

# Neuropsychology of the Prodrome to Psychosis in the NAPLS Consortium

## Relationship to Family History and Conversion to Psychosis

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**Context:** Early detection and prospective evaluation of clinical high-risk (CHR) individuals who may develop schizophrenia or other psychotic disorders is critical for predicting psychosis onset and for testing preventive interventions.

**Objectives:** To elucidate the neuropsychology of the CHR syndrome, to determine the association of neuropsychological function with conversion to psychosis and family history of psychosis, and to examine whether baseline neuropsychological functioning predicts subsequent psychosis.

**Design:** Longitudinal study with 2½ years of follow-up.

**Setting:** Eight centers participating in the North American Prodrome Longitudinal Study.

**Participants:** Three hundred four prospectively identified CHR individuals meeting Structured Interview for Prodromal Syndromes criteria, 52 non-CHR persons with a family history of psychosis in first- or second-degree relatives (family high-risk group), and 193 normal controls with neither a family history of psychosis nor a CHR syndrome, all of whom underwent baseline neuropsychological evaluations.

**Main Outcome Measures:** A neurocognitive composite score, 8 individual neuropsychological measures, an IQ estimate, and high-risk status.

**Results:** Global (“composite”) neuropsychological functioning was comparably impaired in the CHR and family high-risk groups compared with controls, but profiles differed significantly between groups. Neuropsychological functioning in the CHR group was significantly lower in persons who progressed to psychosis than in those who did not and was worst in the subgroup with a family history of psychosis. Tests of processing speed and verbal learning and memory were most sensitive in discriminating CHR individuals from controls, although reductions were less severe than in established schizophrenia. Neuropsychological functioning did not contribute uniquely to the prediction of psychosis beyond clinical criteria, but worse verbal memory predicted more rapid conversion.

**Conclusions:** These findings document that CHR individuals have significant neuropsychological difficulties, particularly those who later develop psychosis. This dysfunction is generally of moderate severity but less than in first-episode schizophrenia, suggesting that further decline may occur after baseline CHR assessment.

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**S**UBSTANTIAL NEUROPSYCHOLOGICAL deficits, first described by Kraepelin<sup>1</sup> and Bleuler,<sup>2</sup> have subsequently been observed in all phases of schizophrenia, beginning in the premorbid period and continuing throughout life. Patients in the first psychotic episode and during chronic periods manifest large neuropsychological impairments with effect sizes (ESs) averaging approximately 1.0.<sup>3,4</sup> The degree of impairment depends on the domain measured, with verbal memory and processing speed typically eliciting the largest deficits (ES, 1.3-1.6 by Cohen d).<sup>3,4</sup> Moreover, because neuropsychological functions are important as windows into

pathophysiology<sup>5</sup> and because they are strongly associated with functional outcomes in schizophrenia,<sup>6</sup> they may be important in risk prediction of psychosis.

The robust finding of premorbid neuropsychological impairment indicates that these measures may have utility as predictors of schizophrenia, an idea frequently evaluated in persons at genetic (familial) high risk (FHR),<sup>7-9</sup> and recently in clinical high-risk (CHR) or putatively “prodromal” samples.<sup>10</sup> Clinical high risk requires the presence of specific subsyndromal psychotic symptoms, while FHR is defined solely by the presence of a family history (FH) of psychosis.

Compared with healthy control subjects, ESs of neuropsychological deficits in

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offspring and adult nonpsychotic relatives of persons with schizophrenia range between 0.3 and 0.6, reflecting moderate deficits in the absence of psychosis.<sup>11-15</sup> These findings suggest that cognitive deficits are associated with the neural substrates of the illness<sup>16,17</sup> and that they may be attributable largely to inherited variations.<sup>16,18</sup> These impairments have considerable validity because they are not confounded by psychosis or medication. Commonly identified deficits in FHR samples include lower verbal ability, general intelligence (IQ), declarative and working memory, sustained attention, processing speed, and executive and motor functions.<sup>7,8,11-15,17,19,20</sup>

While identification of neuropsychological impairments in FHR samples supports a neurodevelopmental model of vulnerability to schizophrenia,<sup>20-22</sup> their utility for prediction of psychosis is limited by modest lifetime conversion rates of approximately 10%. The problem of relatively low conversion rates in FHR samples and the notion that early detection and intervention may prevent clinical expression of psychosis or functional deterioration have stimulated a new direction in psychiatry research aimed at reducing morbidity and mortality,<sup>23</sup> similar to prevention efforts in other branches of medicine.<sup>24,25</sup> This approach has focused on developing and validating criteria for ascertaining individuals at risk of imminent onset of psychosis and observing them over time.<sup>26-28</sup> Advantages of this approach over FHR methods include more efficient timing of assessments proximate to illness onset and reduction of false-positive rates.<sup>29,30</sup> Because the modal period of onset in schizophrenia is between ages 18 and 30 years, "case identification" during adolescence and young adulthood is essential.

During the past 5 years, at least 10 research groups have published studies of neuropsychological functioning in CHR samples.<sup>10</sup> Findings from cross-sectional CHR studies have consistently documented that neuropsychological deficits are intermediate between control and first-episode psychosis samples,<sup>10,31-54</sup> and one has shown that neuropsychological functioning is related to illness course.<sup>50</sup> Several specific deficits have been observed, most reliably in spatial<sup>35-38</sup> and verbal<sup>46</sup> working memory, verbal declarative memory,<sup>39,40,43,52</sup> and attention.<sup>31,32,40-44,48</sup> Deficits in olfaction<sup>47</sup> and executive functions, as measured by verbal fluency, matrices, and set shifting, and visual form perception have been less consistently tested or identified.\* Some deficits (eg, in sustained attention) may represent stable vulnerability markers,<sup>40,41</sup> while others (such as in verbal memory, working memory, processing speed, and verbal IQ) may be predictive of conversion to psychosis.<sup>39,40,48,49,53</sup>

Despite substantial progress, variability in test batteries and small samples complicate interpretation. Moreover, only 2 studies<sup>36,51</sup> have integrated FHR and CHR methods, and the few studies that compared individuals who did and did not convert to illness were limited by small samples and brief follow-ups. Because many patients with neuropsychiatric disorders manifest neuropsychological deficits, it is important to compare CHR individuals who develop psychosis with those who do not. Longitudinal designs including follow-up into con-

version may identify neuropsychological deficits that predict psychosis.

