimmerman, 1995), respectively. The Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS; Chambers et al., 1985) was administered to approximately a third of the sample that consisted of all subjects under the age of 16. The Scale for the Assessment of Negative Symptoms (SANS), the Scale for the Assessment of Positive Symptoms (SAPS), and the Brief Psychiatric Rating Scale (BPRS) were used to further evaluate clinical symptoms in the AR and FE groups. Family history of psychiatric illness was assessed in all cases, after receiving consent to contact a relative, using the Family History Research Diagnostic Criteria (Andreasen, Endicott, Spitzer, & Winokur, 1977). Current level of functioning was assessed with the Modified Global Assessment of Functioning (GAF-M; Hall & Parks, 1995). The highest GAF score from the past year was determined retrospectively.

Neurocognitive measures. The neurocognitive battery was part of a larger battery of tests that included psychophysiological measures of brain inhibitory functioning, as well as measures of attention and visual information processing. The neurocognitive battery was designed to minimize practice effects over repeated administration (e.g., use of different forms of the Hopkins Verbal Learning Test—Revised [HVLT–R] at baseline and follow-up) and assess five different neurocognitive domains: processing speed, working memory, verbal learning, executive functioning, and general intelligence or IQ (see Table 2). Neurocognitive domains were used instead of individual tests to reduce the number of statistical comparisons. Contributing variables for each domain were chosen on a theoretical basis (Eastvold et al., 2007). The small sample size in this study did not allow for confirmation of

Table 2
Neurocognitive Measures

Neurocognitive domain	Measure
Executive functioning (EF)	WCST: Perseverative Responses total; SCWT: Interference (total correct after 45 s)
Processing speed (PS)	NA (total completion time); SCWT: Color Naming (total number named within 45 s)
Verbal learning (VL)	HVLT–R: Total Recall (number of correct words recalled after 3 presentations of a 12-word list)
Working memory (WM)	WAIS–III: Letter–Number Sequencing (total number correct); WMS–III: Spatial Span Backwards
General intelligence (IQ)	WAIS/WISC–III: Vocabulary total; WAIS/WISC–III: Block Design total

Note. WCST = Wisconsin Card Sorting Test (Heaton et al., 1993); SCWT = Stroop Color and Word Test (Golden, 1978); NA = Numerical Attention (Franklin, Heaton, Nelson, Filley, & Seibert, 1988); HVLT–R = Hopkins Verbal Learning Test—Revised (Benedict & Zgaljardic, 1998); WAIS–III = Wechsler Adult Intelligence Scale—Third Edition (Wechsler, 1997a); WISC–III = Wechsler Intelligence Scale for Children—Third Edition (Wechsler, 1991); WMS–III = Wechsler Memory Scale—Third Edition (Wechsler, 1997b).

the factor structure underlying each of the domains. However, these neurocognitive domains were identified on the basis of demonstrated impairments in schizophrenia spectrum populations (e.g., Cadenhead et al., 1999). Verbal learning was the only domain represented by a single test, that is, the HVLT–R total recall over three trials, as we had to drop the HVLT–R delayed recall subtest from the analyses because of its ceiling effects. After normalizing all nine neurocognitive variables using a log-transformation method, we computed standardized scores for both time points on the basis of the baseline mean and standard deviation of the NC group: (individual subject score – mean of NC group)/*SD* of NC group. The *z* scores for Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtiss, 1993) Perseverative Responses and Numerical Attention were inverted so that higher scores were indicative of better performance. Finally, composite scores for each neurocognitive domain—except for verbal learning, which consisted of only one variable—were created by averaging the *z* scores of contributing variables using equal weights. A global neurocognitive performance index was then created by averaging the five composite variables after ensuring that they were all normally distributed. Adolescents were combined with adults to maximize sample size, and the WISC–III Vocabulary and Block Design subtests were used in lieu of the WAIS-III subtests for subjects younger than age 16. Standardized scores for the IQ domain were created separately for the > 16 and ≤ 16 age groups relative to the NC group. Two FE and two AR subjects were dropped from the analyses because they had missing baseline or follow-up scores on the verbal learning or processing speed domains.

