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Neurocognition and Transition to Psychosis: Baseline Functioning in the Second Phase of the North American Prodrome Longitudinal Study

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Abstract

Importance—Neurocognition is a central characteristic of schizophrenia and other psychotic disorders. Identifying the pattern and severity of neurocognitive functioning during the “near-psychotic”, prodromal, clinical high-risk (CHR) state is necessary to develop accurate predictors of psychosis and more effective and potentially preventative treatments.

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Objective—Identify core neurocognitive dysfunctions associated with the CHR phase, and measure the ability of neurocognitive tests to predict the transition to psychosis. Determine if the neurocognitive deficits are robust or explained by potential confounders.

Design—Case control study. Baseline neurocognitive functioning collected from 2008–2012 in the second phase of the North American Prodrome Longitudinal Study (NAPLS-2).

Setting—A consortium of eight university-based, outpatient programs studying the psychosis prodrome in North America.

Participants—CHR individuals (n=689) and healthy controls (HCs, n=264) consisting of 137 male and 127 female HC and 398 male and 291 female CHR individuals ages 12–35.

Interventions or Exposures—A naturalistic, observational study.

Main Outcome and Measure(s)—Neurocognitive differences between those who did and did not transition to psychosis, differences between medicated and unmedicated groups, and time to conversion. Nineteen neuropsychological tests and four factors derived from factor analysis.

Results—The factors were Executive Function/Visual-Spatial, Verbal, Attention/Working Memory, and Declarative Memory. Amongst widespread mild to moderate impairments, CHR individuals were significantly impaired compared to HCs on Attention/Working Memory and Declarative Memory. CHR converters had large Declarative Memory and Attention/Working Memory deficits (Cohen's d = ~0.8, p <.001) compared with controls and were significantly worse on these dimensions than non-converters. In Cox regression, impaired Declarative Memory and high Verbal (premorbid) ability in addition to age, site and positive psychotic symptoms, significantly predicted time to conversion in those who later transitioned to psychosis. The pattern of impairments could not be accounted for by premorbid or current general cognitive ability, medications, current depression, alcohol or cannabis abuse.

Conclusions and Relevance—Neurocognitive impairment is a robust characteristic of CHR individuals, especially those who later develop psychosis. Tests tapping verbal and visual declarative memory and attention/working memory were most sensitive to imminent psychosis amongst those at CHR. Interventions targeting the enhancement of neurocognitive functioning are warranted in this population.

Keywords

Neurocognition; Clinical High Risk; Prodrome; Psychosis; Schizophrenia; Antipsychotic Medications

INTRODUCTION

Neurocognitive dysfunction is a hallmark feature of schizophrenia[1–5] and, to a lesser extent, of other psychoses[6]; a conceptualization originating roughly 100 years ago[7] with Kraepelin[8] and Bleuler[9]. There is ample evidence of significant but milder impairments during the premorbid phase[10–12], greater deficits during the prodromal or clinical high risk (CHR) period,[13–15] culminating in relatively severe deficits in the first episode[16] and chronic phases[17]. This suggests an evolution of neurocognitive dysfunction in individuals developing psychosis, especially schizophrenia[10,14,18,19]. The CHR[20] period is of considerable interest

because it offers a temporal window into the changes occurring during the “near-psychotic” state, before confounders such as chronicity and long-term medication use cloud the picture.

A substantial body of neurocognitive research in CHR populations has been summarized in a number of meta-analyses[13–15]. “Small-to-medium effect size (ES) impairments across most neurocognitive domains studied (Cohen’s $d = -0.26$ to -0.67) and small-to-large ESs ($d = -0.35$ to -0.84) in those who convert to psychosis (CHR+C)” have been reported[14]. Verbal memory and processing speed have emerged as relatively strong predictors of psychosis[13,14,21–24]. However, small samples, different measures, and variable reporting of sample characteristics limit the reliability of these findings. In this second phase of the North American Prodrome Longitudinal Study (NAPLS-2), we assessed the largest CHR sample to date.

First, we sought to identify the key neurocognitive functions impaired in the CHR stage, especially in those who later convert to psychosis. Descriptions of schizophrenia place considerable emphasis on the centrality of dysfunctions in attention[1,2,25,26] and working memory[27,28]. Evidence of severe deficits in declarative memory[29] has more recently emerged in first episode[16,30,31] and CHR[14,21,22] samples. Olfactory identification deficits have also been touted as a possible risk factor[32,33] and processing speed[34] and general cognitive ability have been shown to be robustly impaired in persons who later develop schizophrenia.[10,14] We chose to provide extensive coverage of neurocognitive dimensions thought *a priori* to mark the evolution into frank psychosis.

Second, we investigated if the neurocognitive profiles were characterized by a general deficit syndrome or specific impairments[35]. This is of particular relevance for those individuals who transition to psychotic disorders as it provides critical information about the nature of neurocognition in the earliest phase of psychosis[36]. We hypothesized that the CHR+C group would be characterized by especially salient deficits against a background of general impairments.

