Association of Neurocognition With Transition to Psychosis

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

OBJECTIVES  To identify core neurocognitive dysfunctions associated with the CHR phase, measure the ability of neurocognitive tests to predict transition to psychosis, and determine if neurocognitive deficits are robust or explained by potential confounders.

DESIGN, SETTING, AND PARTICIPANTS  In this case-control study across 8 sites, baseline neurocognitive data were collected from January 2009 to April 2013 in the second phase of the North American Prodrome Longitudinal Study (NAPLS 2). The dates of analysis were August 2015 to August 2016. The setting was a consortium of 8 university-based, outpatient programs studying the psychosis prodrome in North America. Participants were 264 healthy controls (HCs) and 689 CHR individuals, aged 12 to 35 years.

MAIN OUTCOMES AND MEASURES  Neurocognitive associations with transition to psychosis and effects of medication on neurocognition. Nineteen neuropsychological tests and 4 factors derived from factor analysis were used: executive and visuospatial abilities, verbal abilities, attention and working memory abilities, and declarative memory abilities.

RESULTS  This study included 264 HCs (137 male and 127 female) and 689 CHR participants (398 male and 291 female). In the HCs, 145 (54.9%) were white and 119 (45.1%) were not, whereas 397 CHR participants (57.6%) were white and 291 (42.3%) were not. In the HCs, 45 (17%) were of Hispanic origin, whereas 127 CHR participants (18.4%) were of Hispanic origin. The CHR individuals were significantly impaired compared with HCs on attention and working memory abilities and declarative memory abilities. The CHR converters had large deficits in attention and working memory abilities and declarative memory abilities (Cohen d, approximately 0.80) compared with controls and performed significantly worse on these dimensions than nonconverters (Cohen d, 0.28 and 0.48, respectively). These results were not accounted for by general cognitive ability or medications. In Cox proportional hazards regression, time to conversion in those who transitioned to psychosis was significantly predicted by high verbal (premorbid) abilities ($\beta = 0.40$; hazard ratio [HR], 1.48; 95% CI, 1.08-2.04; $P = .02$), impaired declarative memory abilities ($\beta = -0.87$; HR, 0.42; 95% CI, 0.31-0.56; $P < .001$), age ($\beta = -0.10$; HR, 0.90; 95% CI, 0.84-0.97; $P = .003$), site, and a combined score of unusual thought content or delusional ideas and suspiciousness or persecutory ideas items ($\beta = 0.44$; HR, 1.56; 95% CI, 1.36-1.78; $P < .001$).

CONCLUSIONS AND RELEVANCE  Neurocognitive impairment, especially in attention and working memory abilities and declarative memory abilities, is a robust characteristic of CHR participants, especially those who later develop psychosis. Interventions targeting the enhancement of neurocognitive functioning are warranted in this population.
Neurocognitive dysfunction is a hallmark feature of schizophrenia and, to a lesser extent, of other psychoses, a conceptualization originating approximately 100 years ago by Kraepelin and by Bleuler. There is ample evidence of significant but milder impairments during the premorbid phase, greater deficits during the prodromal or clinical high-risk (CHR) period of psychosis, culminating in severe deficits in the first-episode and chronic phases. This transition suggests an evolution of neurocognitive dysfunction in individuals developing psychosis, especially schizophrenia. The CHR period is of 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, obscure the core deficits.

A substantial body of neurocognitive research in CHR populations has been summarized in several meta-analyses. Small to medium effect size (ES) impairments across most neurocognitive domains studied (Cohen’s d range, −0.26 to −0.67) and small to large ES values (Cohen’s d range, −0.35 to −0.84) in those who convert to psychosis (CHR + Cs) have been reported. Verbal memory and processing speed have emerged as strong predictors of psychosis. However, small sample sizes, differing 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, with what is to our knowledge, 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 and working memory. Evidence of severe deficits in declarative memory has more recently emerged in first-episode and CHR samples. Olfactory identification deficits also have been touted as a possible risk factor, and processing speed and general cognitive ability have been shown to be robustly impaired in persons who later develop schizophrenia. 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. This finding is of particular relevance for those individuals who transition to psychotic disorders because it provides critical information about the nature of neurocognition in the earliest phase of psychosis. We hypothesized that the CHR + C group herein 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. Such medications could improve or impair cognition idiosyncratically. Prior CHR neurocognitive studies have not systematically addressed medication status. The large sample in the NAPLS 2 enabled an investigation of a sizable subgroup of CHR + Cs who have never been medicated, thus helping identify neurocognitive function.

Fourth, we explored the potential usefulness of neurocognitive dysfunction for its contribution to transition to psychosis. While it is unlikely that neurocognitive measures will be predictive by themselves of conversion to psychosis, in part because they are impaired in many neuropsychiatric disorders, knowledge of their relative sensitivities in combination with clinical features may help in the real-world prediction of psychosis or disability.