The North American Prodrome Longitudinal Study (NAPLS) is a consortium of 8 research centers, ascertaining CHR individuals and observing them for up to 2½ years.<sup>30,55,56</sup> Although originally developed as independent studies, the sites used similar ascertainment and diagnostic methods, making it possible to form a standardized protocol for mapping data into a new scheme representing the common components across sites,<sup>30,55</sup> yielding the largest database of longitudinally followed CHR cases worldwide.

The primary aims of this study were to characterize the neuropsychology of the psychosis prodrome by comparing performance of CHR individuals with that of normal controls (NCs) and FHR subjects and to examine the value of neuropsychological function for predicting conversion to psychosis. Our hypotheses were that persons who subsequently convert to psychosis are more impaired at baseline than nonconverters, that this effect would be amplified in persons with an FH of psychosis, and that poorer neuropsychological performance would predict more rapid conversion to psychosis.

## METHODS

### SAMPLE

Study protocols and informed consent documents, including procedures for data pooling and secondary data analysis, were approved by the institutional review boards of the participating sites (Emory University; Harvard University; University of California, Los Angeles [UCLA]; University of California, San Diego [UCSD]; University of North Carolina; University of Toronto; Yale University; and Zucker Hillside Hospital). The NAPLS methods and details of the federated database not specific to the present study are described elsewhere.<sup>30,55,56</sup> Nine reports of neuropsychological function have been published on 4 smaller CHR samples by NAPLS centers: 3 from the Prevention Through Risk Identification, Management, and Education (PRIME) multisite study (including Yale, University of North Carolina, and University of Toronto sites),<sup>31-33</sup> 2 from Zucker-Hillside,<sup>37,40</sup> 2 from UCLA,<sup>44,50</sup> and 2 from UCSD.<sup>48,49</sup> However, these neuropsychological data were not previously combined, did not include a 2.5-year follow-up (a smaller PRIME study included a 2-year follow-up<sup>33</sup>), and did not evaluate the impact of neuropsychological functioning on conversion to psychosis in relation to FH and other possible predictors.

Participants from the NAPLS database who completed any baseline neuropsychological testing were included, yielding 304 CHR individuals, 52 persons with an FH of psychosis without prodromal symptoms, and 193 NCs without an FH of psychosis or prodromal symptoms. Of the 304 CHR subjects, 269 (88.5%) were observed for up to 2½ years to assess for conversion to psychosis. The 35 CHR participants without any follow-up were excluded from analyses that took conversion status into account. Of the 304 CHR subjects, 89 (29.3%) converted to psychosis, of whom 73 (82.0%) had baseline neurocognitive data.

### ASSESSMENT PROCEDURES

The Structured Interview for Prodromal Syndromes<sup>57,58</sup> criteria were used for study entry, and the Structured Clinical Interview for DSM-IV<sup>59,60</sup> was most commonly used to assess general psychopathology. Structured Interview for Prodromal Syndromes criteria<sup>57</sup> for a CHR syndrome emphasize onset or worsening of

\*References 31, 32, 35, 36, 40, 43, 46-48, 52, 54.

attenuated positive symptoms in the past 12 months in at least 1 of 5 symptom domains: unusual thought content, suspicion/paranoia, grandiosity, perceptual anomalies, and disorganized communication. Subjects also qualified for a CHR syndrome if they showed onset of brief intermittent positive psychotic symptoms in the past 3 months but below the threshold required for a DSM-IV Axis I psychotic disorder diagnosis or if they had a genetic risk for psychosis and deterioration of 30% or more on the Global Assessment of Functioning scale in the past 12 months, where genetic risk is defined by having an FH of psychosis or a diagnosis of schizotypal personality disorder.<sup>61,62</sup> All NAPLS sites demonstrated good reliability by using the Structured Interview for Prodromal Syndromes criteria ( $\kappa$  values ranged from 0.80 to 1.00 across sites).<sup>57</sup> At each site, raters were MA, PhD, or MD specialists in mental health.

## FOLLOW-UP ASSESSMENTS

The Structured Interview for Prodromal Syndromes was readministered at 6-month intervals up to 30 months. If clinical deterioration was observed during interim periods, a reassessment was conducted before regularly scheduled assessments. Because treatment was not standardized, information on dosing and duration of antipsychotic treatments was unavailable for the majority of cases.

## BASELINE NAPLS NEUROPSYCHOLOGICAL ASSESSMENT PROTOCOL

Cognitive performance variables presented unique challenges in the development of an omnibus protocol.<sup>55</sup> Sixty-eight neurocognitive measures derived from 40 separate tests were used across sites. Criteria for test inclusion in the federated database included the following: (1) representation across at least 4 sites; (2) comparability of test versions, administration procedures, and scoring; and (3) coverage of presumed areas of separable cognitive impairment in schizophrenia.<sup>63</sup> Thirteen cognitive variables, derived from 8 tests, were initially selected for the omnibus battery. However, to enhance commonality, to carry out multivariate statistical analyses, and to create a composite score for use in prediction analyses, the number of variables examined in these analyses was reduced to 8: Vocabulary,<sup>64-67</sup> measuring verbal comprehension; Block Design,<sup>64-66</sup> measuring visual-perceptual organization; Continuous Performance Test-Identical Pairs (CPT-IP) digits,<sup>68</sup> measuring vigilance; Digit Symbol-Coding (hereinafter referred to as "Coding")<sup>64-66</sup> and Trail Making Test Part B,<sup>69</sup> both measuring speed of processing; Controlled Oral Word Association (COWA) test<sup>70</sup> for verbal fluency and Wisconsin Card Sorting Test<sup>71,72</sup> for problem solving, both measures of executive functioning; and a verbal learning and memory variable, consisting of story recall tests from the Wechsler Memory Scale<sup>73,74</sup> for participants 17 years or older and Children's Memory Scale<sup>75</sup> for those younger than 17 years, as well as list learning on the Hopkins Verbal Learning Test-Revised,<sup>76</sup> Rey Auditory Verbal Learning Test,<sup>77</sup> and California Verbal Learning Test adult and child versions.<sup>78,79</sup> Additional information regarding variable construction is available in an online supplement (available at <http://www.archgenpsychiatry.com>).