Third, we examined differences between medicated and unmedicated CHR individuals. Many of these young people take a range of medications including antipsychotics.[37] Such medications could improve or impair cognition idiosyncratically. Prior CHR neurocognitive studies have not systematically addressed medication status. The large sample in NAPLS-2 enabled an investigation of a sizeable subgroup of CHR+C individuals who have never been medicated, and thus help to identify an unadulterated picture of neurocognitive function.

Finally, we explored the potential usefulness of neurocognition for predicting transition to psychosis. While it is unlikely that neurocognitive measures will be highly predictive by themselves of conversion to psychosis, in part because they are impaired in many neuropsychiatric disorders[38,39], knowing their relative sensitivities in combination with clinical features may help in the real-world prediction of psychosis or disability[24,40,41].

METHODS

Participants

NAPLS-2 is a consortium of eight programs studying the psychosis prodrome in North America, as in NAPLS-1. The methodology and clinical features of the NAPLS-2 study are detailed elsewhere[42,43]. From a sample of 764 CHR participants and 279 healthy controls (HCs) ranging in age from 12–35, 689 CHR and 264 HC participants provided baseline neurocognitive data. The study protocols and informed consents were approved by the ethical review boards of all sites, and all procedures comply with the ethical standards of the relevant committees on human experimentation and with the Helsinki Declaration, as revised in 2008.

Inclusion and exclusion criteria

The CHR sample met the Criteria of Prodromal Syndromes (COPS)[20], based on the Structured Interview for Psychosis Risk Syndromes (SIPS)[20], or if under age 19, criteria for schizotypal personality disorder (n=21) or COPS. Participants were excluded if they had a lifetime Axis I psychotic disorder, estimated IQ's < 70 on both measures of IQ, a central nervous system disorder, or DSM-IV substance dependence in the past 6 months. Other non-psychotic DSM-IV disorders were not exclusionary (e.g., substance abuse disorder, major depression) unless they clearly caused or better accounted for prodromal symptoms. Antipsychotic medications were allowed, provided there was clear evidence that psychotic symptoms were not present when the medication was started. HCs could not meet criteria for any prodromal syndrome, current or past psychotic or Cluster A personality disorder, or have first-degree relatives with a history of psychotic disorder or psychotic symptoms.

Measures

The SCID was used to rule out psychosis and to identify DSM-IV Axis I or cluster A disorders.[44] For some analyses, we used a rescaled sum of unusual thought content/delusional ideas (P1) and suspiciousness/persecutory ideas items (P2) from the SIPS positive symptoms[45]. Transition to psychosis was determined by meeting SIPS Presence of Psychotic Symptoms (POPS) criteria[20]. Assessments were at baseline, 12 and 24 months. Current alcohol and marijuana use was assessed with the Alcohol and Drug Use Scale (AUS/DUS[46]). The Calgary Depression Scale for Schizophrenia (CDSS[47,48]) was used to assess depression.

The neuropsychological battery was designed to cover a range of functions using well-established clinical neuropsychological tests, as well as experimental measures of sensory, perceptual, or cognitive functions hypothesized to be important indicators of CHR status or conversion to psychosis. These included the MATRICS battery[49–52], the Wechsler Abbreviated Scale of Intelligence (WASI) for general intellectual ability[53] and the Wide Range Achievement Test-4 (WRAT-4) reading task to estimate premorbid ability[54]. Experimental measures included the Babble test (for auditory perception[55]), the University of Pennsylvania Smell Identification Test (UPSIT[56]) for olfactory identification, a visual and verbal paired associate memory test (PAM[57]), and three auditory attention & working memory continuous performance tests (ACPT[58–60]). One summary measure from each test

was chosen *a priori* as the best estimate of the function of that test. We factor analyzed (FA) the test battery to reduce the number of variables. Supplementary (S) text and Table S1 provide extensive detail on the battery.

Statistical Analysis

We examined missing data prior to implementing multiple imputation (MI)[61,62]. From a sample of 1043, 953 received baseline neurocognitive testing (91.4%). Of the CHR sample that transitioned to psychosis during the two-year follow-up (n=93), 89 received testing (95.7%). Overall data completeness for the tested sample (n=953) was 96.6% for 19 test variables. After MI, we conducted a FA of the 19 neurocognitive variables (see Supplementary text). All analyses were done with SPSS, version 23.[63]

Groups were HCs, CHR converters (CHR+C) and non-converters (CHR-NC). T-tests, Kolmogorov-Smirnov Z and Chi Square tests were used to assess demographic comparability. Due to differences in age and maternal education, we controlled for both using MANCOVA and also controlled for site as a random effects factor with a linear mixed model. We covaried for estimated and premorbid IQ to test the role of general intellectual ability in cognitive dysfunctions. We compared medicated vs. nonmedicated groups of CHR +C vs HC, and CHR+C vs CHR-NC by conducting MANOVA with planned comparisons using residualized factor scores generated from the linear mixed models.