Methods
Participants
In this case-control study across 8 sites, baseline neurocognitive functioning data were collected from January 2009 to April 2013 in the NAPLS 2. The dates of the analysis were August 2015 to August 2016. The NAPLS 2 is a consortium of 8 programs studying the psychosis prodrome in North America, as in the NAPLS 1. The methods and clinical features of the NAPLS 2 are detailed elsewhere. From a sample of 279 healthy controls (HCS) and 764 CHR individuals ranging in age from 12 to 35 years, 264 HCs and 689 CHR individuals provided baseline neurocognitive data. The study protocols were approved by the ethical review boards or human studies committees of all sites, including Beth Israel Deaconess Medical Center, Boston, Massachusetts; Emory University, Atlanta, Georgia; University of Calgary, Alberta, Canada; University of California, Los Angeles; University of California, San Diego; The University of North Carolina at Chapel Hill; Yale University, New Haven, Connecticut; and Zucker Hillside Hospital, Queens, New York. All procedures comply with the ethical standards of the relevant committees on human experimentation and with the Declaration of Helsinki, as revised in 2008. All participants provided written informed consent.

Inclusion and Exclusion Criteria
The CHR sample met the Criteria of Prodromal Syndromes (COPS), based on the Structured Interview for Prodromal Syndromes (SIPS), or if younger than 19 years, criteria for...
schizotypal personality disorder (n = 21) or COPS. Individuals were excluded if they had a lifetime Axis I psychotic disorder, estimated IQs less than 70 on both measures of IQ, a central nervous system disorder, or DSM-IV substance dependence in the past 6 months. Other nonpsychotic DSM-IV disorders were not exclusionary (eg, substance abuse disorder and major depression) unless they clearly caused or better accounted for prodromal symptoms. Antipsychotic medication use was allowed, provided there was clear evidence that psychotic symptoms were not present when the medication was started. The HCs could not meet criteria for any prodromal syndrome, report 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 Structured Clinical Interview for DSM was used to rule out psychosis and to identify DSM-IV Axis I or cluster A personality disorders. For some analyses, we used a rescaled sum of the unusual thought content or delusional ideas and suspiciousness or persecutory ideas items from the SIPS-positive symptoms criteria. Transition to psychosis was determined by meeting the SIPS Presence of Psychotic Symptoms criteria. Assessments were at baseline, 12 months, and 24 months. Current alcohol and cannabis use was assessed with the Alcohol and Drug Use Scale. The Calgary Depression Scale for Schizophrenia and the Structured Clinical Interview for DSM was used to rule out 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 tests included the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB), the Wechsler Abbreviated Scale of Intelligence (WASI) for general intellectual ability, and the Wide Range Achievement Test 4 (WRAT-4) reading task to estimate premorbid ability. Experimental measures included the Babble test (for auditory perception), the University of Pennsylvania Smell Identification Test for olfactory identification, a visual and verbal Paired Associate Memory test, and 3 Auditory Continuous Performance Tests. One summary score from each test was chosen a priori as the best estimate of the function of that test. We factor analyzed the test battery to reduce the number of variables. The eText and eTable 1 in the Supplement provide extensive detail on the battery.

**Statistical Analysis**
We examined missing data before implementing multiple imputation. From a sample of 1043 individuals, 953 (91.4%) received baseline neurocognitive testing. Of the CHR sample of 93 individuals who transitioned to psychosis during the 2-year follow-up, 89 (95.7%) received testing. Among the tested sample of 953 individuals, 634 scores (3.5%) from 18,107 total neuropsychological data points were missing. After multiple imputation, we conducted a factor analysis of the 19 neuropsychological variables (eText in the Supplement). All analyses were performed with statistical software (SPSS, version 23.0; IBM Corporation).

Study groups were HCs, nonconverters (CHR − NCs), and CHR + Cs. We used t tests, Kolmogorov-Smirnov z tests, and χ² tests to assess demographic comparability. Because of differences in age and maternal educational level, we controlled for both using multivariate analysis of variance (MANOVA) and controlled for site as a random-effects factor with a linear mixed model. We covaried for estimated current and premorbid IQs to test the role of general intellectual ability in cognitive dysfunctions. We compared medicated vs unmedicated groups of HCs vs CHR + Cs and of CHR + Cs vs CHR − NCs 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 educational level from all neurocognitive indexes (4 factors derived from factor analysis). Area under the curve was calculated by the receiver operating characteristic curve program in SPSS. Prediction of conversion to psychosis and time to conversion was assessed by logistic and Cox proportional hazards regressions. Covariates were selected based on similar prediction analyses conducted in the first phase of the NAPLS and the second phase 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 and then subjected to backward selection with a criterion P = .10. Candidates who survived at P ≤ .05 within domains were entered into an omnibus model. Effect sizes were calculated with Cohen d. Bonferroni-corrected significance for the mean comparisons was set for individual tests at P < .003 (0.05 divided by 19) and for factors at P < .013 (0.05 divided by 4).

