WEB-ONLY CONTENT

Neuropsychology of the Prodrome to Psychosis in the NAPLS Consortium

Relationship to Family History and Conversion to Psychosis

Larry J. Seidman, PhD; Anthony J. Giuliano, PhD; Eric C. Meyer, PhD; Jean Addington, PhD; Kristin S. Cadenhead, MD; Tyrone D. Cannon, PhD; Thomas H. McGlashan, MD; Diana O. Perkins, MD, MPH; Ming T. Tsuang, MD, PhD; Elaine F. Walker, PhD; Scott W. Woods, MD; Carrie E. Bearden, PhD; Bruce K. Christensen, PhD; Keith Hawkins, PsyD; Robert Heaton, PhD; Richard S. E. Keefe, PhD; Robert Heinssen, PhD; Barbara A. Cornblatt, PhD, MBA; for the North American Prodrome Longitudinal Study (NAPLS) Group

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METHODS

SUPPLEMENTAL INFORMATION ON THE BASELINE NAPLS NEUROPSYCHOLOGICAL ASSESSMENT PROTOCOL

Some tests, such as the Wechsler intelligence scales, included child and adult versions because of the age range of participants. Additionally, some studies were initiated earlier than others and used earlier test forms (ie, Wechsler Adult Intelligence Scale–Revised).[65] Wechsler full-scale estimated IQ represents a composite of several versions of the Wechsler intelligence scales (Wechsler Intelligence Scale for Children, third edition,[64] Wechsler Adult Intelligence Scale–Revised,[65] Wechsler Adult Intelligence Scale, third edition,[66] and Wechsler Abbreviated Intelligence Scale[67]). This is an estimated full-scale IQ based on 2 subtests, Vocabulary and Block Design (with a small number who received the Wechsler Abbreviated Intelligence Scale Matrix Reasoning instead of Block Design). Similarly, the subtest scaled scores (Vocabulary, Block Design, and Digit Symbol–Coding [called "Coding" hereinafter]) represent composites of several versions of the Wechsler intelligence scales. The following test variables were the same across sites: Trail Making Test Part B (seconds), Continuous Performance Test–Identical Pairs Digits discriminability (d′), Controlled Oral Word Association (FAS version, except for 1 site that used the CFL version) total words, and Wisconsin Card Sorting Test Perseverative Errors.

The Verbal Memory variable represents a composite score composed of list learning and story recall measures. List learning represents a composite of measures used at different sites (Hopkins Verbal Learning Test–Revised, Rey Auditory Verbal Learning Test, California Verbal Learning Test adult and child versions) and based on the percentage correct across trials (to account for different numbers of words on different tests) and then standardized against the performance of the control group. Story recall represents a composite of measures used at different sites (Children's Memory Scale Stories[75]; Wechsler Memory Scale, third edition,[74] Logical Memory I; or Wechsler Memory Scale–Revised[73] Logical Memory I) and was based on the percentage of units recalled in the immediate recall conditions, standardized against the controls. Standardization resulted in controls having a mean of 0 and a standard deviation of 1. Overall, the composite Verbal Memory variable represents the mean of the list learning and story recall standardized scores in cases in which both measures were administered or, in cases in which only 1 measure was administered, the standardized score for either list learning or story recall.

SUPPLEMENTAL STATISTICAL ANALYSES

We used the multiple imputation procedure in SPSS 17.0 (SPSS Inc, Chicago, Illinois). There are 2 sources of error contained in imputed values: uncertainty in the form of sampling variability and in the correctness of the imputed values. Therefore, multiple imputations (ie, 2 or more complete data sets) are generated because this method has the advantage of averaging over the sources of error to calculate less biased parameter estimates.[80-82] After imputation, parameter estimates and standard errors for each data set are pooled to create a single set of estimates and standard errors. Planned analyses are then conducted on each imputed data set, and the results are combined by means of formulas provided by Rubin.[80]