To examine group cognitive profiles we residualized out age and maternal education from all neurocognitive indices (four factors derived from FA). Area under the curve (AUC) was calculated by the ROC program in SPSS. Prediction of conversion to psychosis and time to conversion was assessed by logistic and Cox regression. Covariates were selected based on similar prediction analyses conducted in NAPLS-1[64] and NAPLS-2[45] and entered into the model if they were associated with survival time and predicted conversion status in logistic regression. Survival time was time to the last SIPS interview or conversion, whichever occurred first. Candidate covariates were added to the model as a block then subjected to backward selection with a criterion p value of 0.10. Candidates that survived at $p \leq .05$ within domain were entered into an omnibus model. ESs were calculated with Cohen's *d*. Bonferroni corrected significance for mean comparisons was set for individual tests at $p<.00263$ (.05/19) and for factors at $p< .0125$ (.05/4).

RESULTS

Demographics (Table 1)

There were 137 male and 127 female HCs and 398 male and 291 female CHR individuals. HCs were significantly older, had significantly more education, and HC mothers had significantly more education. The groups did not differ in sex or race distribution, father's education, or ethnicity. There were no significant differences on any demographic characteristic between CHR+C and CHR-NC groups.

Clinical (Table 1)

Groups did not significantly differ in frequency of alcohol or marijuana use or on depression. There were no significant correlations between these clinical characteristics and neurocognitive factors. The CHR+C group had a significantly shorter follow-up period than the CHR-NC subgroup, reflecting time to conversion and attrition. CHR+C and CHR-NC subjects received a variety of medications including anti-psychotics, anti-depressants, stimulants, and others, but there were no significant differences in rates between the two CHR groups.

Factor Analysis (Table 2)

Supplementary text explains factor selection. The factors (F) were: F1 – Executive Function (EF)/Visual-Spatial; F2 – Verbal; F3 – Attention/Working Memory (WM); F4- Declarative Memory. Two tests laden with sensory-perceptual processes (olfaction and audition) had very low (UPSIT) or negligible loadings (Babble) initially and were dropped from the FA. They were analyzed with the other individual tests. The bivariate correlations among tests are in Table S2.

Neurocognition Group Comparisons: CHR vs. Controls (Table 3)

The CHR group performed significantly worse than HCs on all 19 tests combined (MANOVA $F\,[19, 933] = 6.71$, $p < .001$), on the four factors combined ($F\,[4, 948] = 24.18$, $p < .001$) and controlling for age, maternal education, and site on 2/4 factors, Attention/WM $[1,948]=56.52$, $p< .001$; Declarative Memory $F[1,948]=22.83$, $p<.001$) and on 14/19 individual tests. The largest ES (Attention/WM) was of moderate magnitude. The average ES across the 19 tests was small, $d = 0.30$. Model-corrected profiles are shown in Figure 1. Controlling separately for WASI IQ and WRAT4 Reading, Attention/WM and Declarative Memory factors remained significantly different between groups. CHR-HC differences remained significant on 12/14 individual tests covarying WRAT Reading. Covarying WASI IQ yielded fewer significant differences.

CHR+C vs. Controls

CHR+C participants performed significantly worse than HCs ($F\,[19,333] =5.95$, $p < .001$) using all tests. The four factor MANOVA ($F\,[4, 348] = 22.82$, $p < .001$) showed significant differences. In models controlling for age, site, and maternal education, CHR+C subjects performed significantly worse on 3/4 factors: Attention/WM ($d = 0.80$), Declarative Memory ($d = 0.77$), and EF/Visual-Spatial ($d = 0.36$). The average ES across the 19 tests was $d= 0.47$. Figure 2 illustrates model adjusted ESs. CHR+C subjects performed significantly worse on Attention/WM, Verbal, and Declarative Memory and 12/14 individual tests after controlling for WRAT Reading. They showed fewer significant test differences after covarying WASI IQ.

Impairments were comparable comparing 252 currently unmedicated HCs with 51 unmedicated CHR+Cs, with 38 currently medicated CHR+Cs, and between 236 never medicated HCs with 29 never medicated CHR+Cs. The smaller group of CHR+C's on antipsychotic medications was significantly impaired on Attention/WM and Declarative Memory compared to HCs. Moreover, there were no significant cognitive differences

between currently unmedicated CHR+Cs vs. medicated CHR+Cs, or between never medicated CHR+Cs vs. medicated CHR+Cs, or between CHR+Cs with and without antipsychotic medications. (Supplementary Text, Table S3 and Figure S1 for details).

CHR+C vs. CHR-NC (table 3)

The CHR+C group performed significantly worse than CHR-NC (MANOVA F [19,669] = 1.90, p = .01; four factor MANOVA F [4, 684] = 6.51, p < .001), specifically on Attention/Working Memory (*d*=.28) and Declarative Memory (*d* = 0.48) after controlling for age, site, and maternal education. CHR+C performed significantly worse in mixed linear model contrasts only on BVMT-R (*d* = 0.40) and PAM (d = 0.39). The average ES across the 19 tests was d = 0.20. Covarying WASI IQ and WRAT Reading, CHR+C's performed significantly better on Verbal, and worse on Declarative Memory, and on the BVMT-R and PAM tasks.