**Results**

**Demographics**
In this naturalistic, observational study, there were 137 male and 127 female HCs and 398 male and 291 female CHR individuals (Table 1 and Table 2). The HCs were significantly older and had significantly more education, and HC mothers also had significantly more education. The groups did not differ in sex or racial distribution, paternal education, or ethnicity. There were no significant differences on any demographic characteristics between CHR − NCs and CHR + Cs.

**Clinical Characteristics**
The groups did not significantly differ in frequency of alcohol or cannabis abuse or current depression (Tables 1 and 2). 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 group, reflecting time to conversion and attrition. The CHR − NCs and CHC + Cs were taking a variety of medications, including antipsychotics, antidepressants, stimulants, and others, but there were no significant differences in rates between the 2 CHR groups.

Table 1. Demographic and Clinical Characteristics in Clinical High-Risk (CHR) Groups and Healthy Controls (HCs)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>HCs (n = 264)</th>
<th>CHRs (n = 689)</th>
<th>CHR − NCs (n = 600)</th>
<th>CHR + Cs (n = 89)</th>
<th>HCs vs CHRs Cohen d</th>
<th>P Value</th>
<th>HCs vs CHR + Cs Cohen d</th>
<th>P Value</th>
<th>CHR + Cs vs CHR − NCs Cohen d</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>19.8 (4.7)</td>
<td>18.5 (4.2)</td>
<td>18.5 (4.3)</td>
<td>18.1 (3.6)</td>
<td>0.30</td>
<td>&lt;.001</td>
<td>0.38</td>
<td>&lt;.01</td>
<td>0.09</td>
<td>.41</td>
</tr>
<tr>
<td>Years of education</td>
<td>12.7 (3.6)</td>
<td>11.2 (2.8)</td>
<td>11.3 (2.8)</td>
<td>11.0 (2.5)</td>
<td>0.49</td>
<td>&lt;.001</td>
<td>0.51</td>
<td>&lt;.001</td>
<td>0.11</td>
<td>.23</td>
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<tr>
<td>WASI IQ score</td>
<td>111.0 (14.1)</td>
<td>103.7 (15.3)</td>
<td>103.9 (15.4)</td>
<td>102.1 (14.6)</td>
<td>0.49</td>
<td>&lt;.001</td>
<td>0.63</td>
<td>&lt;.001</td>
<td>0.12</td>
<td>.30</td>
</tr>
<tr>
<td>WRAT-4 reading</td>
<td>108.6 (16.5)</td>
<td>105.1 (16.4)</td>
<td>105.1 (16.6)</td>
<td>105.6 (15.2)</td>
<td>0.21</td>
<td>&lt;.01</td>
<td>0.19</td>
<td>.13</td>
<td>−0.03</td>
<td>.78</td>
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<tr>
<td>Calgary Depression Scale</td>
<td>4.1 (4.8)</td>
<td>4.6 (4.8)</td>
<td>4.5 (4.8)</td>
<td>5.1 (4.8)</td>
<td>−0.10</td>
<td>.20</td>
<td>−0.21</td>
<td>.12</td>
<td>−0.12</td>
<td>.31</td>
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<tr>
<td>Days from baseline SIPS to final follow-up SIPSb</td>
<td>642.5 (198.7)</td>
<td>540.2 (265.8)</td>
<td>583.9 (236.5)</td>
<td>291.5 (287.2)</td>
<td>0.41</td>
<td>&lt;.001</td>
<td>1.57</td>
<td>&lt;.001</td>
<td>1.20</td>
<td>&lt;.001</td>
</tr>
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</table>

Table 2. Additional Demographic and Clinical Characteristics in Clinical High-Risk (CHR) Groups and Healthy Controls (HCs)*