The values that were imputed were for the 8 variables described previously. Overall, 7.3% of the data (190 of 2600 values) were missing; 51.4% of subjects had no missing data, 40.8% had 1 missing value, and 7.8% had 2 missing values. In terms of individual tests, Wisconsin Card Sorting Test Perseverative Errors contained the most missing data (30.8% missing), which accounted for more than half (100 of 190) of the total missing values, followed by Continuous Performance Test–Identical Pairs Digits d′ (14.8% missing), Verbal Memory (4.0%), Coding (2.8%), Trail Making Test Part B (2.5%), Vocabulary (2.2%), and Block Design (1.5%). Controlled Oral Word Association contained no missing data. Missing values for IQ estimate (3.7%) were then computed on the basis of Vocabulary and Block Design scores. The predictors in the imputation models included the 8 neurocognitive variables and the 3 demographic variables used as covariates (age, sex, and parental education). We created 5 imputed data sets. The imputation method involved fitting a univariate model for each of the neurocognitive variables by using all other variables in the model as predictors and then imputing missing values for each variable being fit. This method was repeated until the maximum number of iterations (5) was reached. Additional constraints were imposed on the imputed values such that estimated values could not exceed the minimum or maximum values present in the data set.

In addition, we recalculated the Kaplan-Meier survival analysis used in our clinical prediction article published by Cannon et al[30] on the smaller, multivariate sample (n=167) used for prediction of conversion in this report. The reanalysis was con-

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ducted to clarify whether the same pattern of predictors was present as in the original report, thus providing a context for understanding the introduction of neuropsychological data into the prediction model. We used the 5 variables that were "uniquely associated" with prediction of conversion. As in the original report,

> we used Kaplan-Meier survival analysis to ascertain the shape of the survival function during the 2½-year follow-up interval, the cumulative rate of conversion, and the incidence rates of conversion within successive 6-month epochs. We also sought to derive a multivariate algorithm that optimizes prediction of conversion to psychosis using Cox's proportional hazards model. In this form of analysis, predictors are modeled in relation to the time since baseline to conversion to psychosis, and subjects who do not experience conversion contribute to the prediction until they are no longer available for observation, at which point they are considered censored.[30(p 30)]

RESULTS

Demographics, raw data, statistical analyses, and samples by sites for the univariate sample are presented in **eTables 1**, **2**, **3**, and **4**. We performed 2 χ^2 tests to determine whether group (clinical high-risk, family high-risk, and normal control) ascertainment differed significantly by site (eTable 4). As expected, sites contributed significantly different samples. On the basis of the 5 sites that contributed multivariate data, $\chi^2_8=189.52$ and $P<.001$. For the 8 sites that contributed univariate data, $\chi^2_{14}=343.8$ and $P<.001$.

In Kaplan-Meier analyses, the same analytic approach used in the Cannon et al[30] report applied to the reduced sample reported in this article yielded largely comparable prediction statistics (ie, the hazard ratios [HRs] for all 5 unique predictors remained high), although 3 of the predictors were no longer statistically significant, being reduced to trends secondary to attenuation in sample size. The results are as follows: genetic risk and functional decline, $\chi^2=10.98$, $P<.001$, HR=2.69; unusual thought content, $\chi^2=2.45$, $P=.12$, HR=1.58; suspiciousness/paranoia, $\chi^2=2.37$, $P=.12$, HR=1.73; social functioning, $\chi^2=12.41$, $P<.001$, HR=3.92; and any substance abuse, $\chi^2=2.11$, $P=.14$, HR=1.64. These data support the generalizability of the findings from the current multivariate sample to the larger NAPLS sample described in Cannon et al[30] and indicate that prediction statistics (eg, positive predictive power) are roughly equivalent across the full sample and the multivariate subsample presented in this report.

eTable 1. Demographic Characteristics for the Univariate Sample[a]

