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Neurocognition and Conversion to Psychosis in Adolescents At High-Risk

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Abstract

This study examined neurocognitive predictors of conversion to Axis I psychosis among *adolescents at high-risk for psychosis* (AHRP). There were no significant differences in neurocognitive performance between adolescents at high-risk for psychosis who converted (AHRP+) and adolescents at high-risk for psychosis who did not convert (AHRP–). Within-sex comparisons revealed a relation between risk status and performance among females, with AHRP+ performing below AHRP–, but this effect did not hold for males. Between-sex comparisons revealed AHRP– males performed worse than AHRP– females on several measures. Across groups, males performed better than their female counterparts on select measures. Results are discussed in terms of implications for use of neurocognitive profiles as bio-risk markers of psychosis, while considering sex differences.

Keywords

psychosis; high-risk; adolescents; cognition; sex differences; bio-risk markers

Neurocognitive deficits are a well-established characteristic of schizophrenia (see Green et al., 2006). Despite strong evidence of poor premorbid intellectual functioning (for a meta-analytic review, see Aylward et al., 1984; Seidman et al., 2006; Reichenberg et al., 2006) and literature suggesting subtle functional impairments in years preceding clinical onset (e.g., Cornblatt et al., 2003), only a few studies have examined neurocognitive functioning among high-risk youth in relationship to vulnerability for conversion to Axis I psychosis.

There are some recent reports of neurocognitive impairments among clinical high-risk individuals (Gschwandtner et al., 2003), including adolescents meeting criteria for schizophrenia prodromal syndrome (Hawkins et al., 2004) and youth with schizotypal personality disorder (SPD; Trotman et al., 2006), though others have not replicated this (Brewer et al., 2006). There are also some reports of a relation between cognitive dysfunction and conversion to psychosis in clinical high-risk groups (Lencz et al., 2006; 2005; Keefe et al., 2006; Brewer et al., 2005). Specifically, two investigations revealed that poorer verbal memory predicted psychosis outcome (Brewer et al., 2005; Lencz et al., 2006). Another showed that a

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composite cognitive score (Keefe et al., 2006) differentiated prodromal patients who converted to psychosis compared to those who remained stable or showed improved symptom profiles.

Interestingly, despite well-established sex differences in cognitive in schizophrenia (Lewine, Walker, Shurett, Caudle & Haden 1996; Hoff & Kremen 2002; for review, see Leung & Chue 2000), few studies have examined sex differences in neurocognitive functioning, including IQ, prior to illness onset (for review, see Aylward, Walker and Bettes, 1984; Weiser et al., 2000; Offord 1974; Jones and Done, 1997; Bilder et al., 2000; Gittelman-Klein and Klen, 1969; Erlenmeyer-Kimling et al., 1984). The vast majority of studies indicate better premorbid functioning during childhood among females (compared to males) who later developed schizophrenia. Noticeably absent from the literature are efforts to examine sex differences in neurocognitive functioning in predicting clinical outcome.

The current prospective study examined the relation between conversion to psychosis and baseline cognitive performance in a sample of clinical high-risk adolescents. Baseline cognitive performance in this high-risk sample was significantly below that of a healthy control group on some measures (Trotman et al., 2006). The present report is concerned with the relation of baseline performance with psychiatric outcome; specifically whether neurocognitive scores differentiate between adolescents at high-risk who transition to Axis I psychotic disorders, namely, adolescents at high-risk for psychosis who convert (AHRP+) and adolescents at high-risk for psychosis who do not convert (AHRP-). Poorer baseline neurocognitive performance among AHRP+ compared to AHRP-, especially in verbal memory, was predicted. Also, given evidence of sex differences in cognition in schizophrenia, the relation of sex with baseline cognitive performance will be examined.

2. Methods

2.1. Participants

This sample comprised adolescents participating in a longitudinal study of youth at-risk for serious mental disorder: the Emory University Adolescent Development Project. Data are presented on 37 adolescents, ages 11 to 18 years (mean=14.30, SD=1.68), who underwent an initial cognitive and psychodiagnostic assessment and a follow-up psychiatric outcome assessment four years later. This sample excludes two AHRP+ participants for whom baseline neurocognitive data were not available.