Prediction Analyses (see Supplementary text)

After exploring a range of possible predictors, Age (b = −.10, Hazard Ratio [HR] = .90, 95% Confidence Interval [CI] = .84–.97, p = .003, P1/P2 symptoms (b = .44, HR = 1.56, 95% CI = 1.36–1.78, p <.001) and dummy codes for 3 sites were retained. The Verbal (b = .40, HR = 1.48, 95% CI = 1.08–2.04, p =.02) and Declarative Memory (b = −.87, HR = .42, 95% CR = .31–.56, p <.001) factors were retained. Similar results were observed in logistic regression analyses predicting conversion. Cox regression was then run with strongest loading individual component tests (BVMT-R, HVLT-R, and PAM for Declarative Memory; WRAT4 Reading and WASI-Vocabulary for Verbal). All covariates were retained, as were BVMT-R (b = .05, HR = .95, 95% CI = .91–.99, p = .009), HVLT-R (b = −.05, HR = .95, 95% CI = .91–1.00, p = .04), WRAT4 Reading (b = .05, HR = 1.05, 95% CR = 1.01–1.10, p = .009) and PAM (b = −1.83, HR = .16, 95% CI = .05–.54, p = .003). Declarative Memory had the highest AUC (.624) followed by Attention/WM (AUC = .568). The highest AUCs for Declarative Memory tests were PAM (.607), BVMT-R (.604), and HVLT-R (.576) and for Attention/WM were BACS Symbol Coding (.584), Trails A (.582), ACPT Q3A Memory (.579) and ACPT QA Vigilance (.568) (Table S4).

DISCUSSION

In the largest and most detailed study of CHR prodromal cases, using a multi-site, case-control design and standardized assessments, we demonstrated that individuals at CHR were impaired in virtually all neurocognitive dimensions compared to controls, and this could not be accounted for by premorbid or current general cognitive ability, current depression, medications, alcohol or cannabis abuse. ESs in comparison to HCs for Declarative Memory and Attention/WM were large (d=~0.8) for CHR+C participants. Compared to CHR-NC, CHR+C participants were significantly impaired in Attention/WM and Declarative Memory, the latter significantly predicting conversion to psychosis and time to event in concert with positive symptoms. Comparable impairments were observed in never-medicated and currently unmedicated CHR-NCs and CHR+C's. These data demonstrate the sensitivity of neurocognitive function as a component risk marker for psychosis.

Our findings support theoretical models hypothesizing Attention/WM impairments, and even more strongly, impaired Declarative Memory, as central to the CHR stage.[20–22] The results are consistent with NAPLS-1, in which Declarative Memory had the largest ES decrement and roughly the same magnitude in CHR+C.[13,14] The distinct profile of performance across domains, especially in CHR+C, suggests that at the incipient psychotic phase, specific forms of neurocognition are affected and are predictive of later psychosis.

Within CHR participants, there was considerable variability in neurocognitive performance. CHR-NC's impairments (mean $d = 0.30$), were on the order of other psychiatric disorders in young people, such as attention-deficit/hyperactivity disorder (ADHD)[65]. CHR+Cs impairments (mean $d = 0.47$) were approximately 57% larger, although smaller than those observed in first episode schizophrenia[16] (Table S5). Analyses of individual variability and longitudinal analyses are needed to identify how profile and severity differ according to comorbid disorders, final diagnoses (e.g., schizophrenia vs. bipolar psychosis) and pre- and post-conversion.

A key question was how neurocognitive deficits are associated with medication status. Psychotropic-naive and unmedicated subgroups had significant impairments comparable to the overall CHR subgroups. Treated groups, including with antipsychotic medications, were largely comparable to those without treatment, except they had somewhat greater Attention/WM impairment. These observations emphasize the essential nature of neurocognitive impairment in the CHR stage and de-emphasize the role of medications as confounders in our results. Our design precludes conclusions about causality and future work should study the effect of medications on neurocognition in CHR populations in a prospective design.

There were a number of other potentially important observations. The unexpectedly higher Verbal score (reflecting WRAT4 Reading) that was retained in logistic and Cox regressions in concert with impaired Declarative Memory was not a significant predictor in univariate comparisons. This pattern of high verbal premorbid ability and impaired memory, coupled with P1/P2 composite appears to be a pernicious combination predicting conversion and needs replication. Importantly, the BVMT-R (a visual-memory test) showed comparably large impairments as the two verbal memory tasks, highlighting that Declarative Memory deficits in CHR are not solely verbal, and that Declarative Memory impairments are key neurocognitive risk markers[66].

Neurocognitive tests used in concert with other clinical and psychobiological measures may enhance prediction of psychosis or functional outcome. For example, in analyses limited to two tests selected from literature review[14] prior to these neuropsychological analyses, NAPLS-2 investigators found that the HVLT-R and BACS Symbol Coding added modest but significant independent predictive power above the clinical measures in a risk calculator algorithm for psychosis conversion[45] and this was replicated in an independent non-NAPLS sample[67]. Similar results have been observed in other studies[24,40,41]. In this study, we showed that other tests, including BVMT-R, PAM, and ACPT QA Vigil added significant independent variance beyond P1-P2 symptoms, augmenting the importance of neurocognitive markers.

Strengths and Limitations

NAPLS-2, because of its large sample from diverse geographical areas, extensive neurocognitive coverage, remarkably complete neurocognitive dataset, and large never-medicated sample, allowed for a strong confirmation of neurocognitive hypotheses. The NAPLS-2 study built upon and improved the NAPLS-1 assessment, confirming and expanding prior results (Table S5). This broad range of measures expanded the scope of what is known about CHR neurocognition.