## DATA ANALYTIC PLAN

Data analyses consisted of 2 approaches: a *univariate approach* that included all subjects for whom data were available in an individual cognitive domain and a *multivariate approach* that included all cognitive domains and construction of a composite score. To support the multivariate approach, a series of decision rules for acceptable subject inclusion were created and

imputation steps were implemented. This resulted in a *multivariate* sample ( $n = 325$ ) that is a subset (59.2%) of the *univariate* sample ( $n = 549$ ), including reduced samples of CHR subjects (167 subjects [55% of the CHR subjects in the *univariate* sample]), FHR (49 [94%]), and NCs (109 [56%]). Because of substantial subject loss in the *multivariate* sample, both samples were analyzed and compared. The univariate analyses are presented in an online supplement, and significant findings are integrated within the "Results" section.

## Formation of the Multivariate Sample

Inclusion in the multivariate sample required subjects to have a minimum of 75% complete data (ie, completed at least 6 of 8 tests), thus reducing the total missing data to less than 10%, which was our maximum threshold for data loss before imputation. Multiple imputation methods were used to address missing data. In contrast to listwise deletion, which has the disadvantages of loss of observations and reduced statistical power, multiple imputation permits analysis of complete data by calculating estimates of missing values with the use of other variables in the model as predictors.<sup>80-82</sup> Details of the data imputation methods are in the online supplement.

## Group Contrasts

The groups compared were CHR, FHR, and NC. The CHR group was further subdivided into converters to psychosis (CHR+) and nonconverters (CHR-). Six comparisons were made within both the multivariate and univariate samples: (1) CHR vs NC, (2) FHR vs NC, (3) CHR vs FHR, (4) CHR+ vs NC, (5) CHR- vs NC, and (6) CHR+ vs CHR-. A small subgroup of CHR+ with a positive FH (CHR+FH+) were analyzed within the univariate sample because of its larger CHR+FH+ subsample.

## Statistical Analyses

Statistical analyses were performed with SPSS version 17 (SPSS Inc, Chicago, Illinois) or SAS version 9.1 (SAS Institute Inc, Cary, North Carolina) statistical software. One-way analysis of variance and  $\chi^2$  tests were conducted to compare groups on demographics. For the multivariate sample, neuropsychological measures were compared by multivariate analysis of variance (MANOVA), multivariate analysis of covariance (MANCOVA), univariate analysis of covariance, and profile analysis.

In some contrasts, groups were significantly different on education, parental education, sex, and ethnicity. Because ethnicity and parental education were correlated and because parental education is strongly associated with neurocognition, parental education was controlled for. In contrast, subjects' own education is likely to be affected by illness and was not controlled for. Because small differences in age can influence neuropsychological functioning in adolescence, analyses controlled for age as well as parental education and sex. We also tested for the effects of site. To examine whether neuropsychological impairments were significant beyond general intellectual impairment, we used MANCOVA controlling for age, sex, and full-scale IQ (FSIQ) estimate<sup>83</sup> (after removing Vocabulary and Block Design tests that compose estimated FSIQ from the profiles). To test whether the shape of neuropsychological profiles differed for selected contrasts, unadjusted scores were analyzed by means of the general linear model repeated-measures function. For profile analyses, the 8 measures were standardized against the NCs within each of the 5 imputed data sets and then pooled across imputed data sets. In addition, a composite score was constructed as the mean of the 8 standardized scores within each imputed data set and then pooled.

Statistical significance was set at  $P < .05$  by means of 2-tailed tests for multivariate analyses (MANOVA, MANCOVA, profile

**Table 1. Demographic Characteristics of the Multivariate Sample**

	CHR (Total Sample)	FHR <sup>a</sup>	NC	Test Statistic (P Value) <sup>b</sup>	Post Hoc Contrasts <sup>c</sup>	CHR Conversion to Psychosis		
						CHR+	CHR-	Test Statistic (P Value)
Age, mean (SD), y [n]	18.2 (4.9) [167]	18.7 (4.1) [49]	18.8 (4.5) [109]	<i>F</i> =.57 (.57)		18.9 (3.9) [54]	17.8 (5.2) [113]	<i>t</i> =1.32 (.19)
Subject education, mean (SD) [n]	10.4 (3.1) [166]	10.7 (2.7) [44]	11.5 (3.2) [107]	<i>F</i> =4.24 (.02)	CHR < NC	11.0 (2.8) [54]	10.0 (3.2) [112]	<i>t</i> =1.78 (.08)
Parental education, mean (SD) [n] <sup>d</sup>	5.4 (1.6) [167]	4.9 (2.1) [49]	5.9 (2.0) [109]	<i>F</i> =5.29 (.006)	FHR < NC	5.1 (1.5) [54]	5.6 (1.6) [113]	<i>t</i> =-2.07 (.04)
Female sex, No. (%)	60/167 (35.9)	26/49 (53.1)	61/109 (56.0)	$\chi^2=12.12$ (.002)	CHR < FHR, NC	17/54 (31.5)	43/113 (38.1)	$\chi^2=0.69$ (.41)
Race, No. (%)								
White	139/167 (83.2)	32/49 (65.3)	74/108 (68.5)	$\chi^2=11.03$ (.004)	CHR > FHR, NC	42/54 (77.8)	97/113 (85.8)	$\chi^2=1.7$ (.19)
African American	15/167 (9.0)	7/49 (14.3)	12/108 (11.1)	$\chi^2=1.2$ (.55)		7/54 (13.0)	8/113 (7.1)	$\chi^2=1.55$ (.21)
Asian	6/167 (3.6)	0/49 (0)	7/108 (6.5)	$\chi^2=3.83$ (.15)		3/54 (5.6)	3/113 (2.7)	$\chi^2=.888$ (.35)
Multiracial	7/167 (4.2)	10/49 (20.4)	15/108 (13.9)	$\chi^2=14.12$ (.001)	FHR > NC > CHR	2/54 (3.7)	5/113 (4.4)	$\chi^2=.047$ (.83)
Latino/Latina ethnicity, No. (%)	23/156 (14.7)	14/47 (29.8)	18/103 (17.5)	$\chi^2=5.57$ (.06)		8/51 (15.7)	15/105 (14.3)	$\chi^2=.054$ (.82)

Abbreviations: CHR, clinical high-risk; CHR+, CHR subjects who converted to psychosis; CHR-, CHR nonconverters; FHR, family high-risk; NC, normal control.