Recruitment methods, inclusion/exclusion criteria and a discussion of the rationale for studying at-risk youth can be found in Trotman et al (2006). Many ultra high risk and clinical high-risk studies in the literature are marked by a wide range of Axis I comorbidities (e.g., Rosen et al., 2006; Lencz et al., 2003). By contrast, all high-risk individuals in the current sample who converted were diagnosed only with an Axis I disorder with psychotic features. This was likely a function of the sampling strategy. Recruitment focused on individuals with schizotypal and other symptoms linked with risk specifically for developing psychosis.

Assent and written consent was obtained from all participants and a parent in accordance with the guidelines of the Emory University Human Subjects Review Committee.

The current sample (n=37; 24M/13F) included youth at high-risk for psychosis, defined as participants who upon initial assessment met DSM-IV-TR diagnostic criteria for schizotypal personality disorder (n=35) in addition to two participants with another personality disorder (schizoid and antisocial/histrionic personality disorder) who later converted to Axis I psychosis. No participants met criteria for an Axis I disorder upon entry. Twelve of the 37 (=32.4%) AHRP converted to DSM-IV-TR Axis I psychosis including schizoaffective disorder (n=4), schizophrenia undifferentiated type (n=3), psychotic disorder not otherwise specified

(n=1), major depressive disorder recurrent severe with psychotic features (n=1), and bipolar I disorder mixed episode severe with psychotic features (n=3). Demographic characteristics are presented in Table 1.

Priority was given to recruitment of participants with no current or prior treatment with psychotropic medication. Nevertheless, a subgroup of participants was on one or more psychotropics. This is consistent with national trends marked by a significant increase in number of adolescents with adjustment problems who are prescribed psychotropic medications (Zito et al., 2003). These include stimulants, antidepressants and, to a lesser extent, antipsychotics. The current sample reflects this trend in that the most common psychotropic was stimulants (32.4%), followed by antidepressants (18.9%), and then antipsychotics (13.5%). Most psychotropics were prescribed by pediatricians, off-label, and primarily aimed at managing conduct problems rather than psychotic symptoms. Although psychotropic medications can affect cognitive functioning, there is no evidence of an adverse medication effect on cognitive performance in the Emory University Adolescent Development Project (see Trotman et al., 2006).

2.2. Diagnostic Measures

The Structured Interview of DSM-IV Personality Disorders (SIDP-IV; Pfohl et al., 1997) and the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID-IV; First et al., 1998) were administered to obtain Axis II and Axis I diagnoses, respectively. Interviewers demonstrated high inter-rater reliabilities based on minimum study criterion .80 (Pearson correlation).

2.3. Determination of Conversion Status

Given genetic evidence of shared etiological factors among DSM psychotic disorders (Cardno et al., 2002; Riley & Kendler, 2006), researchers studying at-risk youth currently emphasize Axis I *psychosis* as the outcome variable (e.g., Mittal & Walker, in press). The current study used DSM-IV-TR Axis I psychosis as the targeted outcome variable with which to determine 'conversion' status.

2.4. Neurocognitive Measures

Intellectual ability was assessed using the Vocabulary, Similarities, Picture Completion, Arithmetic and Block Design subtests of the Wechsler Intelligence Scales for Children, Third Edition (WISC-III, Wechsler 1991; ages 11–15 years) or the Wechsler Adult Intelligence Scales, Third Edition (WAIS-III, Wechsler 1997; ages 16–18 years), depending on participant's age. Selected subtests represented the range of functional domains probed by the Wechsler Intelligence Scales (WIS).

2.4.1 Wechsler Memory Scales—The Wechsler Memory Scales, Third Edition (WMS-III, Wechsler 1997) was used to assess memory. Selected subtests included Logical Memory I & II (immediate and delayed verbal memory), Family Pictures I & II (immediate and delayed spatial memory) and Letter-Number Sequencing (working memory/complex attention/executive functions). These subtests were previously demonstrated to be sensitive to deficits in individuals with schizophrenia and SPD (Conklin et al., 2000; Mitropoulou et al., 2002; Touloupoulou et al., 2003).

