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Neuropsychological profiles in individuals at clinical high risk for psychosis: Relationship to psychosis and intelligence

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ABSTRACT

Background: Characterizing neuropsychological (NP) functioning of individuals at clinical high risk (CHR) for psychosis may be useful for prediction of psychosis and understanding functional outcome. The degree to which NP impairments are associated with general cognitive ability and/or later emergence of full psychosis in CHR samples requires study with well-matched controls.

Methods: We assessed NP functioning across eight cognitive domains in a sample of 73 CHR youth, 13 of whom developed psychotic-level symptoms after baseline assessment, and 34 healthy comparison (HC) subjects. Groups were matched on age, sex, ethnicity, handedness, subject and parent grade attainment, and median family income, and were comparable on WRAT-3 Reading, an estimate of premorbid IQ. Profile analysis was used to examine group differences and the role of IQ in profile shape.

Results: The CHR sample demonstrated a significant difference in overall magnitude of NP impairment but only a small and nearly significant difference in profile shape, primarily due to a large impairment in olfactory identification. Individuals who subsequently developed psychotic-level symptoms demonstrated large impairments in verbal IQ, verbal memory and olfactory identification comparable in magnitude to first episode samples.

Conclusions: CHR status may be associated with moderate generalized cognitive impairments marked by some degree of selective impairment in olfaction and verbal memory. Impairments were greatest in those who later developed psychotic symptoms. Future study of olfaction in CHR samples may enhance early detection and specification of neurodevelopmental mechanisms of risk.

1. Introduction

The literature on cognitive functioning during the putative prodrome to psychosis suggests cognitive impairments are generally intermediate between those of healthy comparison (HC) subjects and first episode psychosis (Eastvold et al., 2007; Francey et al., 2005; Keefe et al., 2006; Pukrop et al., 2006; Simon et al., 2007; Jahshan et al., 2010; Seidman et al., 2010). Of particular interest are findings specific to clinical high risk (CHR) individuals who develop psychosis over the course of follow-up, suggesting possible neuropsychological (NP) predictors of psychosis onset (Brewer et al., 2005; Brewer et al., 2003; Keefe et al., 2006; Lencz et al., 2006; Seidman et al., 2010). In the largest published study to date,

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NP function was more impaired at baseline in those who later developed psychosis than in those who did not (Seidman et al., 2010). When placed in the context of clinical factors predicting psychosis (e.g., severity of attenuated positive symptoms, family history, social functioning, and substance abuse), however, NP functioning did not add to the prediction algorithm (Cannon et al., 2008). Just the same, verbal memory may have added value in predicting faster transition to psychosis (Seidman et al., 2010). The relative value of both specific NP measures and general cognitive ability in predicting and understanding psychosis onset warrants additional study.

1.1. "Specific" deficits during the prodrome to psychosis

A number of "specific" deficits (presumably above and beyond any general deficit) have been documented in CHR samples, most reliably spatial working memory (Bartok et al., 2005; Myles-Worsley et al., 2007; Smith et al., 2006; Wood et al., 2003), verbal learning and memory (Brewer et al., 2005; Eastvold et al., 2007; Hawkins et al., 2004; Lencz et al., 2006; Seidman et al., 2010), attention (Francey et al., 2005; Gschwandtner et al., 2006; Hambrecht et al., 2002; Hawkins et al., 2004; Niendam et al., 2006) and processing speed (Seidman et al., 2010). Executive functions such as working memory, verbal fluency, and set-shifting have also been implicated, but less consistently (Eastvold et al., 2007; Gschwandtner et al., 2003; Gschwandtner et al., 2006; Hambrecht et al., 2002; Hawkins et al., 2004; Lencz et al., 2006; Myles-Worsley et al., 2007; Pukrop et al., 2006; Simon et al., 2007). In the few studies with clinical follow-up, poorer baseline verbal memory and olfactory identification have been identified as potential proximate predictors of later psychosis (Brewer et al., 2005; Brewer et al., 2003; Eastvold et al., 2007; Lencz et al., 2006; Seidman et al., 2010).

The possible predictive value of olfactory identification deficits, although measured in only one prior CHR study (Brewer et al., 2005), is intriguing. The ability to name odors is reliably impaired in adults with schizophrenia (SCZ) and in some studies, in individuals at familial high risk (FHR; Mesholam-Gately and Seidman, 2006; Moberg and Turetsky, 2006). In one study of SCZ, this impairment (as measured by the University of Pennsylvania Smell Identification Test, UPSIT) was not significantly associated with performance on measures of attention, executive function, or IQ, suggesting some specific utility (Seidman et al., 1992). Moreover, neurobiological studies have identified abnormalities in the olfactory bulb (Turetsky et al., 2000) and olfactory event related potentials of those with SCZ (Turetsky et al., 2003), suggesting abnormalities in specific neural substrates.