<sup>a</sup>Our FHR group includes all people with a positive family history who were not prodromal regardless of whether they were seeking help. This is the one difference between the groupings in this article and the report by Woods et al.<sup>36</sup> Their FHR group (n=40) was smaller because, if subjects had a positive family history and were seeking help, they were included in a help-seeking comparison group. Other than that difference, our original groups from which tested subjects were drawn are identical to those of Woods et al for the CHR (n=377) and NC (n=196) groups.

<sup>b</sup>Statistical tests reflect comparisons among CHR, FHR, and NC groups only.

<sup>c</sup>Bonferroni-corrected post hoc contrast (*P*<.05).

<sup>d</sup>Scored as follows: 1, less than high school; 2, some high school; 3, high school graduate; 4, some college; 5, associate's degree; 6, bachelor's degree; 7, some postgraduate education; and 8, graduate degree.

analyses, and composite score). Bonferroni correction was used to control the type I error rate for univariate analyses (.05/8 or ≤.00625). Comparisons that remained significant at the Bonferroni-corrected level are shown in boldface in the tables and presented in the "Results" section. Effect sizes (unadjusted) were calculated with Cohen *d*.<sup>84</sup>

Primary analyses were followed by tests of association between neurocognitive functioning and psychosis progression for the multivariate sample. To identify the cognitive variables most predictive of psychosis progression, we first examined the predictive value of the baseline composite score, FSIQ, Coding, and Verbal Memory in separate Cox regression models. The latter 3 were chosen because they are most sensitive in FHR and patients with schizophrenia, respectively.<sup>3,4,8</sup> A multivariate Cox regression using backward selection was conducted to identify which of the 8 cognitive test scores have unique predictive associations with conversion. A second set of multivariate Cox regressions was used to determine whether any of the 10 cognitive variables added unique prediction beyond the multivariate NAPLS clinical algorithm previously reported.<sup>30</sup>

## RESULTS

### DEMOGRAPHIC CHARACTERISTICS

#### Multivariate Sample

Comparing CHR and FHR participants with NCs showed no significant group differences in age (**Table 1** and eTable 1). The CHR subjects attained significantly less education than NCs. The FHR group showed significantly less parental education than NCs. The CHR group had significantly fewer females than the FHR and NC groups. The groups differed on race, with significantly more whites in the CHR than other groups. Parental education was significantly lower in the CHR+ than CHR- subgroup.

#### Univariate Sample

Demographic comparisons were the same in the univariate and multivariate sample comparisons with the following additions: (1) parental education was significantly lower in the CHR group than in NCs; (2) there were significantly fewer African Americans in the CHR than other groups; (3) the FHR group had significantly fewer Asian Americans than other groups; and (4) the CHR+ and CHR- subgroups did not differ significantly on any variable (eTable 1).

The 167 CHR subjects in the multivariate sample did not differ significantly on any demographic variable from the additional 137 CHR subjects who together formed the univariate sample. (Results are available on request from the first author.)

### NEUROPSYCHOLOGICAL FUNCTIONING

#### CHR vs NCs

**Multivariate.** Raw data are presented in **Table 2** and statistical results in **Table 3**. The MANOVA and MANCOVA for the 8 tests were statistically significant. The MANCOVA, controlling for FSIQ (covariate effect; *F*=0.26, *P*=.62, *d*=0.16), was significant, and Coding (*d*=0.56), COWA (*d*=0.48), Verbal Memory (*d*=0.45), CPT-IP (*d*=0.39), and the composite score (*d*=0.45) were significant. See **Figure 1** for profile.

**Univariate.** Raw data are presented in eTable 2 and results in eTable 3. Significant tests were Coding (*d*=0.58), Verbal Memory (*d*=0.54), COWA (*d*=0.47), and CPT-IP digits (*d*=0.43).

**Table 2. Neuropsychological Test Scores for the Multivariate Sample**

Variable	Mean (SE) <sup>a</sup>				
	CHR (n=167)	FHR (n=49)	NC (n=109)	CHR+ (n=54)	CHR- (n=113)
WIS FSIQ	105.4 (1.50)	98.2 (1.80)	108.2 (1.50)	102.0 (2.80)	107.0 (1.70)
Vocabulary <sup>b</sup>	11.3 (0.28)	9.8 (0.37)	11.9 (0.32)	10.2 (0.48)	11.8 (0.33)
Block Design <sup>b</sup>	10.8 (0.28)	9.6 (0.37)	11.2 (0.37)	10.4 (0.54)	10.9 (0.33)
Coding <sup>b</sup>	8.8 (0.27)	8.7 (0.39)	10.7 (0.32)	8.4 (0.45)	9.0 (0.33)
TMT-B, s	68.9 (3.30)	72.7 (3.70)	59.0 (3.00)	80.6 (7.40)	63.3 (3.20)
CPT-IP Digits d'	1.35 (0.08)	1.46 (0.14)	1.73 (0.09)	1.31 (0.14)	1.37 (0.09)
COWA raw score	34.9 (0.85)	33.9 (1.60)	40.3 (1.10)	32.8 (1.60)	35.9 (0.98)
WCST Perseverative Errors	8.4 (0.36)	7.5 (0.78)	8.2 (0.60)	9.8 (0.77)	7.8 (0.38)
Verbal Memory, z score <sup>c</sup>	-0.54 (0.11)	-0.07 (0.12)	0 (0.09)	-0.86 (0.22)	-0.39 (0.12)
Composite score, z score <sup>d</sup>	-0.33 (0.06)	-0.36 (0.07)	0 (0.06)	-0.55 (0.12)	-0.23 (0.06)

Abbreviations: CHR, clinical high-risk; CHR+, CHR subjects who converted to psychosis; CHR-, CHR nonconverters; COWA, Controlled Oral Word Association; CPT-IP Digits d', Continuous Performance Test-Identical Pairs (digits) signal detection measure of discriminability; FHR, family high-risk; NC, normal control; TMT-B, Trail Making Test Part B; WCST, Wisconsin Card Sorting Test; WIS FSIQ, Wechsler Intelligence Scale full-scale IQ estimate.