2.4.2. Estimated Full Scale Intelligence Quotient (FSIQ)—An index of estimated FSIQ was derived based on performance on the Vocabulary and Block Design subtests of the WIS. This estimated FSIQ is a good measure of *g* and correlates well with the Full Scale IQ (Sattler and Saklofske, 2001; Sattler and Ryan, 2001). Tables A-22 and C-21 (Sattler, 2001) were used to convert the sum of the scaled scores into an estimated FSIQ for both the WISC-

III and WAIS-III, respectively. Both the WISC-III and WAIS-III estimated FSIQ demonstrate good reliability (WISC: $r_{xx}=0.91$ and $r=0.86$, Sattler and Saklofske, 2001; WAIS: $r_{xx}=0.93$; Sattler and Ryan, 2001).

2.4.3. Neurocognitive Composite Index—A composite index of cognitive functioning was derived by averaging scaled scores across all subtests described above. Chronbach's alpha reliability coefficient (using the total AHRP sample, $n=37$) was excellent ($=0.89$).

2.5. Analyses

Independent samples t-tests and Pearson Chi-Square tests were employed to compare groups on demographic characteristics using two-tailed tests. Independent samples t-tests were employed using one-tailed tests (given the directional nature of the hypotheses), first for within- and between-sex, and second, within- and between-conversion status group comparisons on baseline neurocognitive performance. Although psychotropic medications can affect cognitive functioning, there is no evidence of an adverse medication effect on cognitive performance in the Emory University Adolescent Development Project (see Trotman et al., 2006).

3. Results

3.1. Group Differences in Demographic Characteristics

There were no significant differences between AHRP+ and AHRP− groups on sex [$\chi^2(1)=1.722$, $p=0.189$], race [$\chi^2(3)=1.308$, $p=0.727$], age [$t(35)=-0.114$, $p=0.262$] or an index of socioeconomic status (SES), namely average years of parental education [$t(34)=-1.67$, $p=0.104$]. AHRP+ and AHRP− groups were comparable within-sex on age (males: $p=0.358$; females: $p=0.539$), race (males: $p=0.801$; females: $p=0.629$) and SES (males: $p=0.062$; females: $p=0.775$). For the total AHRP group, there were no significant associations between sex, race, age or SES with performance on any of the cognitive measures (using two-tailed Pearson correlations).

3.2. Baseline Neurocognitive Functioning: AHRP+ vs. AHRP−

As can be seen in Table 2, there were no significant group differences on any cognitive measures at baseline.

3.3. Sex Differences in Patterns of Baseline Neurocognitive Functioning

Scores for the AHRP+ and AHRP− groups by sex are listed in Table 3.

3.3.1. AHRP+ vs. AHRP− Within-Sex Comparisons—As can be seen in Table 3, among females, AHRP+ performed significantly poorer than AHRP− on Similarities ($p=0.047$), Logical Memory I ($p=0.035$) & II ($p=0.012$), Family Pictures I ($p=0.046$), Letter-Number Sequencing ($p=0.040$), and the Cognitive Summary Index ($p=0.044$). This pattern held at the trend level on Arithmetic ($p=0.094$) and Family Pictures II ($p=0.086$). Among males, AHRP+ outperformed AHRP− on Logical Memory II at the trend level ($p=0.096$). This was unexpected. No other results were significant.

3.3.2. AHRP Males vs. AHRP Females—Across all AHRPs (independent of conversion status), males performed significantly better than females on Picture Completion (males: 10.92 (3.69), females: 8.69 (3.12); $t(35)=1.842$, $p=0.037$). No other results were significant.

3.3.3. AHRP+ Males vs. AHRP+ Females—Males performed significantly better than females on Logical Memory II (males: 10.17 (2.93); females: 6.50 (3.73); $t(10)=1.895$,

$p=0.044$) and, at the trend level, on Logical Memory I (males: 9.67(2.58); females: 6.50(4.18); $t(10)=1.58$, $p=0.073$). No other results were significant.