<table>
<thead>
<tr>
<th>Variable</th>
<th>HCs (n = 264)</th>
<th>CHRs (n = 689)</th>
<th>CHR − NCs (n = 600)</th>
<th>CHR + Cs (n = 89)</th>
<th>χ² Statistic</th>
<th>P Value</th>
<th>χ² Statistic</th>
<th>P Value</th>
<th>χ² Statistic</th>
<th>P Value</th>
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<td>Weekly instances of alcohol useb</td>
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<tr>
<td>≥1-2</td>
<td>41/259 (15.8)</td>
<td>104/669 (15.5)</td>
<td>92/581 (15.8)</td>
<td>12/88 (13.6)</td>
<td>0.01</td>
<td>.91</td>
<td>0.24</td>
<td>.62</td>
<td>0.28</td>
<td>.60</td>
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<tr>
<td>&lt;1-2</td>
<td>218/259 (84.2)</td>
<td>565/669 (84.5)</td>
<td>489/581 (84.2)</td>
<td>76/88 (86.4)</td>
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<tr>
<td>Weekly instances of cannabis useb</td>
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<tr>
<td>≥1-2</td>
<td>21/259 (8.1)</td>
<td>63/669 (9.4)</td>
<td>55/581 (9.5)</td>
<td>8/88 (9.1)</td>
<td>0.39</td>
<td>.53</td>
<td>0.08</td>
<td>.77</td>
<td>0.01</td>
<td>.91</td>
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<td>&lt;1-2</td>
<td>238/259 (91.9)</td>
<td>606/669 (90.6)</td>
<td>526/581 (90.5)</td>
<td>80/88 (90.9)</td>
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<tr>
<td>Male</td>
<td>137/264 (51.9)</td>
<td>398/669 (57.8)</td>
<td>343/600 (57.2)</td>
<td>55/89 (61.8)</td>
<td>2.70</td>
<td>.10</td>
<td>2.06</td>
<td>.15</td>
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<td>.41</td>
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<td>Female</td>
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<td>291/689 (42.2)</td>
<td>257/600 (42.8)</td>
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<td>Not white</td>
<td>119/264 (45.1)</td>
<td>291/689 (42.2)</td>
<td>251/600 (41.8)</td>
<td>40/89 (44.9)</td>
<td>0.60</td>
<td>.44</td>
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<td>.99</td>
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<td>.59</td>
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<td>45/264 (17.0)</td>
<td>127/689 (18.4)</td>
<td>111/600 (18.5)</td>
<td>16/89 (18.0)</td>
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<td>.62</td>
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<td>.84</td>
<td>.01</td>
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<td>High school or less</td>
<td>82/264 (31.1)</td>
<td>232/689 (33.7)</td>
<td>201/600 (33.5)</td>
<td>31/89 (34.8)</td>
<td>1.20</td>
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<td>0.79</td>
<td>.37</td>
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<td>.78</td>
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<td>College or more</td>
<td>177/264 (67.0)</td>
<td>421/689 (61.1)</td>
<td>368/600 (61.3)</td>
<td>53/89 (59.6)</td>
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<td>Maternal educationb</td>
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<td>High school or less</td>
<td>46/264 (17.4)</td>
<td>198/689 (28.7)</td>
<td>177/600 (29.5)</td>
<td>21/89 (23.6)</td>
<td>12.80</td>
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<td>.19</td>
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<td>.25</td>
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<td>College or more</td>
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<td>68/89 (76.4)</td>
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<td>Medication statusc</td>
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<tr>
<td>Never medicated</td>
<td>234/264 (88.6)</td>
<td>249/689 (36.1)</td>
<td>222/600 (37.0)</td>
<td>27/89 (30.3)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>.22</td>
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<td>Currently medicated</td>
<td>7/264 (2.7)</td>
<td>287/689 (41.5)</td>
<td>249/600 (41.5)</td>
<td>38/89 (42.7)</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.05</td>
<td>.83</td>
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<td>Current antipsychotics</td>
<td>0/264</td>
<td>139/689 (20.1)</td>
<td>117/600 (19.5)</td>
<td>22/89 (24.7)</td>
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<td>NA</td>
<td>1.30</td>
<td>.25</td>
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<td>Current antidepressants</td>
<td>2/264 (0.8)</td>
<td>176/689 (25.5)</td>
<td>158/600 (26.3)</td>
<td>18/89 (20.2)</td>
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<td>NA</td>
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<td>.22</td>
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<td>Current stimulants</td>
<td>2/264 (0.8)</td>
<td>47/689 (6.8)</td>
<td>39/600 (6.5)</td>
<td>8/89 (9.0)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.75</td>
<td>.38</td>
</tr>
</tbody>
</table>

Abbreviations: CHR + Cs, CHR converters to psychosis; CHR − NCs, CHR nonconverters; SIPS, Structured Interview for Prodromal Syndromes; WASI, Wechsler Abbreviated Scale of Intelligence; WRAT-4, Wide Range Achievement Test 4.

* Data are presented as mean (SD).

b Some individuals have missing data.

* Some individuals were taking more than 1 medication.
Factor Analysis
The eText in the Supplement explains factor selection. The 4 factors examined were executive and visuospatial abilities, verbal abilities, attention and working memory abilities, and declarative memory abilities (Table 3). Two tests laden with sensory-perceptual processes (olfaction and audition) had very low (University of Pennsylvania Smell Identification Test) or negligible (Babble test) loadings initially and were dropped from factor analysis. They were analyzed with the other individual tests. The bivariate correlations among tests are summarized in eTable 2 in the Supplement.