<sup>a</sup>The standard errors are based on the pooled average of 5 multiple imputation data sets.

<sup>b</sup>Wechsler subtests are age-corrected scaled scores.

<sup>c</sup>Composite of (1) list learning: percentage correct across trials on Hopkins Verbal Learning Test-Revised, Rey Auditory Verbal Learning Test, or California Verbal Learning Test (adult and child versions) and standardized against the NC group; and (2) story recall: percentage of units recalled on immediate recall condition of Children's Memory Scale Stories; Wechsler Memory Scale-Revised, Logical Memory I; or Wechsler Memory Scale-Third Revision, Logical Memory I, standardized against the NC group.

<sup>d</sup>Mean standardized score of the 8 measures (excluding WIS FSIQ).

**Table 3. Contrast Analyses for the Multivariate Sample Including Adjustments for Demographic Characteristics, IQ, and Site (F Values)**

Variable	CHR vs NC	FHR vs NC	CHR vs FHR	CHR+ vs NC	CHR- vs NC	CHR+ vs CHR-
WIS FSIQ <sup>a</sup>	0.26	8.76 <sup>b</sup>	4.07 <sup>c</sup>	2.34	0.05	1.90
Composite score <sup>a</sup>	9.29 <sup>b</sup>	8.19 <sup>d</sup>	0.07	17.14 <sup>e</sup>	3.40	6.30 <sup>c</sup>
MANOVA <sup>f</sup>	4.87 <sup>e</sup>	4.56 <sup>e</sup>	4.42 <sup>e</sup>	4.39 <sup>e</sup>	3.95 <sup>e</sup>	1.91 <sup>c</sup>
MANCOVA <sup>g</sup>	3.72 <sup>e</sup>	3.71 <sup>e</sup>	4.17 <sup>e</sup>	3.49 <sup>b</sup>	3.09 <sup>b</sup>	1.83
Vocabulary <sup>h</sup>	0.47	<b>10.15<sup>b</sup></b>	5.32 <sup>c</sup>	6.19 <sup>c</sup>	0.43	<b>7.80<sup>b</sup></b>
Block Design <sup>h</sup>	0.19	3.25	2.16	0.49	0.05	0.14
Coding <sup>h</sup>	<b>15.25<sup>e</sup></b>	<b>11.42<sup>b</sup></b>	0.16	<b>14.24<sup>e</sup></b>	<b>9.86<sup>b</sup></b>	1.25
TMT-B <sup>h</sup>	1.99	3.64	0.08	6.52 <sup>c</sup>	0.10	5.23 <sup>c</sup>
CPT-IP Digits d' <sup>h</sup>	<b>9.02<sup>b</sup></b>	2.24	1.07	8.43 <sup>d</sup>	5.75 <sup>c</sup>	0.62
COWA raw score <sup>h</sup>	<b>9.94<sup>b</sup></b>	6.78 <sup>c</sup>	0.26	<b>11.83<sup>e</sup></b>	4.93 <sup>c</sup>	2.42
WCST Perseverative Errors <sup>h</sup>	0.42	2.59	2.84	3.00	2.64	6.33 <sup>c</sup>
Verbal Memory <sup>h</sup>	<b>9.41<sup>b</sup></b>	0.04	<b>8.49<sup>b</sup></b>	<b>14.35<sup>e</sup></b>	4.97 <sup>c</sup>	2.43
MANCOVA <sup>i</sup>	5.59 <sup>e</sup>	2.18	3.49 <sup>b</sup>	4.69 <sup>b</sup>	4.34 <sup>b</sup>	1.39
MANCOVA <sup>j</sup>	5.62 <sup>e</sup>	3.97 <sup>e</sup>	4.14 <sup>e</sup>	4.91 <sup>e</sup>	4.24 <sup>e</sup>	1.46

Abbreviations: CHR, clinical high-risk; CHR+, CHR subjects who converted to psychosis; CHR-, CHR nonconverters; COWA, Controlled Oral Word Association; CPT-IP Digits d', Continuous Performance Test-Identical Pairs (digits) signal detection measure of discriminability; FHR, family high-risk; MANCOVA, multivariate analysis of covariance; MANOVA, multivariate analysis of variance; NC, normal control; TMT-B, Trail Making Test Part B; WCST, Wisconsin Card Sorting Test; WIS FSIQ, Wechsler Intelligence Scale full-scale IQ estimate.

<sup>a</sup>Analysis of covariance covarying sex, age, and parental education.

<sup>b</sup>P < .005.

<sup>c</sup>P < .05.

<sup>d</sup>P < .01.

<sup>e</sup>P < .001.

<sup>f</sup>Dependent variables: Vocabulary, Block Design, Coding, TMT-B, CPT-IP, COWA, WCST Perseverative Errors, and Verbal Memory.

<sup>g</sup>Dependent variables: Vocabulary, Block Design, Coding, TMT-B, CPT-IP, COWA, WCST Perseverative Errors, and Verbal Memory; covariates: sex, age, and parental education.

<sup>h</sup>Analysis of covariance covarying sex, age, and parental education; boldfaced values indicate test remains significant at Bonferroni-corrected level of P ≤ .00625.

<sup>i</sup>Dependent variables: Coding, TMT-B, CPT-IP, COWA, WCST Perseverative Errors, and Verbal Memory; covariates: sex, age, and WIS FSIQ.