3.3.4 AHRP– Males vs. AHRP– Females—Females significantly outperformed males on Vocabulary (females: 13.14(3.58), males: 10.11(3.79); $t(23)=-1.82$, $p=0.041$), Similarities (females: 13.71 (2.14), males: 11.28(2.93); $t(23)=-1.994$, $p=0.029$), Logical Memory I (females: 10.43(1.27), males: 7.83(4.02); $t(22.63)=-2.44$, $p=0.012$), Letter-Number Sequencing (females: 10.29(3.25), males: 7.83 (2.88); $t(23)=-1.849$, $p=0.039$), Logical Memory II (females: 11.00(2.45), males: 7.78 (3.96); $t(23)=-1.99$, $p=0.029$), and the Cognitive Summary Index (females: 10.84(1.83), males: 9.10(2.30); $t(23)=-1.78$, $p=0.044$); and at the trend level on estimated FSIQ (females: 111.29(22.97); males: 97.00(17.34); $t(23)=-1.691$, $p=0.052$). In contrast, males significantly outperformed females on Picture Completion (males: 11.11(3.197), females: 8.14(3.29); $t(23)=2.07$, $p=0.025$).

4. Discussion

Contrary to prior reports (Keefe et al., 2006; Pukrop et al., 2007; Lencz et al., 2006), this study did not reveal baseline neurocognitive performance differences between high-risk adolescents who converted to Axis I psychosis and those who did not. This discrepancy may be attributable to limited statistical power due to smaller sample size. More likely, inconsistencies in the findings are due to the younger mean age (early teens) of the current sample compared to clinical and ultra high risk samples in the literature (mid to late teens/early twenties). Participants are currently just entering the highest risk developmental period for the onset of psychosis; namely, late adolescence/early adulthood. Follow-up assessments of this sample are ongoing, and it is likely that more of the high-risk subjects will convert to psychosis over a more extended period of time.

Related to this, it is possible that neurocognitive functioning shows a developmental lag through the prodrome by virtue of genetic risk and thus, with increasing age, this group demonstrates further cognitive deficit. In this way, it might be expected that discrepant cognitive functioning between at-risk converters and nonconverters may become more apparent with advanced age, as is observed in ultra high risk studies examining older cohorts of adolescents (e.g., Francey et al., 2005; Pukrop et al., 2007). This is consistent with the documented brain changes that accompany adolescence, and may be more pronounced in at-risk youth (for a review, see Lenroot and Giedd, 2006). It is possible that the prodromal period is marked by disruptions in these normal brain maturation processes, impacting neurocognition. Future longitudinal research aimed at tracking at-risk cohorts using multiple assessments across briefer time intervals, beginning in premorbid periods through clinical high-risk to psychosis onset, will help clarify this possibility and the use of neurocognitive profiles (to supplement clinical profiles) in predicting conversion risk.

It is worth noting that though largely similar, there are differences in sampling characteristics between the current study and other prodromal/high-risk studies examining baseline neurocognition. The most cardinal distinguishing factor, however, is again the younger age of the current sample, which renders participants not as ‘imminently’ at-risk compared to older samples more proximal to the age of conversion. In addition, the current sample relies more heavily on ratings of schizotypal symptoms as opposed to, for example, studies utilizing measures indexing ‘attenuated positive symptoms’ (Lencz et al., 2006) or ‘cognitive-perceptive basic symptoms’ or ‘any attenuated or transient psychotic symptoms’ (Pukrop et al., 2007).

Exploratory analyses of sex differences showed that AHRP+ females performed worse than same-sex AHRP– on several neurocognitive measures. There were no significant differences

between male converters and nonconverters. This points to the importance of examining sex differences in the developmental trajectories of cognitive performance in future longitudinal studies of at-risk groups. Moreover, the current paradigm focuses on pubertal maturation, a critical period marked by substantial neurohormonal fluctuations that are sexually differentiated and speculated by some (e.g., Walker and Walder 2002) to play an integral role in the transition to psychosis. It is possible that disruptions in neurohormonal status (Walker et al., 2001) that accompany this transitional developmental period may impact neurocognition via activational and/or organizational effects on brain maturation. This concept is consistent with previous work suggesting a potential role of disruptions in prenatal gonadal hormone levels in adolescents at-risk for schizophrenia (Walder et al., 2006). Of course, the hormone milieu remains only one among several candidates (i.e., genetic factors) that interact towards rendering individuals vulnerable to psychosis.