1.2. The role of current and "premorbid" IQ in neuropsychological profiles

In the literature, "specific" deficits are often defined by statistically significant group differences in a single cognitive domain rather than the specificity of the deficit relative to overall functioning. However, it is well established that performance on different NP tests tends to be positively correlated (Spearman, 1927). Furthermore, both degree of inter-test variability and pattern of strengths and weaknesses on a NP battery may vary according to overall cognitive ability or attention, and vary differently for SCZ relative to HC matched on IQ (Diaz-Asper et al., 2004; Dodrill, 1999; Kremen et al., 2008). Because attentional functions have long been hypothesized to be central to schizophrenia and its risk (Seidman, 1983; Nuechterlein and Dawson, 1984; Cornblatt and Keilp, 1994), we also evaluated the role of attentional impairment in the profiles of CHR versus HC.

The role of current global ability in SCZ has also been studied relative to premorbid IQ estimated with measures of single word reading, a function relatively resilient to illness (Dalby and Williams, 1986; Kremen et al., 1996; Weickert et al., 2000). Given its weaker correlation with measures of nonverbal reasoning and processing speed, single word reading may be associated with different patterns of NP performance than Full Scale measures of IQ (FSIQ). Current full scale and premorbid IQ estimates may thus have different relationships to patterns of NP functioning associated with risk and onset of psychosis. These have not yet been adequately investigated in CHR samples.

Finally, potentially important variables such as age, sex, and sociodemographic status have not been controlled routinely and some HC groups are likely to be "supernormal" as reflected by high group mean IQ scores (e.g., 119, Gschwandtner et al., 2006) or have significantly different estimated premorbid IQ relative to CHR groups (Brewer et al., 2005; Pukrop et al., 2006). Thus, there remains a need to characterize NP functioning and profiles within CHR samples relative to well-matched HC, with particular attention to the influential role of premorbid IQ. Matching on premorbid IQ has been strongly recommended in a review of the CHR literature (Brewer et al., 2006).

1.3. Purpose of this study

This study's primary goal was to characterize the overall NP profile of CHR relative to demographically well-matched HC. We predicted that CHR would differ from HC in overall mean NP profile magnitude and shape, with those subsequently developing psychotic-level symptoms showing the greatest level of NP impairment. More specifically, we predicted relatively greater impairment in verbal memory and olfactory functioning after accounting for global abilities estimated by either single word reading or estimated IQ.

2. Methods

2.1. Participants

The CHR sample consisted of participants in a randomized controlled trial (RCT) of family-aided assertive community treatment (FACT, McFarlane, 1997) through the Portland Identification and Early Referral (PIER) program in Portland, ME (McFarlane, et al., 2010). Entry into the study required residence in Greater Portland, estimated IQ $\geq$ 70, and meeting criteria for one of three putatively prodromal syndromes (Criteria of Prodromal Syndromes, COPS) according to the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 1999). These syndromes are based on the recent onset of brief and intermittent psychotic symptoms (BIPS), recent onset or progression of attenuated positive symptoms (APS),

and/or a substantial drop in functioning in the context of either schizotypal personality disorder or a first-degree family history of psychosis (indicating a genetic risk and deterioration syndrome, GRDS).

Ninety participants age 12 to 25 entered the trial based on COPS criteria. Of these, 80 (89%) participants met APS criteria (8 of whom also met GRDS criteria), 5 (6%) met BIPS criteria (none also met GRDS criteria), and 5 (6%) met GRDS criteria alone. Of the 90 participants, 78 (87%) completed baseline NP assessment. Four participants were removed from NP analyses due to: history of neurosurgery, learning English after beginning elementary school, hearing impairment, or more than 10% missing data on neurocognitive measures. After removal of an extreme outlier, NP data for the remaining 73 were included in the analyses.

HC subjects were recruited from the PIER catchment area to match the CHR sample on demographics. Exclusion criteria included: significant developmental delays, current or past

Table 1
Test variables by domain.