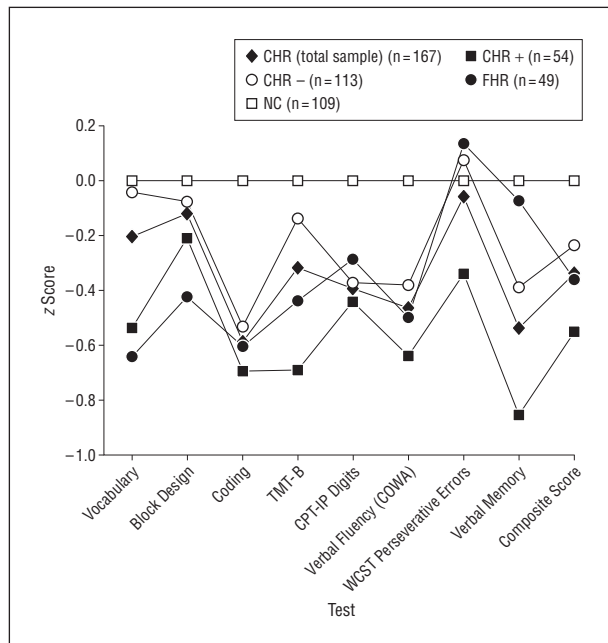
<sup>j</sup>Dependent variables: Vocabulary, Block Design, Coding, TMT-B, CPT-IP, COWA, WCST Perseverative Errors, and Verbal Memory; covariate: North American Prodrome Longitudinal Study site.

**FHR vs NCs**

**Multivariate.** The MANOVA and MANCOVA were statistically significant. The MANCOVA controlling for FSIQ (covariate effect; F = 8.76, P = .004, d = 0.70) was not significant.

Vocabulary (d = 0.70), Coding (d = 0.66), and the composite score (d = 0.75) were significant. See Figure 1 for profile.

**Univariate.** Significant tests were Vocabulary (d = 0.89), Coding (d = 0.66), and COWA (d = 0.59).



**Figure 1.** Neuropsychological profiles of the clinical high-risk (CHR), CHR converter (CHR+), CHR nonconverter (CHR-), and family high-risk (FHR) groups standardized against the normal control (NC) group from the multivariate sample. COWA indicates Controlled Oral Word Association; CPT-IP, Continuous Performance Test–Identical Pairs; TMT-B, Trail Making Test Part B; and WISCST, Wisconsin Card Sorting Test.

#### CHR vs FHR

**Multivariate.** The MANOVA and MANCOVA were statistically significant. The MANCOVA controlling for FSIQ (covariate effect;  $F=4.07$ ,  $P=.045$ ,  $d=0.44$ ) was significant. Verbal Memory ( $d=0.40$ ) was significant. The composite score was not significant ( $d=0.16$ ). When CHR and FHR were compared, a test  $\times$  group interaction was observed ( $F=4.99$ ,  $P<.001$ ), indicating a differential (ie, non-parallel) pattern of scores (Figure 1). There was no main effect for group, indicating comparable overall performance ( $F=0.06$ ,  $P=.82$ ). Table 3 shows that the differential pattern of performance is accounted for by the FHR group exhibiting somewhat greater impairment on Vocabulary, while the CHR group exhibited significantly greater impairment in Verbal Memory.

**Univariate.** No tests were significantly different.

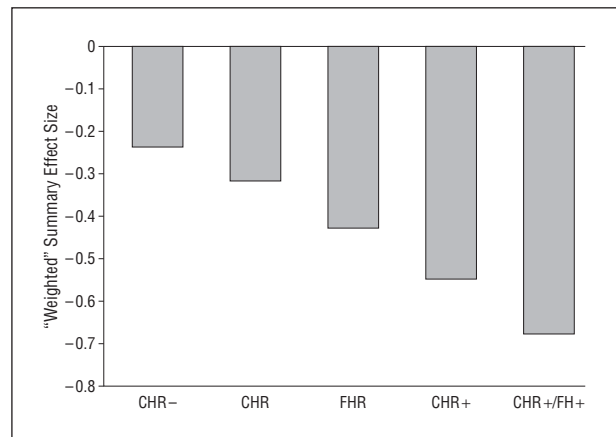
#### CHR+ vs NCs

**Multivariate.** The MANOVA and MANCOVA were statistically significant. The MANCOVA controlling for FSIQ (covariate effect;  $F=2.34$ ,  $P=.13$ ,  $d=0.34$ ) was significant. Coding ( $d=0.69$ ), Verbal Memory ( $d=0.65$ ), Vocabulary ( $d=0.50$ ), and the composite score ( $d=0.72$ ) were significant. See Figure 1 for profile.

**Univariate.** Verbal Memory ( $d=0.79$ ), Coding ( $d=0.68$ ), COWA ( $d=0.68$ ), Vocabulary ( $d=0.65$ ), and CPT-IP digits ( $d=0.62$ ) were significant.

#### CHR- vs NCs

**Multivariate.** The MANOVA and MANCOVA were statistically significant. The MANCOVA controlling



**Figure 2.** Effect sizes reflecting comparisons of different high-risk groups with normal controls. Effect sizes (Cohen  $d$ ) are averaged within group in the univariate sample after weighting for sample size across the 8 neuropsychological test variables. Data suggest a dose-response impact of both conversion and family history of psychosis. Groups are as follows (average number of subjects per test per group in parentheses): normal controls ( $n=144$ ), clinical high-risk (CHR) nonconverters (CHR-) ( $n=155$ ), CHR (total sample) ( $n=242$ ), family high-risk (FHR) ( $n=45$ ), CHR converters (CHR+) ( $n=62$ ), and CHR+ with positive family history (CHR+/FH+) ( $n=13$ ).

for FSIQ (covariate effect;  $F=0.05$ ,  $P=.84$ ,  $d=0.07$ ) was significant. Coding ( $d=0.50$ ) was significant. The composite score was not significant ( $d=0.36$ ). See Figure 1 for profile.