Statistical Analyses

Demographic differences between groups were analyzed using Pearson chi-square tests for discrete variables and analyses of variance (ANOVAs) for continuous variables. The test–retest reliability of each neurocognitive domain was examined by calculating the intraclass correlation coefficients (ICCs). Repeated measures ANOVAs were also conducted to compare the patterns of change in performance over time among the three groups on each of the five neurocognitive domains as well as the global neurocognitive index. Post hoc analyses were performed with Bonferroni corrections.

These data were also analyzed using the simple regression model that can quantify real changes in neurocognitive performance for individual cases, while accounting for confounding factors such as practice effects, normal test–retest variability, and regression to the mean. On the basis of this statistical method, the predicted follow-up score of an individual comes from the equation generated when follow-up scores are regressed on baseline scores of the normal comparison group (McSweeny, Naugle, Chelune, & Luders, 1993). Then, confidence intervals (CI) are established around the discrepancies between predicted score and obtained score. Using the regression method on each domain, it was possible to determine whether a disproportionate number of subjects improved (equal to or better than top 5% of CI) or worsened (equal to or worse than 5% of CI).

Change in symptom severity and level of functioning was assessed within each clinical group via repeated measures ANOVAs, which were followed by bivariate correlations to examine whether neurocognitive changes were associated with changes in clinical symptoms or GAF scores. Finally, we examined how the AR subjects who transitioned to psychosis differed from those who did not in terms of their neurocognitive performance over time.

Results

Sample Characteristics

Comparisons between the three groups on the sociodemographic variables revealed no significant group differences in age, education, parental education, ethnicity, or handedness. However, there were significantly more males than females in the FE group compared with the AR and NC groups (see Table 3).

Test–Retest Reliability of Neurocognitive Domains

The means and standard deviations for the individual tests as well as the standardized scores for the neurocognitive domains are reported in Tables 4 and 5, respectively. Performance between baseline and 6-month follow-up was fairly stable, with moderate to high ICCs across domains for all groups combined (.78 for executive functioning, .87 for processing speed, .75 for verbal learning, .65 for working memory, .93 for general intelligence, and .88 for the global neurocognitive index). Table 5 shows the ICC (using the *z* scores) for each domain in each group separately. Mean *z* score differences (follow-up – baseline) were computed for each group and are displayed in Figure 1.

Table 3
Baseline Demographic Characteristics

Characteristic	Normal controls ($n = 29$)	At risk ($n = 48$)	First episode ($n = 20$)	F/χ^2	p
Mean (*SD*) age (years)					
Baseline	19.0 (5.2)	18.7 (4.2)	20.1 (5.7)	$F(2, 94) = 0.63$	.53
Follow-up	19.9 (5.2)	19.8 (4.1)	21.0 (5.7)		
Gender (% male)	48.3	58.3	85.0	$\chi^2(2) = 6.95$	$<.05$
Ethnicity (% Caucasian)	58.6	60.4	65.0	$\chi^2(24) = 20.03$	.69
Handedness (% right)	89.7	89.1	75.0	$\chi^2(4) = 6.67$	.15
Mean (*SD*) education (years)	11.9 (4.4)	11.2 (2.8)	11.4 (2.8)	$F(2, 94) = 0.38$	.68
Mean (*SD*) parental education (years)	16.1 (2.3)	15.5 (2.3)	15.3 (2.9)	$F(2, 87) = 0.72$	.49
Mean (range) follow-up interval (months)	12 (6–36)	20.5 (6–36)	14.6 (6–36)		

Table 4
Group Means and Standard Deviations for Neurocognitive Measures at Baseline and Follow-Up