Limitations include the fact that most of these tests and factors are complex. Thus, while Declarative Memory is clearly affected, the tasks tapping this domain cannot parse the specific mechanisms underlying the deficits. Further research with more molecular measures of cognition, such as those developed by CENTRACS[68], may allow specification of the cognitive processes underlying the deficits. We did not randomize or counterbalance the order of tests, so we cannot rule out order effects. However, the most impaired tasks were spread out across the battery from the sixth to the last tests in the battery so there is no obvious fatigue effect.

Conclusions

Neurocognitive impairment is common in CHR individuals, and of clinically meaningful magnitude, especially in those who later develop psychosis. Declarative Memory and Attention/WM are important targets for early cognitive enhancing interventions with this population[69–73].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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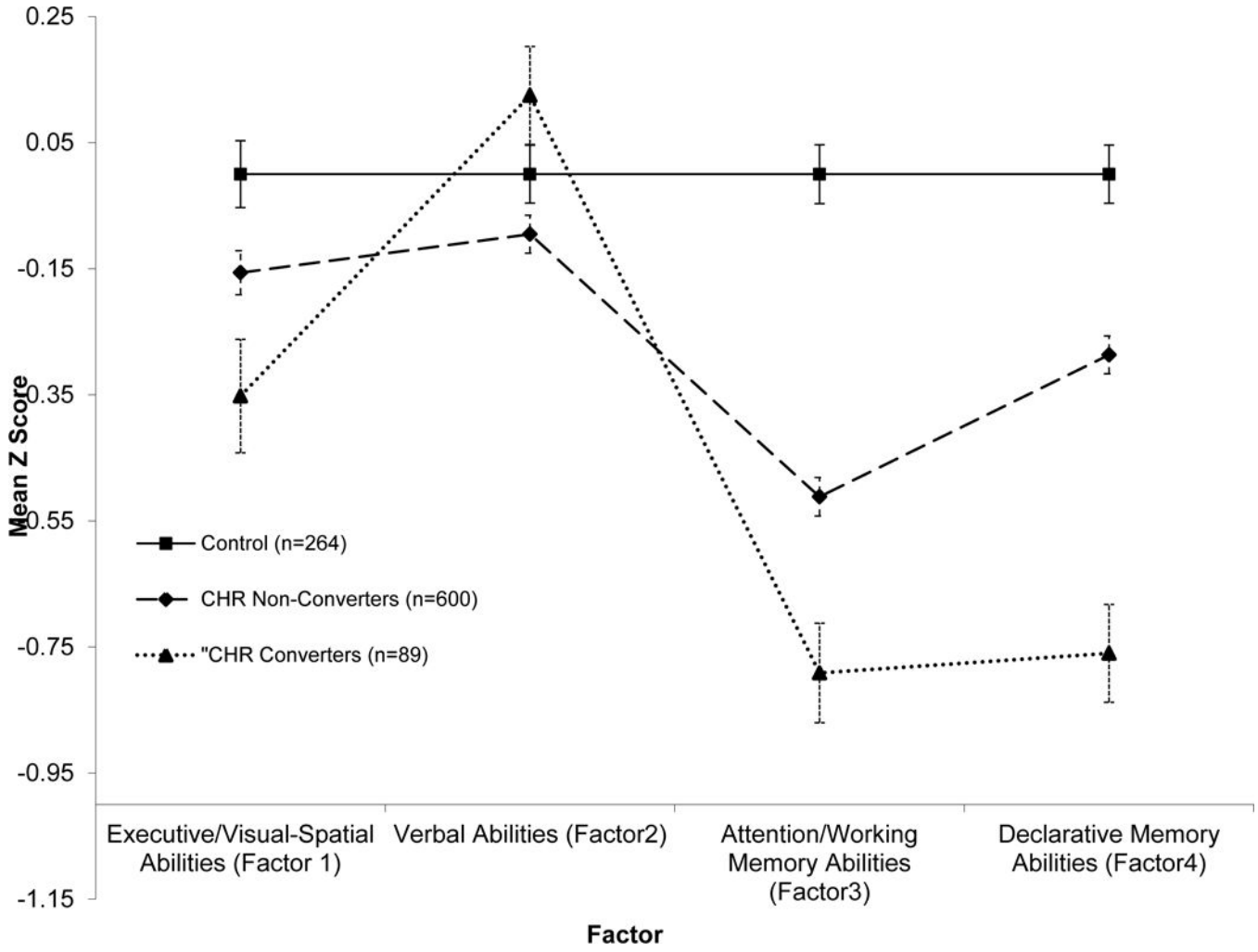
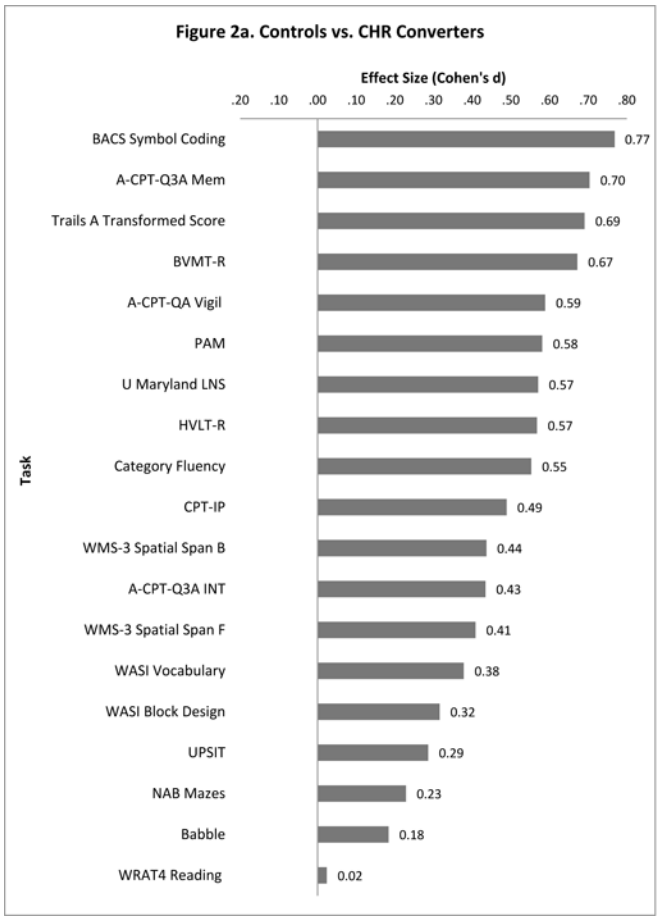