	CHR (Total Sample)	FHR	NC	Test Statistic (*P* Value)[b]	Post Hoc Contrasts[c]	CHR Conversion to Psychosis: CHR+	CHR–: CHR–	Test Statistic (*P* Value)
Age, mean (SD), y [n]	18.4 (4.8) [304]	18.7 (3.9) [52]	18.7 (4.6) [193]	*F*=.29 (.75)		18.5 (3.7) [73]	18.1 (4.9) [196]	*F*=.12 (.47)
Subject education, mean (SD) [n]	10.5 (2.9) [300]	10.7 (2.7) [47]	11.3 (3.4) [191]	*F*=4.43 (.01)	CHR<NC	10.7 (2.6) [73]	10.3 (3.1) [193]	*F*=.663 (.32)
Parental education, mean (SD) [n][d]	5.4 (1.7) [304]	4.9 (2.1) [52]	5.8 (1.8) [193]	*F*=5.79 (.003)	CHR, FHR<NC	5.3 (1.6) [73]	5.5 (1.7) [196]	*F*=.940 (.33)
Female sex, No. (%)	118/304 (38.8)	28/52 (53.8)	103/193 (53.4)	χ^2=11.78 (.003)	CHR<FHR, NC	28/73 (38.4)	78/196 (39.8)	χ^2=.046 (.83)
Race, No. (%)								
White	238/292 (81.5)	32/51 (62.7)	124/191 (64.9)	χ^2=19.97 (<.001)	CHR>FHR, NC	56/72 (77.8)	157/190 (82.6)	χ^2=.809 (.38)
African American	26/292 (8.9)	8/51 (15.7)	29/191 (15.2)	χ^2=5.19 (.07)		9/72 (12.5)	15/190 (7.9)	χ^2=1.33 (.25)
Asian	15/292 (5.1)	0/51 (0)	19/191 (9.9)	χ^2=7.37 (.02)	FHR<CHR, NC	5/72 (6.9)	9/190 (4.7)	χ^2=.503 (.48)
Multiracial	13/292 (4.5)	11/51 (21.6)	19/191 (9.9)	χ^2=18.62 (<.001)	FHR>CHR, NC	2/72 (2.8)	9/190 (4.7)	χ^2=.498 (.48)
Latino/Latina ethnicity, No. (%)	47/290 (16.2)	14/50 (28.0)	25/183 (13.7)	χ^2=5.90 (.05)		13/70 (18.6)	27/187 (14.4)	χ^2=.662 (.42)

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

[a] Subjects were included if they completed at least 1 neuropsychological test. 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.[56] 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.

[b] Statistical tests reflect comparisons among CHR, FHR, and NC groups only.

[c] Bonferroni-corrected post hoc contrast ($P<.05$).

[d] 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.

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eTable 2. Neuropsychological Test Scores for the Univariate Sample

Variable	Mean (SD) [No.]					
	CHR	FHR	NC	CHR+	CHR–	CHR+FH+
WIS FSIQ	105.6 (17.9) [275]	98.1 (12.9) [49]	109.9 (14.8) [173]	101.9 (19.5) [71]	106.9 (17.1) [171]	99.0 (21.0) [13]
Vocabulary[a]	11.3 (3.5) [292]	9.8 (2.6) [52]	12.3 (3.0) [183]	10.2 (3.4) [71]	11.7 (3.5) [187]	10.3 (4.2) [13]
Block Design[a]	10.7 (3.6) [258]	9.6 (2.6) [52]	11.1 (3.4) [182]	10.3 (4.0) [66]	10.8 (3.4) [166]	9.3 (4.4) [12]
Coding[a]	8.9 (3.2) [226]	8.8 (2.7) [47]	10.8 (3.3) [109]	8.6 (3.2) [63]	8.9 (3.4) [139]	8.0 (3.1) [13]
TMT-B, s	68.8 (39.9) [219]	72.7 (25.8) [49]	58.4 (30.8) [113]	78.9 (52.3) [59]	64.0 (33.3) [135]	72.2 (37.2) [12]
CPT-IP Digits d′	1.47 (0.92) [200]	1.51 (0.99) [43]	1.88 (0.98) [158]	1.31 (0.86) [48]	1.50 (0.96) [135]	1.01 (0.79) [7]
COWA raw score	35.1 (11.6) [230]	33.9 (11.1) [49]	40.6 (11.7) [116]	32.5 (12.2) [62]	36.1 (11.0) [144]	33.2 (17.1) [13]
WCST Perseverative Errors	8.7 (5.1) [234]	7.6 (4.2) [14]	7.4 (4.4) [101]	9.5 (5.3) [58]	8.2 (5.0) [155]	9.3 (3.4) [10]
Verbal Memory, *z* score[b]	–0.66 (1.4) [277]	–0.29 (1.0) [52]	0 (1.0) [191]	–1.06 (1.6) [67]	–0.53 (1.3) [179]	–1.26 (1.5) [12]