Domain	Tests and subtests	Description of task/measure
Premorbid IQ, Estimated	Wide Range Achievement Test (WRAT-3) Reading (Blue)	Accurately read and pronounce single words. *Measure:* Standard score
Current IQ, Estimated	Wechsler Abbreviated Scale for Intelligence (WASI):	*Measure:* Standard score based on sum of subtest *T*-scores for two verbal and two nonverbal IQ subtests.
Verbal IQ	WASI Vocabulary WASI Similarities	Accurately verbalize the meaning of words. Describe how two words/items are alike.
Nonverbal IQ	WASI Block Design WASI Matrix Reasoning	Rapidly assemble blocks into 2-dimensional patterns. Identify the correct multiple-choice option to complete a matrix design.
Sustained attention/ working memory:	Continuous Performance Test-Identical Pairs (CPT-IP-II): Practice: Numbers (three-digits)	Lift finger whenever two stimuli in a row (flashed on a computer screen) are exactly alike. *Measure:* Mean d′ of fast and slow subtests for each domain; d′ is a measure of response sensitivity accounting for correct responses and false alarms.
Verbal attention	Four digits	
Nonverbal attention	Shapes	
Verbal memory	California Verbal Learning Test (CVLT, Version II, age ≥16 or Child Version, age <16)	Recall words from a list of 16 (CVLT-II) or 15 (CVLT-C) words read aloud 5 times. *Measure:* Total of trials 1–5, percent of total, *T* score
	Wechsler Memory Scale-III (WMS-III) Logical Memory (age ≥16) or Children's Memory Scale Stories (CMS, age <16)	Immediate recall of two short stories read aloud. *Measure:* Percent of raw score total, scaled score of total units recalled.
Executive function	Delis–Kaplan Executive Function System (D-KEFS)	*Measure:* Raw or scaled score
	Verbal Fluency Condition 3	Generate as many words as possible in 60-seconds switching back and forth between two categories.
	Trail Making Condition 4	Quickly sequence numbers and letters in a two-page array, alternating between numbers and letters.
	Wisconsin Card Sorting Test (WCST-128): Computer Version	Match cards on a number of characteristics based on verbal feedback. *Measure:* Perseverative errors raw, standard scores
	WMS-III (age ≥ 16) or Wechsler Intelligence Scale for Children-IV (WISC-IV, age <16) Letter-Number Sequencing	Repeat a sequence of numbers and letters read aloud after mental resequencing. *Measure:* Percent of total, scaled score
Motor	Finger Tapping Test	Tap a lever as fast as possible with the index finger of each hand over 10 second trials. *Measure*: Mean # of taps across trials
Olfaction	Brief Smell Identification Test (B-SIT)	Choose one of four choices identifying each of 12 odors in a scratch and sniff booklet *Measure:* # correct

Note: Domains for profile analysis are in **bold**. IQ and Sustained Attention/Working Memory are listed in conjunction with broad category tests from which verbal and nonverbal domains were obtained. Standard and Scaled Scores are based on age-based normative data provided for selected tests. Raw or "percent of total" scores were entered into regression analyses for all tests except IQ. Citations for tests are: WRAT-3 (Wilkinson, 1993); WASI (Wechsler, 1999); CPT-IP-II (Cornblatt and Keilp, 1994); WCST (Heaton, 1981); D-KEFS (Delis et al., 2001); WMS-III (Wechsler, 1997); WISC-IV (Wechsler, 2003); CMS (Cohen, 1997); CVLT-II (Delis et al., 2000); CVLT-C (Delis et al., 1994); Finger Tapping Test (Reitan and Wolfson, 1993); B-SIT, a brief version of the University of Pennsylvania Smell Identification Test (UPSIT, Doty et al., 1996; Doty et al., 1984).

psychosis or prodromal positive symptoms, major DSM-IV psychiatric disorder within the past year, medical issues or a current medication regimen with potential impact on cognitive functioning, first or second degree relative with a history of psychosis, sensorimotor handicaps, or a recent, significant decline in functioning. Of the 39 HC assessed, three were excluded for a first or second degree relative with a psychotic disorder, one due to prodromal-level symptoms, and one to reduce an apparent ascertainment bias of superior IQ (>130), leaving 34 HC participants.

2.2. Measures

2.2.1. Clinical assessments

CHR and HC participants were assessed with the SIPS (Miller et al., 1999) and the Structured Clinical Interview for DSM-IV-TR (First et al., 1997). Kappa was 0.78 for inter-rater agreement of clinical raters on classification of presence or absence of the prodromal syndrome. Longitudinal clinical assessment of CHR included monthly symptom assessment with the five-item SIPS positive symptom subscale (P). "Emergency" P-scale assessments were completed when a participant was suspected to have developed psychotic symptoms or was psychiatrically hospitalized.

Given the lack of consensus in the field about what constitutes the threshold for "conversion" to psychosis, including the absence of an operational definition of psychosis in DSM-IV, we used the rating of "6" on at least one SIPS P-scale item to define a putatively psychotic subgroup. The criteria for a "6" rating (severe and psychotic) includes "conviction (with no doubt) at least intermittently" and influence on or interference with thinking, feelings, social relations, or behavior, thus capturing the core of what it means to be psychotic, regardless of specific DSM psychotic disorder diagnosis. Individuals with only brief and intermittent symptoms at this level (i.e., BIPS) may not meet DSM-IV diagnostic criteria for a specific psychotic disorder (based on the frequency and duration of this level of symptom), and thus may still be considered putatively prodromal. However, building on similar models of symptom progression (Cornblatt et al., 2003; Cosway et al., 2000; Häfner et al., 2004), we propose this as a critical threshold for indexing illness progression. In order to capture the progression of symptoms toward illness onset, we identified the subgroup of CHR who were initially (just prior to baseline NP assessment) rated <6 on all SIPS P-scales but subsequently received a rating of 6 over the course of follow-up as "Later Psychotic" (thus excluding those already psychotic, or BIPS, at baseline from this subgroup). This "Later Psychotic" subgroup might be considered at higher risk or in closer proximity to onset of a specific psychotic disorder (e.g., schizophreniform disorder) than those who were never rated at a "6" on the SIPS P-scales during the period of follow-up.