Also, AHRP- males performed worse than their high-risk female counterparts on a variety of neurocognitive measures including (at the trend level) IQ. This is generally consistent with the literature suggesting less severe cognitive impairment among female patients with psychotic disorders (Walder et al., 2006; Goldstein et al., 1998). In contrast, AHRP+ females performed worse than their high-risk male counterparts on a measure of verbal memory. The seemingly contradictory finding may be indicative of a differential sex effect that varies by risk status and is influenced by development. That is, it is possible that although females who transition to psychosis demonstrate poorer baseline verbal memory compared to their male counterparts, cognitive integrity may be relatively less compromised, within-sex, through development including the critical transition to psychosis. As such, it is possible that males, who may be more adversely impacted by neuromaturational processes associated with adolescence, will demonstrate relatively poorer neurocognition upon conversion. This possibility fits with research suggesting that males are more vulnerable to neurodevelopmental abnormalities, which may influence cognition (Hoff and Kremen, 2002). Moreover, much as prenatal gonadal hormone disruptions have been hypothesized to play a role in the genesis of psychosis (Walder et al 2006), so may circulating gonadal hormones play a role during adolescent brain maturation. This remains an empirical question to be addressed in larger scale future research.

With respect to a vulnerability/stress model of schizophrenia (Nuechterlein and Dawson 1984), findings from this and related studies are important irrespective of whether neurocognitive functioning *predicts* conversion to psychosis. Neurocognitive status may serve as one valuable 'vulnerability indicator' (Francey et al., 2005) or 'biorisk marker', among others such as minor physical anomalies, movement abnormalities and neurohormones (Mittal et al 2007), which reflects an underlying predisposition to psychosis. Such studies of bio-risk therefore have the potential to offer important diagnostic information as well as implicate pathophysiology. Ultimately, this may aid in the development of methods and therapeutic interventions aimed at mitigating illness severity and/or preventing onset altogether.

In conclusion, despite the small sample size, the present study revealed significant cognitive performance deficits in female high-risk participants who converted to psychosis. The absence of differences among the males suggests the importance of considering sexually differentiated patterns of cognitive decline in prodromal subjects. However, the present findings should be considered preliminary given the small sample size and the fact that the mean age of the sample places them at the early stage of the modal risk period for psychosis onset.

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Table 1

Demographic characteristics of youth at-risk for psychosis (HRP) including those who converted (HRP+) and those who did non-convert (HRP-) to Axis I psychosis.

	Converted to Axis I Psychosis (AHRP+)	Non-Converted to Axis I Psychosis (AHRP-)	Total Sample (AHRP)	Diff ^c
N	12	25	37	
(Male, Female)	(6, 6)	(18, 7)	(24,13)	n.s.
Mean Age(SD) ^a	14.75(1.60)	14.08(1.71)	14.30(1.68)	n.s.
Male, Female	14.83(1.84), 14.67(1.51)	14.11(1.57), 14.00(2.16)	14.29(1.63), 14.31(1.84)	
Socioeconomic Status ^b	15.23(3.66)	12.57(4.82)	13.36(4.62)	n.s.
	16.5(3.58), 13.7(3.49)	12.43(4.60), 12.88(5.60)		
Ethnicity				
White/Caucasian	9	19	28	n.s.
(M,F)	(5,4)	(15,4)	(20,8)	
African American	3	4	7	
(M,F)	(1,2)	(2,2)	(3,4)	
Asian American	0	1	1	
(M,F)	(0,0)	(0,1)	(0,1)	
Other	0	1	1	
(M,F)	(0,0)	(1,0)	(1,0)	

Note: AHRP+ and AHRP- are comparable within-sex on age, race and SES ($p > .05$; two-tailed).

^a Age at initial assessment upon entry into the study (baseline).

^b Socioeconomic status (SES) is an average of maternal and paternal years of education.

^c Group differences (AHRP+ vs. AHRP-).

Table 2

Means and Standard Deviations for Performance (Scaled Scores^a) on Neurocognitive Measures by Conversion Status Among Adolescents at High-Risk for Psychosis (AHRP).