Neurocognition Group Comparisons

HCs vs CHR Individuals
The CHR group performed significantly worse than HCs on all 19 neuropsychological tests combined (MANOVA $F_{19,9,913} = 6.71, P < .001$), on the 4 factors combined ($F_{4,948} = 24.18, P < .001$), and, after controlling for age, site, and maternal educational level, on 2 of 4 factors (attention and working memory abilities $F_{1,948} = 56.52, P < .001$ and declarative memory abilities $F_{1,948} = 22.83, P < .001$) and on 14 of 19 individual neuropsychological tests. The largest ES (attention and working memory abilities) was of moderate magnitude (Table 4). The mean ES across the 19 neuropsychological tests was small (Cohen $d = 0.30$). Model-corrected profiles are shown in Figure 1. Controlling separately for WASI IQ score and WRAT-4 reading, the attention and working memory abilities and the declarative memory abilities factors remained significantly different between groups. The differences between HCs and CHR individuals remained significant on 12 of 14 individual tests after covarying WRAT-4 reading. Covarying WASI IQ score yielded fewer significant differences.

HCs vs CHR + Cs
The CHR + Cs performed significantly worse than the HCs ($F_{19,9,933} = 5.95, P < .001$) using all tests. The 4-factor MANOVA ($F_{4,948} = 22.82, P < .001$) showed significant differences. In models controlling for age, site, and maternal educational level, CHR + Cs performed significantly worse on 3 of 4 factors, namely, executive and visuospatial abilities (Cohen $d = 0.36$), attention and working memory abilities (Cohen $d = 0.80$), and declarative memory abilities (Cohen $d = 0.77$). The mean ES across the 19 neuropsychological tests was Cohen $d = 0.47$. Effect sizes that are model adjusted are shown in Figure 2. The CHR + Cs performed significantly worse on verbal abilities, attention and working memory abilities, and declarative memory abilities and on 12 of 14 individual tests after controlling for WRAT-4 reading. They showed fewer significant test differences after covarying WASI IQ score.

Impairments were comparable between 252 currently unmedicated HCs and 51 unmedicated CHR + Cs, with 38 currently medicated CHR + Cs, and between 236 never-medicated HCs and 29 never-medicated CHR + Cs. The smaller group of CHR + Cs taking antipsychotic medications was significantly impaired on attention and working memory abilities and on declarative memory abilities compared with HCs. Moreover, there were no significant cognitive differences between currently unmedicated CHR + Cs vs medicated CHR + Cs, between never-medicated CHR + Cs vs medicated CHR + Cs, or between CHR + Cs taking vs not taking antipsychotic medications (eText, eTable 3, and eFigure in the Supplement).