2.2.2. Neuropsychological assessment battery

The NP battery (Table 1) was designed to measure outcomes of the RCT. Specific test scores were assigned to clinically meaningful *a priori* cognitive domains based on conventions in SCZ research (Gur et al., 2007; Nuechterlein et al., 2004). For tests with adult and child versions, child versions were given to all participants under 16. NP testing was conducted by a masters level clinician as soon as possible after initial SIPS assessment. Relevant WAIS-III and WISC-IV subtest scores were used in place of WASI subtest scores for two CHR cases who had been tested previously for clinical reasons relatively close in time to study entry.

2.3. Data analysis

Data distributions were assessed by group for normality and outliers, resulting in log transformation of WCST perseverative errors and time to complete D-KEFS Trail Making Test Condition 4. Eleven missing data points were replaced with the group mean and two missing Similarities *T*-scores were replaced with the mean of the other 3 WASI subtests. Five univariate outlier values were adjusted to one unit beyond the next closest value (Tabachnick and Fidell, 2001). One multivariate outlier was removed from all analyses and one from group analyses of

Table 2
Demographics by group and subgroup.

	HC	CHR	COPS Subgroups		Grouping by Development of Psychotic Level Symptoms	
			APS	BIPS	Later Psychotic	Never Psychotic
N	34	73†	65†	5	13	55†
Age (*SD*)	16.2 (2.5)	16.5 (2.7)	16.5 (2.7)	17.6 (3.1)	16.7 (2.4)	16.4 (2.7)
Male (N/%)	18/53	36/49	31/48	3/60	5/39	28/51
R handed (N/%)	29/85	66/90	60/93	4/80	12/92	50/91
Highest grade (*SD*)	9.2 (2.3)	9.5 (2.6)	9.5 (2.5)	10.6 (2.8)	9.6 (2.3)	9.4 (2.6)
Parent highest grade (*SD*)	14.6 (1.9)	14.3 (1.8)	14.3 (1.8)	13.6 (1.6)	13.5 (1.9)	14.5 (1.9)
Median family income	$50–60 K	$50–60 K	$50–60 K	$80–90 K**	$50–60 K	$50–60 K
Caucasian (N/%)	31/91	67/92	59/91	5/100	13/100	49/89

Note: HC: Healthy Comparison; CHR: Clinical High Risk; APS: Attenuated Psychotic Symptoms; BIPS: Brief Intermittent Psychotic Symptoms; COPS: Criteria of Prodromal Syndromes; COPS Subgroups do not include Genetic Risk and Deterioration Syndrome, GRDS, as separate subgroup as 8 of 11 GRDS subgroup also met APS criteria and thus are included within this group; Three CHR subjects met GRDS criteria alone but are not included here due to small sample size; Later Psychotic: CHR with a rating of "6" on Structured Interview of Prodromal Syndromes (SIPS) positive (P) symptom scale at some point *after* baseline testing; Never Psychotic: CHR who had not received a "6" rating on the SIPS P-scale at baseline or within the follow-up interval; Grouping by Development of Psychotic-Level Symptoms subgroups ($n=68$) exclude those with BIPS ($n=5$); Chi square could not be used to compare groups on Median Family Income due to insufficient counts in each cell. However, there was a significant difference in "mean" family income (albeit with skew to the upper income range due to truncated scale) for the BIPS group relative to healthy comparisons, so this is indicated instead. No other comparisons were significantly different.

†Including one case that was removed as a multivariate outlier for those group analyses not including olfactory scores.

*$p<0.05$ ** $p<0.01$ ***$p<0.001$ relative to HC; no demographic comparisons were significant after Bonferroni correction ($p<0.0013$).

neurocognitive domains without the measure of olfaction. Independent *t* tests and *Chi*-square tests were used to compare groups on demographic, clinical, and neurocognitive variables.

Following Kremen et al. (2004), NP test scores for the HC group were regressed on age, sex, and mean parental education to obtain regression parameters and calculate predicted scores. Residuals (predicted minus observed scores) were then standardized according to the HC distribution for each test. Domain scores are the mean standardized residual of tests within each domain. The overall composite score is the mean of standardized residuals across domains.

Profile analysis was used to assess differences in profile magnitude (group effect), flatness (domain effect), and parallelism (group by domain interaction, or difference in profile shape by group). Eighteen CHR were missing olfactory scores because the Brief Smell Identification Test (BSIT) was added after study entry. Analyses conducted on the smaller sample (55 of 73) "with olfaction" were repeated with the larger sample "without olfaction" to improve power as the two groups did not differ significantly on baseline demographic or NP measures.