	Baseline		Follow-up	
Neurocognitive measure	*M*	*SD*	*M*	*SD*
Normal controls ($n = 29$)				
WCST Perseverative responses	7.4	3.7	5.1	2.5
SCWT Interference	44.3	8.4	45.8	10.1
Numerical Attention	168.8	37.3	168.4	59.0
SCWT Color Naming	71.8	12.5	74.0	12.6
HVLT–R Total Recall	27.8	3.5	28.5	4.0
WAIS–III Letter–Number Sequencing	12.2	3.4	13.0	3.2
WMS–III Spatial Span Backwards	9.0	1.5	9.2	1.8
WAIS/WISC–III Vocabulary	47.5	9.4	48.9	8.4
WAIS/WISC–III Block Design	48.6	11.8	50.9	11.3
At risk ($n = 48$)				
WCST Perseverative responses	10.4	8.1	7.5	5.4
SCWT Interference	43.2	11.3	45.3	10.6
Numerical Attention	195.1	62.6	185.3	56.1
SCWT Color Naming	68.4	11.7	70.9	11.8
HVLT–R Total Recall	26.3	4.8	27.6	5.2
WAIS–III Letter–Number Sequencing	10.6	2.5	11.6	2.9
WMS–III Spatial Span Backwards	8.3	2.2	8.19	2.3
WAIS/WISC–III Vocabulary	41.4	12.2	44.6	11.1
WAIS/WISC–III Block Design	45.3	11.4	49.9	12.4
First episode ($n = 20$)				
WCST Perseverative responses	11.7	7.9	10.1	8.2
SCWT Interference	36.6	7.9	37.4	8.2
Numerical Attention	220.1	95.6	208.5	84.2
SCWT Color Naming	61.4	10.2	63.4	11.1
HVLT–R Total Recall	21.8	4.5	25.6	4.4
WAIS–III Letter–Number Sequencing	10.3	2.2	10.6	2.4
WMS–III Spatial Span Backwards	7.6	2.0	7.8	1.9
WAIS/WISC–III Vocabulary	36.5	9.7	39.5	10.3
WAIS/WISC–III Block Design	41.2	13.3	45.2	14.0

Note. WCST = Wisconsin Card Sorting Test; SCWT = Stroop Color and Word Test; NA = Numerical Attention; HVLT–R = Hopkins Verbal Learning Test—Revised; WAIS–III = Wechsler Adult Intelligence Scale—Third Edition; WISC–III = Wechsler Intelligence Scale for Children—Third Edition; WMS–III = Wechsler Memory Scale—Third Edition.

Pattern of Change in Neurocognitive Performance at the Group Level

The repeated measures ANOVA for the global neurocognitive index showed significant group main effects averaged across time, as well as significant improvement over time averaged across groups, but no significant group by time interactions. On the basis of post hoc comparisons, both the FE ($p < .001$) and AR ($p = .03$) groups performed significantly worse than the NC group in overall neurocognitive functioning. As predicted, the AR group's overall performance over time ($M = -0.35$) fell between the FE ($M = -0.82$) and NC ($M = 0.11$) groups' performance (see Figure 2).

The repeated measures ANOVA across the individual ability domains revealed significant group main effects (averaged across time) in all domains. The FE group performed significantly worse than both the AR ($p = .046$) and NC ($p = .003$) groups in verbal learning. The FE group also performed significantly worse than the NC group in executive functioning ($p = .002$), processing speed ($p = .03$), and general intelligence ($p = .01$). Both the AR ($p = .01$) and FE ($p = .04$) groups had a significantly poorer performance in working memory than the NC group. Time effects (averaged across groups) were significant for all domains except working memory (see Table 6).

Group by time interaction was only significant for verbal learning, $F(1, 90) = 5.25$, $p = .01$, partial $\eta^2 = .10$. Post hoc tests revealed significant differences between the FE group and both the NC ($p = .01$) and AR ($p = .01$) groups. Figure 3 shows that whereas the NC and AR groups remained essentially stable over time in their verbal learning performance, the FE group significantly improved in that domain. Because of group differences in gender distribution, the same analyses were repeated with the addition of gender as a between-subjects variable. There were no significant gender by group, gender by time, or gender by group by time interactions.

Note that all 48 AR subjects, including those who converted to psychosis over time, were included in the analyses reported above. The results did not change when we excluded the 6 converters and performed the same analyses. We also conducted a repeated measures ANOVA, as an exploratory analysis, to compare the subgroup that converted (AR-C, $n = 6$) with the one that did not (AR, $n = 42$) and found a significant group by time interaction in working memory, $F(1, 44) = 4.09$, $p = .049$, partial $\eta^2 = .08$. Whereas the nonconverters remained stable over time in their working memory performance, the AR-C group significantly deteriorated in that domain (see Figure 3).