CHR + Cs vs CHR − NCs
The CHR + C group performed significantly worse than the CHR − NC group (MANOVA $F_{19,669} = 1.90, P = .01$ and 4-factor MANOVA $F_{4,684} = 6.51, P < .001$), specifically on attention and working memory abilities (Cohen $d = 0.28$) and on declarative memory abilities (Cohen $d = 0.48$) after controlling for age, site, and maternal educational level (Table 4). The CHR + Cs performed significantly worse in mixed linear model contrasts only on the Brief Visuospatial Memory Test–Revised (BVMT-R) (Cohen $d = 0.40$) and Paired Associate Memory (PAM) test (Cohen $d = 0.39$). The mean ES across the 19 neuropsychological tests was Cohen $d = 0.20$. After WASI IQ score and WRAT-4 reading were...
Table 4. Neuropsychological Performance in Clinical High-Risk (CHR) Groups and Healthy Controls (HCs)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HCs (n = 264)</th>
<th>CHRs (n = 689)</th>
<th>CHR − NCs (n = 600)</th>
<th>CHR + Cs (n = 89)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>WRAT-4 reading</td>
<td>60.4 (6.4)</td>
<td>58.2 (7.5)</td>
<td>58.1 (7.7)</td>
<td>58.8 (5.5)</td>
<td>.12 .09 .84 .37</td>
</tr>
<tr>
<td>WASI vocabulary</td>
<td>59.9 (9.5)</td>
<td>54.4 (10.2)</td>
<td>54.4 (10.4)</td>
<td>54.2 (8.9)</td>
<td>&lt;.001&lt;sup&gt;b,c&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c&lt;/sup&gt; .002&lt;sup&gt;d&lt;/sup&gt; .85</td>
</tr>
<tr>
<td>WASI block design</td>
<td>49.1 (14.4)</td>
<td>45.2 (15.6)</td>
<td>45.5 (15.5)</td>
<td>42.8 (15.6)</td>
<td>.03 .08 .01 .10</td>
</tr>
<tr>
<td>ACPT-QA vigilance, % hits</td>
<td>97.2 (4.9)</td>
<td>94.5 (8.5)</td>
<td>94.8 (8.2)</td>
<td>92.2 (10.2)</td>
<td>&lt;.001&lt;sup&gt;b,c&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c,d&lt;/sup&gt; .004</td>
</tr>
<tr>
<td>ACPT-QA memory, % hits</td>
<td>87.6 (10.9)</td>
<td>80.6 (15.2)</td>
<td>81.2 (14.9)</td>
<td>76.7 (16.7)</td>
<td>&lt;.001&lt;sup&gt;b,c,d&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c,d&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c,d&lt;/sup&gt; .006</td>
</tr>
<tr>
<td>ACPT-QA working memory and interference, % hits</td>
<td>61.0 (20.8)</td>
<td>54.8 (22.0)</td>
<td>55.4 (21.8)</td>
<td>50.5 (23.2)</td>
<td>.002&lt;sup&gt;a&lt;/sup&gt; .007 &lt;.001&lt;sup&gt;b,c,d&lt;/sup&gt; .04</td>
</tr>
<tr>
<td>Trail Making A</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>&lt;.001&lt;sup&gt;b,c,d&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c,d&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c,d&lt;/sup&gt; .01</td>
</tr>
<tr>
<td>BACS symbol coding</td>
<td>64.3 (12.9)</td>
<td>56.8 (12.9)</td>
<td>57.3 (13.0)</td>
<td>53.4 (12.0)</td>
<td>&lt;.001&lt;sup&gt;b,c&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c&lt;/sup&gt; .01</td>
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<tr>
<td>HVLT-R</td>
<td>27.4 (4.2)</td>
<td>25.5 (5.1)</td>
<td>25.7 (5.1)</td>
<td>24.4 (5.3)</td>
<td>&lt;.001&lt;sup&gt;b,c&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c&lt;/sup&gt; .02</td>
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<tr>
<td>WMS-3 spatial span B</td>
<td>8.6 (1.8)</td>
<td>7.9 (2.0)</td>
<td>7.9 (2.0)</td>
<td>7.6 (2.3)</td>
<td>&lt;.001&lt;sup&gt;b,c&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c&lt;/sup&gt; .001&lt;sup&gt;c&lt;/sup&gt; .16</td>
</tr>
<tr>
<td>University of Maryland LNS</td>
<td>16.3 (3.4)</td>
<td>14.6 (3.7)</td>
<td>14.7 (3.6)</td>
<td>13.8 (4.2)</td>
<td>&lt;.001&lt;sup&gt;b,c&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c&lt;/sup&gt; .02</td>
</tr>
<tr>
<td>NAB mazes</td>
<td>21.0 (4.8)</td>
<td>20.1 (5.1)</td>
<td>20.2 (5.2)</td>
<td>19.7 (4.9)</td>
<td>.05 .09 .06 .37</td>
</tr>
<tr>
<td>BVMTR</td>
<td>27.6 (5.4)</td>
<td>25.4 (6.1)</td>
<td>25.7 (6.0)</td>
<td>23.3 (6.6)</td>
<td>&lt;.001&lt;sup&gt;b,c&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c&lt;/sup,d&lt;sup&gt;e&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c,d&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Category Fluency</td>
<td>25.7 (5.7)</td>
<td>23.5 (5.8)</td>
<td>23.7 (5.8)</td>
<td>22.5 (5.8)</td>
<td>&lt;.001&lt;sup&gt;b,c&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c&lt;/sup&gt; .02</td>
</tr>
<tr>
<td>CPT-IP d’ signal detection</td>
<td>2.8 (0.7)</td>
<td>2.4 (0.8)</td>
<td>2.4 (0.8)</td>
<td>2.3 (0.8)</td>
<td>&lt;.001&lt;sup&gt;b,c&lt;/sup,d&lt;sup&gt;e&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c&lt;/sup,d&lt;sup&gt;e&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c&lt;/sup&gt; .40</td>
</tr>
<tr>
<td>PAM, % hits</td>
<td>68.0 (18.0)</td>
<td>63.0 (18.0)</td>
<td>63.0 (18.0)</td>
<td>57.0 (18.0)</td>
<td>.001&lt;sup&gt;d&lt;/sup&gt; .009 &lt;.001&lt;sup&gt;b,c&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Babble test</td>
<td>2.9 (2.4)</td>
<td>3.2 (3.0)</td>
<td>3.2 (3.1)</td>
<td>3.5 (2.2)</td>
<td>.14 .19 .13 .45</td>
</tr>
<tr>
<td>University of Pennsylvania Smell Identification Test</td>
<td>34.6 (3.7)</td>
<td>33.5 (4.5)</td>
<td>33.6 (4.5)</td>
<td>33.0 (4.9)</td>
<td>.01 .02 .02 .30</td>
</tr>
<tr>
<td>Executive and visuospatial abilities</td>
<td>0.13 (0.85)</td>
<td>−0.05 (0.86)</td>
<td>−0.03 (0.85)</td>
<td>−0.20 (0.88)</td>
<td>.01 .04 .004&lt;sup&gt;c&lt;/sup&gt; .08</td>
</tr>
<tr>
<td>Verbal abilities</td>
<td>0.19 (0.79)</td>
<td>0.07 (0.89)</td>
<td>0.09 (0.90)</td>
<td>0.07 (0.75)</td>
<td>.36&lt;sup&gt;d&lt;/sup&gt; .20&lt;sup&gt;d&lt;/sup&gt; .30&lt;sup&gt;d&lt;/sup&gt; .05&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Attention and working memory abilities</td>
<td>0.34 (0.66)</td>
<td>−0.13 (0.80)</td>
<td>−0.10 (0.78)</td>
<td>−0.33 (0.92)</td>
<td>&lt;.001&lt;sup&gt;b,c,d&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c,d&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c,d&lt;/sup&gt; .01&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Declarative memory abilities</td>
<td>0.19 (0.66)</td>
<td>−0.07 (0.77)</td>
<td>−0.03 (0.75)</td>
<td>−0.38 (0.82)</td>
<td>&lt;.001&lt;sup&gt;b,c&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c,d&lt;/sup&gt; &lt;.001&lt;sup&gt;b,c,d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: ACPT, Auditory Continuous Performance Test; AQ, Attention Quotient; BACS, Brief Assessment of Cognition in Schizophrenia symbols boiling test; BVMTR, Brief Visuospatial Memory Test-Revised; CHR + Cs, CHR converters to psychosis; CHR − NCs, CHR nonconverters; CPT-IP, Continuous Performance Test-Identical Pairs; HVLT-R, Hopkins Verbal Learning Test-Revised; LNS, Letter Number Span; NAB, Neuropsychological Assessment Battery mazes; PAM, Paired Associate Memory; WASI, Wechsler Abbreviated Scale of Intelligence; WMS-3, Wechsler Memory Scale-Third Edition spatial span; WRAT-4, Wide Range Achievement Test 4.