Figure 1.
Neuropsychological Profile By Diagnostic Group Adjusted for Age, Maternal Education and Site



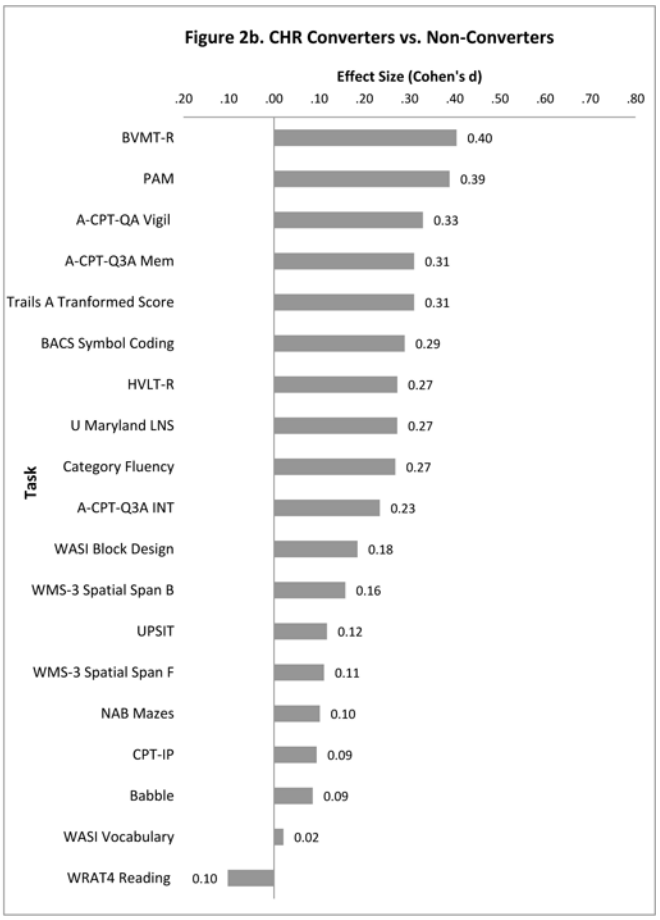


Figure 2.

Effect Sizes (Cohen's d) for Individual Tests Adjusted for Age, Maternal Education and Site, for Controls, Clinical High Risk (CHR) Participants, and CHR Converters

Table 1

Demographic and Clinical Characteristics Between Clinical High-Risk (CHR) Groups and Healthy Control (HC) Participants