Table 5
Standardized Scores on Neurocognitive Domains per Group at Baseline and Follow-Up

	Baseline		Follow-up		
Neurocognitive domain	*M*	*SD*	*M*	*SD*	*r*
Normal controls (n = 29)					
Executive functioning	−0.01	0.75	0.45	0.72	.75
Processing speed	0.01	0.85	0.08	1.18	.85
Verbal learning	0.02	1.01	0.19	1.13	.76
Working memory	0.00	0.81	0.18	0.83	.87
General intelligence	0.00	0.86	0.19	0.75	.95
Global index	0.00	0.65	0.22	0.63	.96
At risk (n = 48)					
Executive functioning	−0.39	1.18	0.08	1.01	.79
Processing speed	−0.52	1.15	−0.23	1.09	.89
Verbal learning	−0.48	1.53	−0.16	1.81	.73
Working memory	−0.64	1.28	−0.56	1.54	.57
General intelligence	−0.52	1.03	−0.12	0.99	.90
Global index	−0.51	0.91	−0.20	0.91	.86
First episode (n = 20)					
Executive functioning	−0.97	1.03	−0.49	1.22	.69
Processing speed	−0.93	1.31	−0.65	1.29	.81
Verbal learning	−1.94	1.74	−0.54	1.36	.78
Working memory	−0.87	0.95	−0.48	0.79	.42
General intelligence	−1.05	1.26	−0.62	1.26	.94
Global index	−1.07	0.70	−0.56	0.77	.70

Pattern of Change in Neurocognitive Performance at the Individual Level

Our objective was to go beyond group mean comparisons by assessing meaningful changes in individual patients within each of the AR and FE groups. Given our small sample sizes, those analyses were conducted in a strictly exploratory manner. To determine for each patient whether the difference between baseline and follow-up domain and total scores represented a meaningful change or a normal variability or fluctuation in performance, we employed a regression-based statistical approach that has been used in neuropsychological research and has been found to have fairly good specificity and sensitivity in detecting change (Heaton et al., 2001b). This prediction approach adjusts for practice effects and regression to the mean with repeated assessment by using

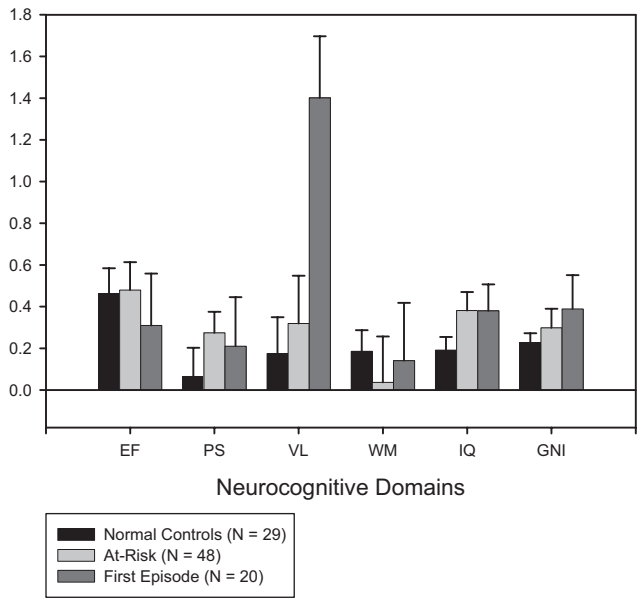

Figure 1. Mean z score differences (follow-up – baseline) and standard errors for each group. The higher the difference score, the better the performance at follow-up. EF = executive functioning; PS = processing speed; VL = verbal learning; WM = working memory; IQ = general intelligence; GNI = global neurocognitive index.

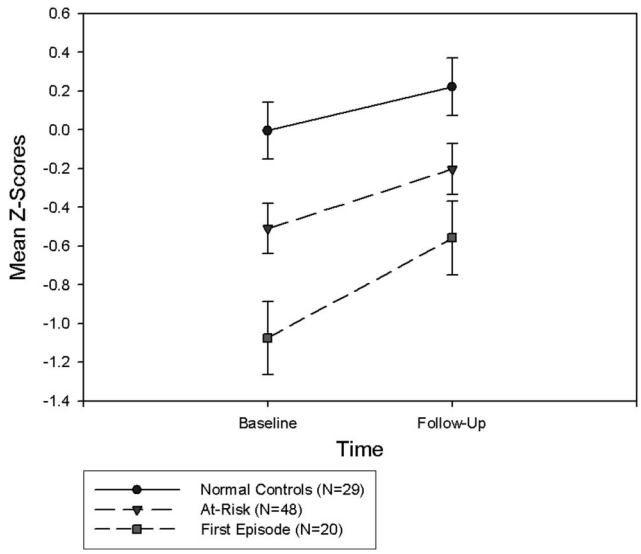

Figure 2. Overall neurocognitive performance, as measured by the global neurocognitive index, at baseline and follow-up for each group. The bars represent the standard errors.