* P values are adjusted for age, site, and maternal education.  
<sup>a</sup> Values are significant at the Bonferroni level after controlling for WRAT-4 reading.  
<sup>b</sup> Bonferroni-corrected significance for the mean comparisons was set for individual tests at P < .003 and for factors at P < .013.  
<sup>c</sup> Values are significant at the Bonferroni level after controlling for WASI IQ score.

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

![Graph showing neuropsychological profile](jamapsychiatry.com)
Figure 2. Effect Sizes (Cohen $d$) for Individual Tests Adjusted for Age, Site, and Maternal Education for Clinical High-Risk Converters to Psychosis (CHR + Cs), Clinical High-Risk Nonconverters (CHR − NCs), and Healthy Controls (HCs)

Effect sizes are rank ordered from largest to smallest. ACPT indicates Auditory Continuous Performance Test (QA are simply the letters; Q3A, the number of letters between an “A” and a “Q”); BACS, Brief Assessment of Cognition in Schizophrenia symbol coding; BVMT-R, Brief Visuospatial Memory Test–Revised; CPT-IP, Continuous Performance Test–Identical Pairs; HVLT-R, Hopkins Verbal Learning Test–Revised; LNS, Letter Number Span; NAB, Neuropsychological Assessment Battery mazes; PAM, Paired Associate Memory; UPSIT, University of Pennsylvania Smell Identification Test; WASI, Wechsler Abbreviated Scale of Intelligence; WMS-3, Wechsler Memory Scale–Third Edition spatial span; and WRAT-4, Wide Range Achievement Test 4.

95% CI, 0.05-0.54; $P = .003$), and WRAT-4 reading ($β = 0.05$; HR, 1.05; 95% CI, 1.01-1.10, $P = .009$). Declarative memory abilities had the highest area under the curve at 0.568, followed by attention and working memory abilities with an area under the curve of 0.568. The highest areas under the curve for declarative memory abilities tests were the PAM test at 0.607, BVMT-R at 0.604, and HVLT-R at 0.576, and the highest areas under the curve for attention and working memory abilities were Brief Assessment of Cognition in Schizophrenia (BACS) symbol coding at 0.584, Trail Making A at 0.582, ACPT working memory at 0.579, and ACPT vigilance at 0.568 (eTable 4 in the Supplement).