	HC (n=264)	CHR (n=689)	CHR-NC (n=600)	CHR+C (n=89)	HC v. CHR	HC v. CHR+C	CHR-C v. CHR-NC
Variable	**Mean (SD)**				**Cohen's d (p)**		
Age in years	19.8 (4.7)	18.5 (4.2)	18.5 (4.3)	18.1 (3.6)	.30 (<.001)	.38 (<.01)	.09 (.41)
Years of education	12.7 (3.6)	11.2 (2.8)	11.3 (2.8)	11.0 (2.5)	.49 (<.001)	.51 (<.001)	.11 (.23)
WASI IQ Estimate	111.0 (14.1)	103.7 (15.3)	103.9 (15.4)	102.1 (14.6)	.49 (<.001)	.63 (<.001)	.12 (.30)
WRAT-4 Reading	108.6 (16.5)	105.1 (16.4)	105.1 (16.6)	105.6 (15.2)	.21 (<.01)	.19 (.13)	−.03 (.78)
Calgary Depression Scale	4.1 (4.8)	4.6 (4.8)	4.5 (4.8)	5.1 (4.8)	−.10 (.20)	−.21 (.12)	−.12 (.31)
Days from Baseline SIPS to Final Follow-up SIPS[1,2]	642.5 (198.7)	540.2 (265.8)	583.9 (236.5)	291.5 (287.2)	.41 (<.001)	1.57 (<.001)	1.20 (<.001)
Number (%)					**χ^2 (p)**		
Alcohol Use[1]					.01 (.91)	.24 (.62)	.28 (.60)
1-2x/week or more	41 (15.8)	104 (15.5)	92 (15.8)	12 (13.6)			
Less than 1–2x/week	218 (84.2)	565 (84.5)	489 (84.2)	76 (86.4)			
Cannabis Use[1]					.39 (.53)	.08 (.77)	.01 (.91)
1–2x/week or more	21(8.1)	63 (9.4)	55 (9.5)	8 (9.1)			
Less than 1–2x/week	238 (91.9)	606 (90.6)	526 (90.5)	80 (90.9)			
Sex					2.7 (.10)	2.06 (.15)	.68 (.41)
Male	137 (51.9)	398 (57.8)	343 (57.2)	55 (61.8)			
Female	127 (48.1)	291 (42.2)	257 (42.8)	34 (38.2)			
Race[1]					.60 (.44)	<.001 (1.0)	.29 (.59)
Not White	119 (45.1)	291 (42.3)	251 (42.0)	40 (45.0)			
White	145 (54.9)	397 (57.6)	348 (58.0)	49 (55.1)			
Hispanic or Latino[1]	45 (17.0)	127 (18.4)	111 (18.5)	16 (18.0)	.25 (.62)	.04 (.84)	.01 (.91)
Father's education[1]					1.2 (.27)	.79 (.37)	.08 (.78)
High school or less	82 (31.1)	232 (33.7)	201 (33.5)	31 (34.8)			
College and more	177 (67.0)	421 (61.1)	368 (61.3)	53 (59.6)			
Mother's education					12.8 (<.001)	1.6 (.19)	1.3 (.25)
High school or less	46 (17.4)	198 (28.7)	177 (29.5)	21 (23.6)			

	HC (n=264)	CHR (n=689)	CHR-NC (n=600)	CHR+C (n=89)	HC v. CHR	HC v. CHR+C	CHR-C v. CHR-NC
Variable	**Mean (SD)**				**Cohen's d (p)**		
College and more	218 (82.6)	491 (71.3)	423 (70.5)	68 (76.4)			
Medication Status[1,3]							
Never Medicated	234 (90.3)	249 (36.3)	222 (37.2)	27 (30.3)	—	—	1.5 (.22)
Currently Medicated	7 (2.7)	287 (41.8)	249 (41.7)	38 (42.7)	—	—	.05 (.83)
Current Antipsychotics	0	139 (20.3)	117 (19.6)	22 (24.7)	—	—	1.3 (.25)
Current Antidepressants	2 (0.8)	176 (25.7)	158 (26.5)	18 (20.2)	—	—	1.5 (.22)
Current Stimulants	2 (0.8)	47 (6.7)	39 (6.5)	8 (9.0)	—	—	.75 (.38)

*p < 0.05,

**p < 0.01,

***p < 0.001.

Categorical variables tested by Chi Square test. Expanded alcohol and cannabis use (6 categories) and parental education (8 categories) were tested with Kolmogorov-Smirnov test with the same results as listed; Continuous variables tested by t-test. Cohen's d used for effect sizes.

[1]Some subjects have missing data.

[2]SIPS is Structured Interview for Prodromal Symptoms,

[3]Some people taking more than one medication. HC = Healthy Control; CHR = Clinical High Risk; CHR+C = CHR Converter; CHR – NC = CHR Non-Converter

Table 2

Factor Analysis of 17 Test Scores[1]

Rotated Factor Matrix after Varimax rotation with Kaiser normalization

	Factor			
	1	2	3	4
WRAT4 Reading	.188	**.769**	.241	.133
WASI Vocabulary	.203	**.747**	.206	.313
WASI Block Design	**.733**	.392	−.015	.273
A-CPT-QA Vigil	.166	.186	**.416**	.210
A-CPT-Q3A Mem	.150	.127	**.505**	.242
A-CPT-Q3A INT	.390	.168	.387	.177
Trails A Transformed Score	**.451**	.148	.328	.103
BACS Symbol Coding	.365	.189	**.514**	.300
HVLT-R	.087	.217	.332	**.570**
WMS-3 Spatial Span F	**.506**	.086	.313	.113
WMS-3 Spatial Span B	**.520**	.107	.280	.228
U Maryland LNS	.275	**.430**	**.418**	.349
NAB Mazes	**.602**	.108	.137	.152
BVMT-R	.371	.158	.163	**.527**
Category Fluency	.179	.212	.303	.391
CPT-IP	.242	**.431**	**.512**	.135
PAM	.178	.102	.131	**.519**

[1]Nineteen tests were administered in the study. The Babble task did not correlate meaningfully with any of the other tasks, and the UPSIT was weakly correlated. Both loaded very weakly in initial Factor Analyses, and thus they were both excluded from the final Factor Analysis.