To explore the role of overall intellectual ability in profile differences, we repeated the profile analyses with WRAT-3 Reading standard score (StS) as a covariate, and with Reading StS and then FSIQ as additional between subjects variables based on a median split of the entire sample (median = 106 and 104, respectively). To examine the possible role of attention in overall profile patterns, we repeated the profile analyses covarying the d′ of our simplest attention (vigilance) task, the 3 digit trial of the CPT-IP-II. Univariate results are reported only after a finding of significant multivariate effects, except in cases of nearly significant trends or report of effect sizes for exploratory analyses (analyses of the role of intellectual ability) or comparison with other studies. All tests were two-tailed. Greenhouse–Geisser values are reported whenever assumptions of sphericity were violated.

3. Results

3.1. CHR sample characterization

HC were well matched to CHR participants on demographic variables (Table 2). The two groups did not differ significantly on age, gender or racial distribution, handedness, highest grade completed, parent education, or family

Table 3
Neuropsychological data by group and subgroup.

	HC	CHR	COPS Subgroups		Grouping by Development of Psychotic Level Symptoms	
			APS	BIPS	Later Psychotic	Never Psychotic
N	34	73†	65†	5	13	55†
N with age<16/≥16	17/17	40/33	36/29	2/3	6/7	31/24
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)	*M* (*SD*)
WRAT-3 reading StS	105.7 (12.0)	104.6 (11.3)	104.7 (11.5)	106.6 (9.5)	105.5 (9.7)	104.2 (11.9)
WASI Full Scale IQ	109.4 (11.1)	102.7 (12.8)*	103.7 (13.1)*	92.6 (7.2)	98.0 (10.1)**	104.8 (13.2)
WASI VIQ	110.8 (13.9)	102.8 (13.4)**	103.8 (13.8)*	95.4 (6.9)*	96.1 (12.9)**	105.1 (13.4)
WASI PIQ	105.7 (9.4)	101.9 (13.9)	102.7 (13.9)	91.0 (8.3)**	99.8 (9.8)	103.4 (14.7)
CPT-IP Verbal d′	1.38 (0.57)	1.38 (0.73)	1.37 (.69)	1.54 (1.44)	1.37 (0.56)	1.37 (0.70)
CPT-IP Nonverbal d′	2.05 (0.81)	1.90 (0.70)	1.9 (0.73)	1.74 (0.48)	1.77 (0.64)	1.95 (.73)
Mean % Memory	0.67 (0.09)	0.62 (0.13)*	0.62 (0.13)*	0.58 (.11)	0.56 (0.10)**	0.63 (0.14)
CMS Stories I ††	12.9 (3.1)	11.1 (4.1)	11.2 (4.2)	11.0 (2.8)	9.6 (4.2)*	11.4 (4.1)
WMS-III Log Mem I ††	10.5 (2.9)	10.2 (3.2)	10.5 (3.2)	8.0 (2.6)	8.7 (3.9)	10.9 (3.0)
CVLT-C Trial 1–5 *T*	54.0 (5.2)	49.5 (12.1)	49.7 (11.6)	56.5 (3.5)	46.0 (10.1)	49.7 (12.8)
CVLT-II Trial 1–5 *T*	54.6 (6.5)	49.1 (13.1)	49.7 (13.4)	48.0 (11.4)	44.7 (9.3)**	50.5 (14.3)
Mean Executive Function††	11.5 (2.0)	10.1 (1.7)**	10.1 (1.8)**	9.8 (2.8)	9.9 (1.5)*	10.15 (1.8)*
WISC-IV Letter-Numb††	10.5 (2.5)	9.8 (2.0)	9.7 (2.1)	10.0 (1.4)	9.4 (1.5)	9.9 (2.2)
WMS-III Letter-Numb††	9.6 (2.6)	9.8 (2.8)	9.9 (2.9)	8.3(2.3)	9.2 (1.8)	10.12 (3.1)
D-KEFS Trails Con 4††	9.7 (2.1)	9.5 (2.7)	9.5 (2.8)	10.0 (2.7)	9.4 (2.1)	9.5 (2.9)
D-KEFS Fluency Con3††	11.7 (3.1)	10.4 (2.6)*	10.4 (2.7)*	11.4 (0.89)	9.8 (3.1)	10.4 (2.6)*
WCST Perseverative Errors StS	114.1 (15.5)	104.8 (17.4)**	103.8 (17.3)**	116.2 (7.7)	105.1 (16.3)	103.7 (18.0)**
Mean Finger Tapping	46.2 (5.76)	44.7 (7.1)	44.2 (7.0)	49.0 (8.3)	43.7 (7.0)	44.6 (7.1)
Mean Dominant	48.0 (6.2)	47.1 (7.9)	46.8 (8.1)	49.6 (8.1)	47.3 (7.0)	46.9 (8.2)
Mean Nondominant	44.4 (6.1)	42.1 (7.8)	41.2 (7.3)*	48.4 (9.2)	40.1 (7.0)*	42.0 (7.6)
BSIT Olfaction Raw†††	11.0 (0.7)	**9.9 (1.5)*****	**10.0 (1.5)*****	10.0 (1.4)*	9.71 (2.2)**	**10.0 (1.3)*****
MSR with Olfaction	0.00	−0.51***	**−0.49*****	−0.63*	**−0.89*****	−0.44**
MSR without Olfaction	0.00	−0.39*	−0.37*	−0.53	−0.72**	−0.32