Table 6
Statistics for the Repeated Measures ANOVA

	Group effect			Time effect		
Neurocognitive domain	$F(2, 90)$	p	Partial η^2	$F(1, 90)$	p	Partial η^2
Executive functioning	6.02	.004	.12	24.57	<.001	.21
Processing speed	3.53	.033	.07	5.86	.018	.06
Verbal learning	5.72	.005	.11	17.66	<.001	.16
Working memory	5.07	.008	.10	2.65	.11	.03
General intelligence	5.14	.008	.10	31.35	<.001	.26
Global index	8.57	.001	.16	35.36	<.001	.28

linear regression of follow-up scores on baseline scores in the normal comparison group to generate a formula for predicting a follow-up score from any baseline score. Then, it estimates the expected range of follow-up performance on each domain on the basis of a 90% confidence interval. The latter is the predicted score +/– ($1.64 \times SE_{residual}$), where $SE_{residual}$ is the standard deviation of the residual from the regression equation of the NC group.

On the basis of the results shown in Table 7, a greater proportion of AR subjects than predicted fell outside the confidence interval on the general intelligence domain, showing a trend toward improvement that was not accounted for by practice effects and regression to the mean. Two of the AR subjects who converted to psychosis (AR-C) performed worse than expected over time on the working memory and processing speed domains. As for the FE subjects, a large proportion showed deterioration in working memory, processing speed, executive functioning, and general intelligence. Yet, a high percentage of FE subjects tended to show an improvement in the verbal learning domain above what would be expected on the basis of practice, which is consistent with the interaction effect obtained through the repeated measures ANOVA.

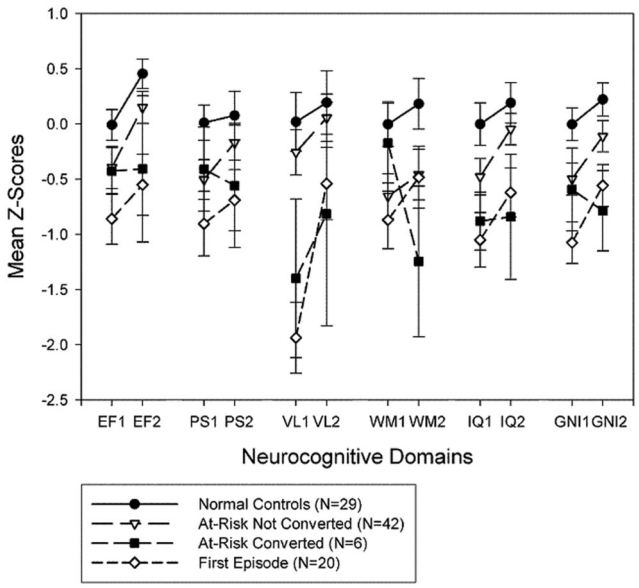

Figure 3. Pattern of performance over time and across domains for each group, including the subgroup of at-risk subjects who converted to psychosis and the one that did not. EF = executive functioning; PS = processing speed; VL = verbal learning; WM = working memory; IQ = general intelligence; GNI = global neurocognitive index; 1 = baseline; 2 = follow-up. The bars represent the standard errors.

Associations Between Change in Neurocognitive Performance and Clinical and Social Functioning Change

Repeated measures ANOVA showed significant improvements in symptom rating measures (BPRS, SAPS, SANS) and GAF scores in both patient groups. The AR subjects significantly improved in all their SIPS ratings (see Table 8).

To determine whether the changes observed in neurocognitive performance were related to changes in functional outcomes, we created difference scores for the neurocognitive, clinical, and functioning variables and performed Pearson's correlations between those difference scores within each patient group. Improvement in the global neurocognitive index was associated with improvement in SIPS positive symptoms in the AR group ($r = -.36$, $p = .02$) and GAF in the FE group ($r = .34$), although the latter correlation was not statistically significant ($p = .15$). There were additional modest but nonsignificant correlations between the verbal learning improvement in the FE group and improvement in BPRS ($r = -.32$) and SAPS ($r = -.38$).