Bolded numbers are those with factor loadings of .40 or larger

Factor 1: Executive/Visual-Spatial

Factor 2: Verbal

Factor 3: Attention/Working Memory

Factor 4: Declarative Memory

Table 3

Neuropsychological Performance Between Clinical High-Risk (CHR) Groups and Healthy Control (HC) Participants

Neuropsychological Tasks and Factors	HC (n = 264)	CHR (n = 689)	CHR-NC (n=600)	CHR-C (n=89)	HC v. CHR	HC v. CHR-NC	HC v. CHR+C	CHR-NC v. CHR+C
	Mean (SD)				Statistical Significance (P values)			
WRAT4 Reading	60.4 (6.4)	58.2 (7.5)	58.1 (7.7)	58.8 (5.5)	.12	.09	.84	.37
WASI Vocabulary	59.9 (9.5)	54.4 (10.2)	54.4 (10.4)	54.2 (8.9)	**<.001**	**<.001**	**.002**	.85
WASI Block Design	49.1 (14.4)	45.2 (15.6)	45.5 (15.5)	42.8 (15.6)	.03	.08	.01	.10
A-CPT-QA Vigil – % Hits	97.2 (4.9)	94.5 (8.5)	94.8 (8.2)	92.2 (10.2)	**<.001**	**<.001**	**<.001**	.004
A-CPT-Q3A Mem – % Hits	87.6 (10.9)	80.6 (15.2)	81.2 (14.9)	76.7 (16.7)	**<.001**	**<.001**	**<.001**	.006
A-CPT-Q3A INT – % Hits	61.0 (20.8)	54.8 (22.0)	55.4 (21.8)	50.5 (23.2)	**.002**	.007	**<.001**	.04
Trails A transformed score	0.04 (0.0)	0.04 (0.0)	0.04 (0.0)	0.03 (0.0)	**<.001**	**<.001**	**<.001**	.01
BACS Symbol Coding	64.3 (12.9)	56.8 (12.9)	57.3 (13.0)	53.4 (12.0)	**<.001**	**<.001**	**<.001**	.01
HVLT-R	27.4 (4.2)	25.5 (5.1)	25.7 (5.1)	24.4 (5.3)	**<.001**	**<.001**	**<.001**	.02
WMS-3 Spatial Span F	9.3 (2.0)	8.6 (2.1)	8.6 (2.0)	8.3 (2.4)	**<.001**	**<.001**	**.001**	.33
WMS-3 Spatial Span B	8.6 (1.8)	7.9 (2.0)	7.9 (2.0)	7.6 (2.3)	**<.001**	**<.001**	**<.001**	.16
U Maryland LNS	16.3 (3.4)	14.6 (3.7)	14.7 (3.6)	13.8 (4.2)	**<.001**	**<.001**	**<.001**	.02
NAB Mazes	21.0 (4.8)	20.1 (5.1)	20.2 (5.2)	19.7 (4.9)	.05	.09	.06	.37
BVMT-R	27.6 (5.4)	25.4 (6.1)	25.7 (6.0)	23.3 (6.6)	**<.001**	**<.001**	**<.001**	**<.001**
Category Fluency	25.7 (5.7)	23.5 (5.8)	23.7 (5.8)	22.2 (5.8)	**<.001**	**<.001**	**<.001**	.02
CPT-IP – d[1]	2.8 (0.7)	2.4 (0.8)	2.4 (0.8)	2.3 (0.8)	**<.001**	**<.001**	**<.001**	.40
PAM – % Hits	68 (18.0)	63 (18.0)	63 (18.0)	57 (18.0)	**.001**	.009	**<.001**	**.001**
Babble	2.9 (2.4)	3.2 (3.0)	3.2 (3.1)	3.5 (2.2)	.14	.19	.13	.45
UPSIT	34.6 (3.7)	33.5 (4.5)	33.6 (4.5)	33.0 (4.9)	.01	.02	.02	.30
1. Executive/Visual-Spatial	0.13 (0.85)	−0.05 (0.86)	−0.03 (0.85)	−0.20 (0.88)	.01	.04	**.004**	.08
2. Verbal	0.19 (0.79)	−0.07 (0.89)	−0.09 (0.90)	0.07 (0.75)	.36	.20	.30	.05
3. Attention/Working Memory	0.34 (0.66)	−0.13 (0.80)	−0.10 (0.78)	−0.33 (0.92)	**<.001**	**<.001**	**<.001**	**.01**
4. Declarative Memory	0.19 (0.66)	−0.07 (0.77)	−0.03 (0.75)	−0.38 (0.82)	**<.001**	**<.001**	**<.001**	**<.001**

d[1] is d prime, a measure of signal detection; P values reflect age, site, and maternal education corrected models. Bonferroni corrected p values are shown in bold for effect sizes: p <.0026 for individual tasks, <.0125 for factors. Undlerlined Values: Significant at Bonferroni level after controlling for WASI IQ. Shaded Values: Significant at Bonferroni level after controlling for WRAT4 Reading. HC = Healthy Control; CHR = Clinical High Risk; CHR+C = CHR Converter; CHR – NC = CHR Non-Converter