Note: Standardized scores are provided when adequate normative data were available to facilitate comparison across child and adult tests and across different studies and measures; *T*: *T*-score; StS: Standard Score; MSR: Mean Standardized Residual based on HC distribution with mean of HC for each test = 0, *SD* = 1. For group abbreviations please see notes for Tables 2 and 3. For full test names and variables please see Table 1. Significance of individual comparisons is provided as indicated below; we highlighted in **bold** those results that remained significant after Bonferroni correction for the number of domain comparisons ($p<0.0008$). The 3 CHR subjects who only met the Genetic Risk and Deterioration Syndrome (GRDS) criteria were not shown here due to the small sample size. Grouping by Development of Psychotic-Level Symptoms subgroups ($n=68$) exclude those with BIPS ($n=5$).

†Including one case that was removed as a multivariate outlier except in analyses of the subgroup with olfactory scores for which it was not an outlier and in profile subgroup analyses.

††Scores are scaled scores (Mean = 10, *SD* = 3).

†††*Ns* are smaller for olfactory functioning as follows: (CHR: 55, APS: 49, BIPS: 4, Later Psychotic: 7, Never Psychotic: 44).

*$p<0.05$ ** $p<0.01$ ***$p<0.001$ relative to HC.

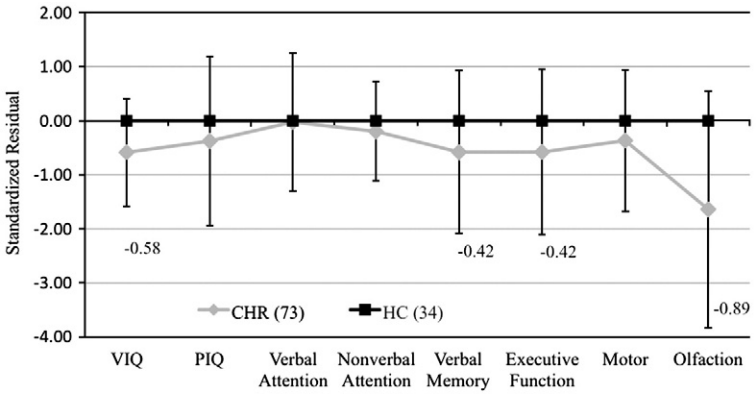

Fig. 1. NP Profile of clinical high risk (CHR) sample relative to healthy comparisons (HC). *Note*: Standardized residuals are based on a HC distribution with $M=0$ and $SD=1$. Error bars represent *SD* for CHR. Cohen's *d* effect sizes are inserted for domains with significant independent *t* test relative to HC. Olfactory scores were available on subset of CHR ($n=55$).

income. Moreover, CHR subgroups were highly similar to HC on demographic variables, with one exception: the BIPS subgroup had higher family income.

3.2. Neuropsychological performance and profile analysis of CHR relative to HC

CHR and HC were highly similar on WRAT-3 Reading (Table 3). However, 38.4% (16% is expected) of CHR current WASI IQ estimates fell more than one standard deviation (*SD*) below the HC mean. The overall NP profile for CHR compared to HC is illustrated in Fig. 1. With and without olfaction included, CHR demonstrated a moderate and significant generalized deficit in NP functioning relative to HC (Cohen's $d=-0.74$ and -0.52, respectively). Profile analysis indicated a significant moderate to large difference in profile magnitude by group ($p<0.001$ and $p=0.018$, respectively). Overall, however, profiles of both groups were relatively "flat"; the overall variation of performance did not differ significantly by NP domain at the multivariate level. Differences in profile *shape* by group were significant at the univariate level only, and only when olfaction was included ($p<.007, \eta_p^2=0.037$). Nearly significant individual effects for both CVLT and story memory contributed to the overall verbal memory impairment; executive functioning deficits were accounted for primarily by significantly lower verbal fluency and higher WCST perseverative errors.

3.3. NP performance for subgroup developing "severe and psychotic" symptoms after baseline

Fifty-seven (78%) of 73 CHR with baseline NP data received at least two years of clinical follow-up; the other 16 CHR had a mean 7 months follow-up interval. Of the 68 without psychotic-level symptoms at baseline, 13 developed psychotic-level symptoms during the period of follow-up: one was diagnosed with schizophrenia, three with schizoaffective, three with mood, and six with brief psychosis or psychosis NOS disorders. Fig. 2 shows their mean baseline NP profile. The effect sizes for VIQ, verbal memory and olfactory deficits in this group are large. Interestingly, whereas only one (7.7%) of the 13 had a WRAT-3 Reading score more than one *SD* below the HC mean, 8 (61.5%) had current IQ estimates over one *SD* below the HC