**Univariate.** Significant tests were Coding ( $d=0.57$ ), Verbal Memory ( $d=0.46$ ), and CPT-IP digits ( $d=0.39$ ).

#### CHR+ vs CHR-

**Multivariate.** The MANOVA was significant and the MANCOVA showed a marginal trend ( $P=.08$ ). The MANCOVA controlling for FSIQ (covariate effect;  $F=1.90$ ,  $P=.17$ ,  $d=0.26$ ) was not significant. The composite score ( $d=0.40$ ) and Vocabulary ( $d=0.46$ ) were significant. A test of profile shape showed no significant test  $\times$  group interaction ( $F=1.65$ ,  $P=.14$ ). A main effect of test was observed ( $F=8.56$ ,  $P<.001$ ), indicating that differential performance was observed across tests, independent of the groups. In addition, there was a main effect of group, indicating that the profiles differed in overall neuropsychological performance ( $F=6.47$ ,  $P=.01$ ). See Figure 1.

**Univariate.** Vocabulary was significant ( $d=0.43$ ).

#### CHR+FH+ vs NCs

**Univariate.** Because the sample was small (CHR+FH+ maximum,  $n=13$ ), only the univariate sample data were analyzed. Statistically significant, large effects were obtained on Verbal Memory ( $d=0.99$ ), CPT-IP digits ( $d=0.98$ ), and Coding ( $d=0.87$ ). The overall mean ES, weighted for the sample size for each test, suggested a dose response and was largest in the CHR+FH+ group (Figure 2).

**Site.** Although group ascertainment differed significantly by site (see online supplement), MANCOVAs using site showed minimal impact, affecting only 1 of 6 contrasts (CHR+ vs CHR-; Table 3).

**Table 4. Effect Sizes (Unadjusted Cohen d) for Persons Who Later Develop Psychosis or Schizophrenia From Premorbid and CHR (Converters) Phases and Persons With First-Episode Schizophrenia**

Variable	Premorbid <sup>a</sup>	CHR vs NC (From Multivariate Analysis) (n=109)		CHR vs NC (From Univariate Analysis)			First Episode <sup>b</sup>
		CHR- (n=113)	CHR+ (n=54)	No. of NC	CHR- (No.)	CHR+ (No.)	
Full-scale IQ	-0.54	-0.07	-0.34	173	-0.19 (171)	-0.46 (71)	-1.01
Vocabulary		-0.03	-0.50	182	-0.18 (187)	-0.65 (71)	-0.94
Block Design		-0.08	-0.20	182	-0.09 (166)	-0.22 (66)	-0.90
Coding		-0.50	-0.69	109	-0.57 (139)	-0.68 (63)	-1.59
TMT-B		-0.13	-0.49	113	-0.17 (135)	-0.48 (59)	-0.91
CPT-IP Digits d'		-0.38	-0.43	158	-0.39 (135)	-0.62 (48)	-0.71 <sup>c</sup>
COWA raw score		-0.40	-0.65	116	-0.40 (144)	-0.68 (62)	-0.69
WCST Perseverative Errors		-0.08	-0.28	101	-0.17 (155)	-0.43 (58)	-0.81
Verbal Memory <sup>d</sup>		-0.35	-0.65	191	-0.46 (179)	-0.79 (67)	-1.41

Abbreviations: CHR, clinical high-risk; CHR+, CHR subjects who converted to psychosis; CHR-, CHR nonconverters; COWA, Controlled Oral Word Association; CPT-IP Digits d', Continuous Performance Test-Identical Pairs (digits) signal detection measure of discriminability; NC, normal control; TMT-B, Trail Making Test Part B; WCST, Wisconsin Card Sorting Test.

<sup>a</sup>From Woodberry et al.<sup>8</sup>

<sup>b</sup>From Mesholam-Gately et al.<sup>4</sup>

<sup>c</sup>Derived from the average score of various CPT tasks including CPT-IP in Mesholam-Gately et al.<sup>4</sup>

<sup>d</sup>Derived from list learning and immediate story recall measures. The Cohen d reported in the table for the first-episode group is an arithmetical average of the Wechsler Memory Scale Logical Memory (d=-1.47) and the California Verbal Learning Test Sum Trials 1 through 5 (d=-1.34) in Mesholam-Gately et al.<sup>4</sup>

**Sensitivity of Individual Tests.** Twelve of 48 tests (25%) in the multivariate sample and 16 of 48 tests (33%) in the univariate sample (which included 45% more subjects) were statistically significant at the Bonferroni level. Coding was significant 4 of 6 times and Verbal Memory was significant 3 of 6 times in each sample, indicating that they were most likely to show impairment. Block Design, Trail Making Test Part B, and Wisconsin Card Sorting Test perseverative errors were not significant at the Bonferroni level in any comparisons, suggesting that they are less affected in high-risk samples.

**Prediction of Progression to Psychosis With Neuropsychological Tests.** Cox regression models were estimated to identify baseline cognitive variables that were most predictive of time to conversion to psychosis. In the first set of analyses, only 4 selected variables were examined. The composite score ( $\chi^2=3.05, P=.08$ ), FSIQ ( $\chi^2=2.63, P=.11$ ), and Coding ( $\chi^2=0.14, P=.71$ ) were not significant. In contrast, Verbal Memory was a significant predictor of time to conversion ( $\chi^2=6.1, P=.01$ ) and demonstrated a hazard ratio of 0.79, suggesting that CHR subjects with impaired verbal memory were likely to progress to psychosis more rapidly. A second analysis used backward selection to identify which among the 8 cognitive variables were the best predictors of rate of progression to psychosis. The log-rank test was not significant ( $\chi^2=13.18, P=.11$ ). A third Cox regression examined whether the cognitive variables (composite, FSIQ, Coding, and Verbal Memory) added to the multivariate NAPLS prediction model.<sup>30</sup> None contributed uniquely to the prediction of psychosis beyond clinical variables.