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.

[a] Wechsler subtests are age-corrected scaled scores.

[b] 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 for Children's Memory Scale, Wechsler Memory Scale–Revised, and Wechsler Memory Scale–Third Edition, Logical Memory I, standardized against the NC group.

eTable 3. Contrast Analyses (ANCOVAs) Adjusted for Sex, Age, and Parental Education for Univariate Sample (*F* Values)[a]

Variable	CHR vs NC	FHR vs NC	CHR vs FHR	CHR+ vs NC	CHR– vs NC	CHR+ vs CHR–	CHR+FH+ vs NC
WIS FSIQ	4.98[b]	18.00[c]	–4.63[b]	9.78[d]	1.91	3.53	4.16[b]
Vocabulary	5.68[b]	**23.25**[c]	–6.55[b]	**20.03**[c]	1.02	**11.03**[d]	2.81
Block Design	1.11	4.38[b]	–1.80	1.91	0.22	0.74	1.93
Coding	**19.28**[c]	**12.66**[c]	–0.33	**13.42**[c]	**13.65**[c]	0.60	**8.50**[d]
TMT-B	3.24	4.30[b]	–0.13	6.69[b]	0.39	4.97[b]	0.73
CPT-IP Digits d′	**14.95**[c]	3.50	0.50	**12.21**[d]	**8.94**[d]	1.29	**9.03**[d]
COWA raw score	**12.22**[d]	**7.84**[e]	–0.43	**15.07**[c]	5.87[b]	4.30[b]	2.85
WCST Perseverative Errors	2.17	0.82	0.99	4.43[b]	0.15	2.19	1.04
Verbal Memory	**29.75**[c]	2.42	5.32[b]	**38.45**[c]	**18.99**[c]	6.55[b]	**15.56**[c]

Abbreviations: ANCOVAs, analyses of covariance; 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; FH+, family history of psychosis; 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.

[a] Boldfaced values for the 8 primary measures (excluding WIS FSIQ) indicate test remains significant at Bonferroni-corrected level of $P \leq .00625$.

[b] $P < .05$.

[c] $P < .001$.

[d] $P < .005$.

[e] $P < .01$.

eTable 4. Number of Subjects by Group and Site for the Univariate/Multivariate Samples[a]

Site	No. by Group, Univariate/Multivariate			
	CHR	FHR	NC	Total
UNC	47/40	0/0	35/34	**82/74**
Emory	11/0	1/0	29/0	**41/0**
Harvard	0/0	37/37	54/54	**91/91**
ZHH	45/38	4/4	23/21	**72/63**
Toronto	37/28	3/3	0/0	**40/31**
UCLA	38/0	0/0	4/0	**42/0**
UCSD	57/0	2/0	48/0	**107/0**
Yale	69/61	5/5	0/0	**74/66**
Total	**304/167**	**52/49**	**193/109**	**549/325**

Abbreviations: CHR, clinical high-risk; FHR, family high-risk; NC, normal control; UCLA, University of California, Los Angeles; UCSD, University of California, San Diego; UNC, University of North Carolina; ZHH, Zucker Hillside Hospital.

[a] Subjects in the univariate sample completed 1 or more neurocognitive tests. Subjects in the multivariate sample completed 6 or more neurocognitive tests.

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