Discussion

Our study is among the first to examine the course of neurocognitive functioning in the putative prodrome and first episode of schizophrenia using a matched normal comparison group to control for practice effects. The groups were comparable with respect to age, ethnicity, handedness, education, and parental education, although there was a higher proportion of males in the FE group. Neurocognitive functioning was found to be relatively stable in all groups, with moderate practice effects and moderate to high test–retest correlations across domains. The repeated measures ANOVA showed significant group and time main effects for the global neurocognitive index. The AR group's overall performance fell between the NC and FE groups' performance. There were significant group differences in all individual ability domains, significant time effects for executive functioning, processing speed, verbal learning, and general intelligence, as well as a significant group by time interaction for verbal learning. The FE group demonstrated a significant improvement in the verbal learning domain over the test–retest interval. The addition of gender as a grouping variable did not change the results.

Table 7
Test–Retest Changes (in Percentages) Based on the Simple Regression Model

	Better than 90% CI			Worse than 90% CI		
Neurocognitive domain	AR (n = 42)	AR-C (n = 6)	FE (n = 20)	AR (n = 42)	AR-C (n = 6)	FE (n = 20)
Executive functioning	2.4	0.0	5.0	2.4	16.7	20.0
Processing speed	7.1	0.0	5.3	2.4	33.3	21.1
Verbal learning	7.5	0.0	31.6	7.5	16.7	5.3
Working memory	11.9	0.0	5.0	16.7	33.3	20.0
General intelligence	21.4	16.7	10.0	9.5	16.7	20.0
Global index	2.4	0.0	0.0	2.4	16.7	10.0

Note. AR = at risk not converted; AR-C = at risk converted; FE = first episode. Predicted score = intercept + (unstandardized regression coefficient × baseline score); 90% CI (confidence interval) = predicted score +/– (1.64 × $SE_{residual}$); $SE_{residual}$ = standard deviation of residual from regression equation of normal comparison group; equations: CI = .31 + (.58 × baseline) +/– 1.29 for executive functioning; CI = .15 + (.75 × baseline) +/– 1.05 for processing speed; CI = .18 + (.69 × baseline) +/– 1.45 for verbal learning; CI = .18 + (.79 × baseline) +/– .85 for working memory; CI = .19 + (.81 × baseline) +/– .48 for general intelligence; CI = .17 + (.75 × baseline) +/– .98 for global index.

For each individual subject, we determined whether the observed fluctuations represented meaningful changes or normal variability in performance. After adjusting for both practice effects and regression to the mean using the simple regression model, a higher than expected percentage of AR subjects showed a real improvement in general intelligence. Moreover, a sizable proportion of the FE group demonstrated improvement in verbal learning above and beyond practice effects. Although there was no statistically significant decline over time in any of the domains (based on the analyses conducted at the group level), some of the AR subjects who later converted to psychosis showed deterioration in working memory and processing speed. Similarly, a higher than expected number of FE subjects fell outside the expected distribution in the working memory, processing speed, executive functioning, and general intelligence domains, showing a trend toward worsening despite overall improvement in clinical symptoms and social functioning.

Although these results need replication with larger sample sizes, they suggest that cognitive functions do not follow a unidimensional trajectory in schizophrenia, but rather vary by cognitive domain and position in the course of the illness. This multidimensional picture raises the possibility of more specific treatment targets in the future. For instance, cognitive remediation therapy might be effective in slowing down the declines in working memory and executive functioning during the early stages of schizophrenia (Demily & Franck, 2008). Processing speed could also be amenable to cognitive remediation strategies even before the onset of psychosis (Sartory, Zorn, Groetzinger, & Windgassen, 2005).

Whereas the neuropsychological deficits tend to be fairly stable in chronic schizophrenia (e.g., Harvey et al., 2005; Heaton et al., 2001a), our findings suggest that there may be more changes during the prodromal period and right after the illness sets in. Furthermore, those early changes in overall neurocognitive functioning seem to occur in tandem with changes in positive symptom severity in the AR group. The substantial improvement in clinical symptoms and GAF scores over time in the AR group highlights that the at-risk state can be transient in many young people and that cognitive changes may be difficult to detect in this context. In