#### COMMENT

As predicted, CHR subjects were significantly impaired in neuropsychological functioning compared with NCs after statistically adjusting for age, sex, parental education, and

site as well as for IQ, indicating that impairments were not simply a general intellectual deficit. Impairments were significantly more severe in the CHR+ group than in the CHR- group but modestly so (composite score, d=0.40), suggesting that neuropsychological deficits are associated strongly with risk states for psychosis and additionally with conversion. The CHR and FHR groups were similarly impaired in composite neuropsychological functioning relative to NCs, but their profiles differed distinctly. Thus, risk status based on clinical symptoms and that based on FH both index neuropsychological vulnerability to psychosis, but they appear to be characterized by different impairments. Impairments were most severe in the converters who also had an FH of psychosis, suggesting a synergistic, dose-response effect (Figure 2), although this group was small and the result requires replication. Tests of verbal learning and memory and processing speed were most sensitive in discriminating CHR and control groups, and verbal memory predicted more rapid conversion. However, neuropsychological measures did not significantly enhance the NAPLS clinical prediction algorithm reported previously.<sup>30</sup>

The severity and pattern of impairment in CHR compared with results from first-episode psychosis studies is informative (see **Table 4**). First, it is of interest that the 2 most impaired tests found in first-episode samples, Coding and Verbal Memory, were the 2 most impaired tests in our CHR+ sample. These tasks rely heavily on verbal skills, processing speed, and new learning, functions that are reliably impaired in schizophrenia and clearly presage the disorder. Second, tasks such as Block Design, Trail Making Test Part B, and Wisconsin Card Sorting Test, although impaired in first-episode samples, were less sensitive measures in CHR+ subjects. Tasks that are more visual and less verbal, and explicitly require executive functions, were affected somewhat less than verbal tasks. Alternatively, the psychometric characteristics of the Verbal Memory and Coding tests may be superior to those of other measures, making them more sensitive to the pres-

ence of deficits of any severity. However, because most clinical neuropsychological tests are multifactorial, more refined cognitive neuroscience measures are needed to determine which cognitive mechanisms are impaired.

From a staging perspective, as further explicated in Table 4, neurocognitive deficit apparently increases in severity from prodrome to first episode, and this growing impairment is accompanied by increasing executive dysfunction.<sup>4</sup> This suggests that additional neuropsychological deterioration in those developing psychosis may continue to occur during the late prodromal phase and possibly during and subsequent to the first episode of psychosis. However, this proposition can be addressed definitively only in longitudinal studies that monitor cognitive function in the same subjects. The literature on this issue is sparse, with only 1 published study having similar neuropsychological data collected relatively close to and after the first episode; significant decline was reported on 2 of the 4 tests.<sup>85</sup>

A major strength of this study is its large sample size, larger at baseline and follow-up than any previously published study of neurocognition in CHR individuals. Few published reports on CHR have included neuropsychological functioning in persons who convert to psychosis.<sup>32,33,39,40,48,49,53</sup> With the exception of the Melbourne (n=34)<sup>39</sup> and German (n=44)<sup>52</sup> projects, sample sizes are small (<21 converters). Thus, this study, which compared neuropsychological functioning on as many as 71 converters, provides the most robust data indicating that persons who later convert to psychosis are especially impaired at baseline (composite score  $d=0.72$ ). While the overall (composite score) ES difference between the CHR+ and CHR- groups was modest ( $d=0.40$ ), the effect was consistent in that CHR+ subjects performed worse than CHR- subjects on all 8 neuropsychological measures. On the basis of the Cox regression analyses, only verbal memory was associated with a significant decrease in time to conversion. When the 8 neurocognitive variables, FSIQ, or the composite score were added separately to the multivariate NAPLS prediction algorithms,<sup>30</sup> none of the prediction statistics for the neurocognitive variables was significant, indicating that none added unique variance to prediction beyond clinical variables. It remains possible that future large-scale studies that include a uniformly broader range of neuropsychological tests, particularly measures of olfaction and working memory (shown in previous studies to be associated with conversion but unavailable in this data set), may add unique predictive power to risk algorithms.

The neuropsychological functioning of the FHR sample was consistent with the extant literature, yielding ES differences of 0.20 to 0.70 for many functions. This suggests that a modest proportion of the variance in neuropsychological function is putatively associated with genetic factors, presumably expressing themselves through brain dysfunction.<sup>16,17,21,28,86,87</sup> What is striking about our findings is that CHR and FHR had different patterns of impairment, and thus FHR may contribute additional cognitive impairments to CHR status. This was observed in the larger ESs in the CHR+FH+ subgroup, although small sample size precludes firm conclusions. We found only 2 studies that linked FH and conversion to psychosis, the Edinburgh<sup>51</sup> and Palau<sup>36</sup> high-risk studies. These studies used

very different designs and ascertainment criteria, making findings difficult to integrate. Nonetheless, both studies show a trend for persons with FHR plus prodromal symptoms to be particularly neuropsychologically impaired.

This study has a number of limitations, the most important being variability in the specific tests administered across NAPLS sites resulting in relatively high rates of missing data for some measures and inconsistent sample sizes across tests. We addressed this problem by creating a multivariate sample in which we reduced the number of tests and subjects and then imputed data. Although this resulted in substantial subject loss, we were able to demonstrate that the results were consistent across the smaller multivariate subsample and the full univariate sample as observed by comparable ESs (see Table 4). We also constrained our conclusions about individual tests with Bonferroni corrections. Another limitation was the domains assessed (eg, social cognition, olfaction, and other measures of executive function were not assessed). Future work should combine large samples with a common neuropsychological battery, selected to maximize predictive value. In addition, because it is likely that some CHR subjects will convert to psychosis later,<sup>88</sup> "misclassifying" some subjects as nonconverters may have reduced the differences observed in CHR+ and CHR- contrasts. Subjects were followed up for variable periods, but even a 2.5-year follow-up duration is unlikely to identify all persons who convert. We also had limited data on medication status and other treatment exposures. It will be important in future CHR studies to account for the effects of psychopharmacologic and other treatments.

Despite these limitations, our study is largely consistent with the results of other research groups, including those comparing converters with nonconverters.<sup>53</sup> These findings document that prospective ascertainment of individuals at CHR of psychosis demonstrates significant neuropsychological impairment, especially among those who later convert to psychosis, and these effects are amplified among those with an FH of psychosis. Because neuropsychological tests are relatively inexpensive, have extensive normative data, and are heavily used by school personnel, in conjunction with FH and attenuated clinical symptoms, they may have potential as early indicators of risk of psychosis as well as other important outcomes such as functional disability.

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