Discussion

In the largest and most detailed study of CHR prodromal cases to date, using a multisite, case-control design and standardized assessments, we demonstrated that CHR individuals were significantly impaired in virtually all neurocognitive dimensions compared with HCs, and this finding could not be accounted for by premorbid or current general cognitive ability, current depression, medication use, or alcohol or cannabis abuse. Effect sizes compared with HCs for attention and working memory abilities and for declarative memory abilities were large (Cohen $d$, approximately 0.80) for CHR + Cs. Compared with CHR − NCs, CHR + Cs were significantly impaired in attention and working memory abilities and in declarative memory abilities, with the latter significantly predicting conversion to psychosis and time to event in concert with a rescaled sum of the unusual thought content or delusional ideas and suspiciousness or persecutory ideas items from the SIPS. Comparable impairments were observed in never-medicated and currently unmedicated CHR − NCs and CHR + Cs. These data demonstrate the sensitivity of neurocognitive function as a component risk marker for psychosis.

Our findings support theoretical models hypothesizing attention and working memory abilities impairments and, even more strongly, impaired declarative memory abilities as central to the CHR stage.21,22 The results are consistent with the NAPLS 1, in which declarative memory abilities had the largest ES decrement and approximately the same magnitude in CHR + Cs.22 The distinct profile of performance across domains, especially in CHR + Cs, suggests that, at the incipient psychotic phase, specific forms of neurocognition are affected and are predictive of later psychosis.

Among CHR participants, there was considerable variability in neurocognitive performance. Impairments of CHR − NCs (mean Cohen $d$, 0.30) were on the order of other psychiatric disorders in young people, such as attention-deficit/hyperactivity disorder.65 Impairments in the CHR + Cs (mean Cohen $d$, 0.47) were approximately 56.7% larger, although smaller than those observed in first-episode
schizophrenia16 (eTable 5 in the Supplement). Investigations of individual variability and longitudinal analyses are needed to identify how profile and severity differ according to comorbid disorders, final diagnoses (eg, schizophrenia vs bipolar psychosis), and preconversion and postconversion.

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

There were several other potentially important observations. The unexpectedly higher verbal score (reflecting WRAT-4 reading) that was retained in logistic and Cox proportional hazards regressions in concert with impaired declarative memory abilities was not a significant predictor in univariate comparisons. This pattern of high verbal premorbid ability and impaired memory, coupled with the unusual thought content or delusional ideas and suspiciousness or persecutory ideas items composite, appears to be a pernicious combination predicting conversion and needs replication. Also important, the BVMT-R (a visual-memory test) showed comparably large impairments as the 2 verbal memory tasks, highlighting that deficits of declarative memory abilities in CHR are not solely verbal and that declarative memory abilities 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 2 tests selected from a literature review18 before these neuropsychological analyses, the NAPLS 2 investigators found that the HVLT-R and the Brief Assessment of Cognition in Schizophrenia symbol coding tests added modest but significant independent predictive power above the clinical measures in a risk calculator algorithm for psychosis conversion.45 and this finding was replicated in an independent non-NAPLS 2 sample.67 Similar results have been observed in other studies.24,40,41 In the present study, we showed that other tests, including the BVMT-R, PAM test, and ACPT vigilance test, added significant independent variance beyond the unusual thought content or delusional ideas and suspiciousness or persecutory ideas items symptoms, augmenting the importance of neurocognitive markers.

Our study has strengths and limitations. Because of its large sample from diverse geographical areas, extensive neurocognitive coverage, complete neurocognitive data set, and large never-medicated sample, the NAPLS 2 allowed for a strong confirmation of neurocognitive hypotheses. The NAPLS 2 built on and improved the NAPLS 1 assessment, confirming and expanding prior results (eTable 5 in the Supplement). This broad range of measures increased the scope of what is known about CHR neurocognition.

**Limitations**

Limitations include the fact that most of these tests and factors are complex. Therefore, while declarative memory abilities are 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 the Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia (CENTRACS) Consortium,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. Attention and working memory abilities and declarative memory abilities are important targets for early cognitive, enhancing interventions in this population.69–73
Critical revision of the manuscript for important intellectual content: Seidman, Shapiro, Stone, Woodside, Comblatt, Addington, Bearden, Cadenhead, Cannon, Mathalon, Perkins, Tsuang, Walker, Woods.

Statistical analysis: Seidman, Shapiro, Woodberry, Ronzio, Mathalon.


Administrative, technical, or material support: Seidman, Shapiro, Stone, Comblatt, Bearden, McGlashan, Perkins, Walker, Woods.

Study supervision: Seidman, Shapiro, Stone, Woodberry, Comblatt, Addington, Bearden, Cadenhead, Cannon, McGlashan, Perkins, Tsuang, Woods.

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