Table 8
Clinical and Social Functioning Ratings at Baseline and Follow-Up

Rating	Baseline mean (*SD*)	Follow-up mean (*SD*)	F[a]	p
At risk (n = 48)				
GAF-M	52.1 (9.6)	61.2 (10.9)	23.75	<.001
BPRS	15.6 (5.9)	9.6 (7.4)	27.79	<.001
SAPS	5.4 (3.1)	2.9 (2.8)	28.41	<.001
SANS	6.2 (3.9)	4.5 (3.9)	10.01	.003
SIPS total	34.3 (15.1)	16.1 (12.3)	30.41	<.001
SIPS positive	10.8 (5.0)	3.8 (3.9)	27.54	<.001
SIPS disorganized	6.2 (4.0)	3.5 (3.5)	24.32	<.001
SIPS negative	10.9 (6.9)	6.1 (5.6)	26.67	<.001
SIPS general	6.5 (4.3)	2.7 (3.3)	23.10	<.001
First episode (n = 20)				
GAF-M	42.5 (9.5)	51.7 (7.6)	17.55	.001
BPRS	20.4 (7.2)	11.7 (6.8)	19.78	<.001
SAPS	8.6 (4.6)	5.2 (3.7)	8.53	.009
SANS	9.1 (4.7)	6.4 (4.3)	9.86	.005

Note. GAF-M = Modified Global Assessment of Functioning; BPRS = Brief Psychiatric Rating Scale; SAPS = Scale for the Assessment of Positive Symptoms; SANS = Scale for the Assessment of Negative Symptoms; SIPS = Structured Interview for Prodromal Syndromes.
[a] Degrees of freedom for F statistics for at-risk group = 1, 47; for first-episode group = 1, 19.

contrast to investigations showing a decline in IQ prior to the onset of illness (Gochman et al., 2005), a significant proportion of AR subjects demonstrated an improvement in general intelligence over the 6-month follow-up, even after accounting for practice effects and regression to the mean. Given that our patients are treatment seeking, their baseline performance might have been very poor to start with. Although ascertainment bias tends to be more of an issue at baseline than with respect to change over time, it is possible that this factor might have contributed to the neuropsychological gains in the AR group.

Another important finding is that the FE group showed a considerable improvement in verbal learning despite the fact that we employed alternative forms of the HVLT–R as well as norms for change based on the regression model. The improvement in global cognition and verbal learning in the FE group was associated with an amelioration in functioning and clinical symptomatology, respectively. However, those correlations did not reach statistical significance because of the rather small sample size. Our results are inconsistent with those from the study by Hoff et al. (1999) in which verbal memory showed significantly less improvement in first-episode patients over time relative to that of comparison subjects. In the future, it may help to rule out statistical artifact by comparing this group's pattern of performance over time with that of a group of chronic schizophrenia patients with similar baseline levels of performance on verbal learning. However, we believe that regression to the mean is an unlikely explanation for this finding given that the FE group did not show remarkably large improvements in executive functioning, processing speed, and general intelligence, three domains on which they were substantially worse at baseline.

It is important to note that subjects with poor baseline performance tended to have greater variation over time than initial high scorers and showed more improvement consistent with regression to the mean. Thus, confidence intervals might need to be adjusted for different levels of baseline test performance (e.g., longer width for those who perform poorly at baseline; Temkin, Heaton, Grant, & Dikmen, 1999). Alternatively, more complex models that take into account baseline level of IQ or education can be used, despite the fact that Goldberg et al. (2007) found no evidence that reading level, gender, and age are significant predictors of the magnitude of cognitive gain in first-episode schizophrenia patients. Also, it is uncertain whether norms for change, no matter what statistical model they are based on, can generalize from nonclinical to clinical groups. Therefore, future research will benefit from improving the available normative standards for quantifying real changes in neurocognitive performance for individual cases, while accounting for potentially confounding factors such as practice effects, test–retest reliability issues, and regression to the mean.

There is evidence to suggest that the emergence of schizophrenia is associated with central nervous system synaptic pruning and a dynamic wave of tissue loss (Rapoport, Addington, Frangou, & Psych, 2005). Children and adolescents with schizophrenia show an acceleration of gray matter loss, starting in parietal cortices and spreading to include temporal and frontal lobe structures as the disease progresses (Jacobsen et al., 1998; Thompson et al., 2001). This pathological process likely predates the onset of frank symptoms (Pantelis et al., 2003), and could help explain the working memory decline detected in a large number of AR and FE subjects. Longitudinal brain imaging studies using the same neurocognitive domains and with comparison groups similar to ours may provide insight into the biological mechanisms underlying the changes we detected.