Cognitive Measure	Converted (AHRP+)	Not Converted (AHRP-)	Group Differences
Wechsler Scales of Intelligence			
Picture Completion	9.83 (4.13)	10.28 (3.43)	n.s.
Vocabulary	11.17 (10.96)	4.13 (3.91)	n.s.
Similarities	10.58 (4.25)	11.96 (2.91)	n.s.
Arithmetic	8.50 (3.85)	8.92 (3.40)	n.s.
Block Design	9.50 (3.53)	9.40 (3.65)	n.s.
Estimated FSIQ ^b	102.08 (20.87)	101.00 (19.69)	n.s.
WMS-III^c			
Logical Memory I	8.08 (3.70)	8.56 (3.64)	n.s.
Family Pictures I	8.75 (4.62)	9.56 (3.27)	n.s.
Letter-Number Sequencing	7.92 (3.99)	8.52 (3.12)	n.s.
Logical Memory II	8.33 (3.73)	8.68 (3.85)	n.s.
Family Pictures II	8.75 (4.60)	9.38 (3.57)	n.s.
Cognitive Composite Index^d	9.14 (3.49)	9.59 (2.29)	n.s.

Note: ** $p < .05$, * $p < .10$. Statistical significance is reported using one-tailed t-tests.

^a Scaled scores are indicated with exception of estimated FSIQ, which provides an index value with a mean of 100 and standard deviation of 15.

^b Estimated Full Scale IQ (FSIQ) is a derived index based on performance on the Vocabulary and Block Design subtests of the WIS (see Sattler, 2001)

^c Wechsler Memory Scale-III

^d Average of scaled scores across all neurocognitive measures (except estimated FSIQ).

Table 3

Means and Standard Deviations for Performance (Scaled Scores^a) on Neurocognitive Measures by Conversion Status and Sex Among Adolescents at High-Risk for Psychosis (AHRP).

Cognitive Measure	Converted (AHRP+)	Not Converted (AHRP-)	Group Differences
FEMALES			
Wechsler Scales of Intelligence			
Picture Completion	9.33 (3.08)	8.14 (3.29)	n.s.
Vocabulary	10.83 (4.54)	13.14 (3.58)	n.s.
Similarities	9.67 (4.68)	13.71 (2.14)	**
Arithmetic	7.33 (2.94)	9.86 (3.44)	*
Block Design	8.83 (3.19)	10.71 (4.57)	n.s.
Estimated FSIQ ^b	99.17(20.19)	111.29(22.97)	n.s.
WMS-III^c			
Logical Memory I	6.50 (4.18)	10.43 (1.27)	**
Family Pictures I	7.00 (4.20)	10.71 (3.04)	**
Letter-Number Sequencing	6.83 (3.19)	10.29 (3.25)	**
Logical Memory II	6.50 (3.73)	11.00 (2.45)	**
Family Pictures II	7.33 (4.32)	10.43 (3.31)	*
Cognitive Composite Index^d	8.02 (3.47)	10.84 (1.83)	**
MALES			
Wechsler Scales of Intelligence			
Picture Completion	10.33 (5.24)	11.11 (3.20)	n.s.
Vocabulary	11.50 (4.09)	10.11 (3.79)	n.s.
Similarities	11.50 (3.99)	11.28 (2.93)	n.s.
Arithmetic	9.67 (4.55)	8.53 (3.41)	n.s.
Block Design	10.17 (4.02)	8.89 (3.23)	n.s.
Estimated FSIQ ^b	105.00(23.01)	97.00(17.34)	n.s.
WMS-III^c			
Logical Memory I	9.67 (2.58)	7.83 (4.02)	n.s.
Family Pictures I	10.50 (4.68)	9.11 (3.32)	n.s.
Letter-Number Sequencing	9.00 (4.69)	7.83 (2.88)	n.s.
Logical Memory II	10.17 (2.93)	7.78 (3.96)	*
Family Pictures II	10.17 (4.79)	8.94 (3.68)	n.s.
Cognitive Composite Index^d	10.27 (3.42)	9.10 (2.30)	n.s.

Note: ** $p < .05$, * $p < .10$. Statistical significance is reported using one-tailed t-tests.

^a Scaled scores are indicated with exception of estimated FSIQ, which provides an index value with a mean of 100 and standard deviation of 15.

^b Estimated Full Scale IQ (FSIQ) is a derived index based on performance on the Vocabulary and Block Design subtests of the WIS (see Sattler, 2001)

^c Wechsler Memory Scale-III

^d Average of scaled scores across all neurocognitive measures (except estimated FSIQ).