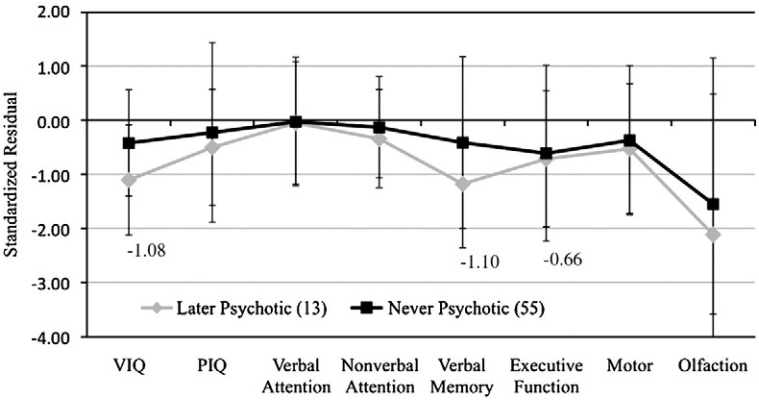

Fig. 2. NP profiles by development of "severe and psychotic" level symptoms. *Note:* Standardized residual is based on healthy comparison (HC) sample with $M=0$; $SD=1$; Later Psychotic: clinical high risk (CHR) with a rating of "6" on the positive symptom "P" scale of the Structured Interview of Prodromal Syndromes (SIPS) at some point *after* baseline; Never Psychotic: CHR who had not received a "6" rating on the SIPS P-scale at baseline or within the follow-up interval. Cohen's *d* is provided for domain scores of the Later Psychotic group that were significantly different from HC at baseline. The Never Psychotic group was significantly different from HC only on Olfaction ($d=-0.92$) and Executive Function ($d=-0.43$). Of note, the Later Psychotic subgroup had a larger effect size for Olfactory impairment ($d=-1.32$) but the independent *t* test was not significant. CHR groups differed significantly on independent *t* test only on VIQ ($p=0.028$).

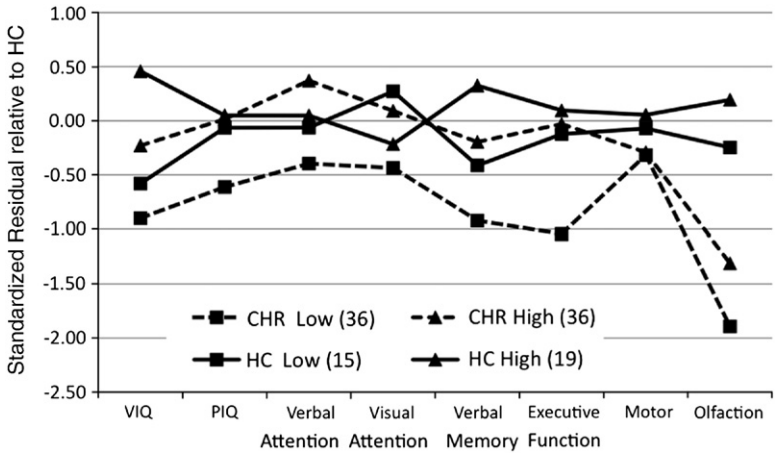

Fig. 3. Group profiles by median split of WRAT-3 Reading score. *Note:* Standardized residual is based on healthy comparison (HC) sample with $M=0$, $SD=1$. CHR = clinical high risk. Low WRAT = WRAT-3 Reading Standard Score (StS) < 106. High WRAT = WRAT-3 Reading StS ≥ 106. Since analyses were conducted with and without olfaction included and domain scores other than olfaction were comparable across larger and smaller samples, the domain scores of the larger sample (72) are provided in the graph for all domains except for olfaction as this score was only available for the smaller sample (31 CHR Low, 24 CHR High). Effects for WRAT level ($p=0.001$, $\eta_p^2=0.125$ with olfaction; $p=0.001$, $\eta_p^2=0.096$ without) were of comparable size to effects for group ($p=0.001$, $\eta_p^2=0.126$ with olfaction; $p=0.015$, $\eta_p^2=0.056$ without). However, differences in profile shape by group at different levels of WRAT were small and nonsignificant with the available power. Post hoc univariate analyses identified nearly significant differences in profile shape by WRAT level within HC ($p=0.058$, $\eta_p^2=0.065$), due to significant differences in relative VIQ and Verbal Memory scores. Profile shapes did not differ between CHR subgroups.

mean. In fact, later development of psychotic level symptoms was significantly correlated with the degree to which estimated IQ was lower than WRAT-3 Reading.