Certain limitations of this study—namely, its naturalistic design, single follow-up over a relatively short period, and modest sample sizes, including the control group—require special consideration. Although longer range studies with larger samples are clearly needed, these limitations should be viewed with the fact that longitudinal assessment in such hard-to-recruit samples is quite challenging and large studies of this type are currently lacking. Progress in this area, therefore, requires incremental contributions of progressively longer term multisite studies, which should be able to determine, for instance, whether those patients who initially show neurocognitive changes stabilize with time or fluctuate back toward their own mean. Perhaps a more serious caveat of the study design was its lack of control over treatment effects that likely confounded our results given that more than two thirds of the FE sample and about one fifth of the AR sample were using antipsychotic medications at baseline. In fact, the medicated AR subjects were the poorer functioning ones, whereas the FE subjects who were not compliant with their medications had significantly more severe negative symptoms and tended to be older. On one hand, the possible contribution of treatment to the performance gains above and beyond practice effects in some domains cannot be logically excluded. However, a recent randomized clinical trial by Goldberg et al. (2007) demonstrated that the rates of improvement across most neurocognitive domains in first-episode schizophrenia patients on either risperidone or olanzapine did not exceed the practice effects in healthy controls. Moreover, this study found small differential medication effects and no significant associations between the magnitude of cognitive change scores and medication dose. On the other hand, the deterioration in working memory performance in some of our FE patients, as well as the AR patients who converted, might have been due to the initiation of treatment with atypical antipsychotic agents (Reilly, Harris, Keshavan, & Sweeney, 2006). Testing the effect of treatment on change in neurocognitive performance in this highly unstable period was not feasible given that patients had various acuteness levels and had been on antipsychotics for different lengths of time (days to months). Yet, when we included treatment as another grouping factor in the analyses, we found no significant treatment by group by time interaction. As McGorry, Yung, Bechdolf, and Amminger (2008) highlighted, early psychosis researchers have often allowed treatment to vary widely in their studies, minimizing this major weakness of the naturalistic design. Therefore, large samples and randomized controlled trials are needed to carefully assess treatment effects on the progression or amelioration of neurocognitive impairments in the prodrome and first episode of schizophrenia, as well as the relationship to outcome measures such as psychotic conversion.

Preliminary inspection of our few AR subjects who transitioned to psychosis revealed that they had the most drastic decline in working memory and processing speed. Given that there is scant research in this area, those findings are important to report, although the small sample size of our converted group did not allow us to determine whether a worsening in the aforementioned domains represents a true predictor of psychotic conversion. Yet, among the five neurocognitive domains we studied, change in working memory and processing speed performance stands out as a possible risk factor that could be added to the risk prediction algorithm developed by the North American Prodromal Longitudinal Studies consortium (Cannon et al.,

2008). It would be useful to explore the extent to which deterioration in those aspects of neurocognitive functioning improves sensitivity and predictive accuracy relative to other known risk factors of conversion to psychosis, such as functional decline, severity of subsyndromal psychotic symptoms (Haroun et al., 2006), and cannabis abuse (Kristensen & Cadenhead, 2007). It is surprising that the group that developed psychosis had a similar or slightly better level of performance in the processing speed and working memory domains at baseline, relative to the AR group that did not convert. This underscores the importance of examining change over time as well as the advantage of longitudinal designs over cross-sectional ones. One caveat is that five of the six converters transitioned to psychosis after the 6-month follow-up period (i.e., at 10, 12, or 18 months), and we did not have 18-month follow-up data on all the AR subjects who participated in the study. Given the relatively brief length of follow-up, the as-yet-unknown term limit on "at-risk" status, and the treatment confound inherent to a naturalistic design, we cannot consider the subjects who did not convert to psychosis over the 6-month follow-up "false positives," as we expect that additional subjects might have converted if they were followed beyond the study duration. Future research examining the patterns of change in neurocognition in larger at-risk samples and over longer follow-up periods will help better characterize the converters from those who do not transition to psychosis or who develop a psychological disorder other than schizophrenia. Whereas the latter group might improve in their state-related deficits with time, the true "prodromal" individuals may be more likely to stay stable or show deterioration in their preexisting cognitive weaknesses.

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