3.4. The role of WRAT-3 Reading, WASI IQ, and attention in neurocognitive profiles

The pattern of profile results remained unchanged when WRAT-3 Reading was entered as a covariate. Although statistical power was low, differences in profile shape by group at different levels of Reading were small ($\eta_p^2=0.010$–0.014). As shown in Fig. 3, the overall profile shape of CHR was strikingly similar at different levels of word reading. When analyses were repeated using a median split of estimated current (WASI) IQ, differences in the profile shape by group at different levels of global impairment were again small ($\eta_p^2=0.006$–0.009) and nonsignificant. As shown in Fig. 4, CHR and HC profiles were very similar at both

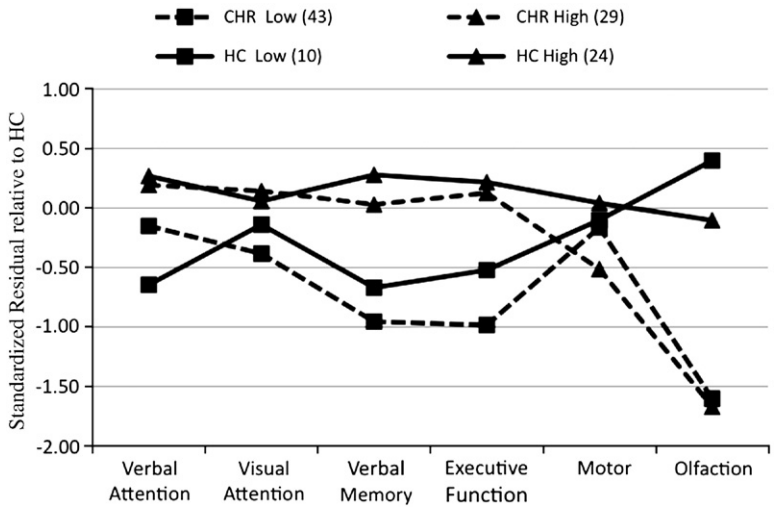

Fig. 4. Group profiles by Median IQ split. *Note:* Standardized residual is based on the healthy comparison (HC) sample with $M=0$, $SD=1$. CHR: clinical high risk; Median IQ split is based on median IQ = 104 for entire sample. Since analyses were conducted with and without olfaction included and domain scores other than olfaction were comparable across larger and smaller samples, the domain scores of the larger sample (72) are provided in the graph for all domains except for olfaction as these were available only for the smaller sample (31 CHR Low, 24 CHR High). Effects for IQ (with olfaction: $p=0.006$, $\eta_p^2=0.086$; without olfaction: $\eta_p^2=0.112$) were of similar magnitude to effects for group (with olfaction: $p=0.005$, $\eta_p^2=0.090$; ns without olfaction), but there was no significant interaction for group by IQ. However, there was a moderate and significant difference in profile shape by group ($p=0.001$, $\eta_p^2=0.056$, ns without olfaction) and a small trend for overall profile shape differences by level of IQ, significant when olfaction was not included (univariate $p=0.010$, $\eta_p^2=0.034$). There was insufficient power to find significance for the apparently small profile shape effect by group at different levels of IQ ($\eta_p^2=0.006$; without olfaction: $\eta_p^2=0.009$).

high and low levels of IQ except on olfactory functioning. That is, the overall *pattern* of NP strengths and weaknesses showed similar variation by level of IQ for both CHR and HC. Finally, basic results of profile analyses did not differ when attention was entered as a covariate.

4. Discussion

This study examined the NP profile magnitude and shape of a CHR sample in comparison with a very closely matched HC group in order to identify severity and specificity of NP impairments. CHR and HC groups were highly similar, not only on key demographic features such as age, gender, handedness, parental education, and family income, but on an estimate of premorbid cognition (WRAT-3 Reading). In comparison to HC, CHR participants demonstrated a moderate to large overall NP impairment (roughly 1/2 to 3/4 of a standard deviation below HC), consistent with published reports (e.g., Seidman et al., 2010, table 4, page 584). Impairment was amplified in CHR participants who later developed psychosis, particularly in verbal IQ, verbal memory, and olfactory identification. These findings confirm and extend previous work demonstrating NP impairment in CHR, especially in those who transition to psychosis. Nevertheless, the high degree of overlap between CHR and HC highlights the importance of well-matched HC in understanding NP development in the context of psychosis risk.

4.1. Overall pattern of NP performance in CHR

Somewhat consistent with three similar analyses (Lencz et al., 2006; Pukrop et al., 2006; Seidman et al., 2010), we found a nearly significant difference in the NP *profile shape* of CHR relative to HC. In contrast to the Lencz et al. and Seidman et al. studies, however, this was primarily due to a large and significant impairment in olfactory identification (Cohen's $d=-0.89$). When olfaction was not included in the analysis, the specific pattern of NP strengths and weaknesses in CHR did not differ significantly from HC. In fact, the functioning of the entire sample did not differ significantly by NP domain. The effect size of olfactory identification impairment was almost twice the size of effects found for other domains (or single test scores) and the single domain distinguishing CHR from HC. The presence of specific deficits may depend in part on the particular measures used and, thus far, measures of verbal memory and olfactory identification have the most support.

4.2. Olfactory identification as a potential marker of risk

In conjunction with one other study of olfaction in CHR (Brewer et al., 2003), our study provides additional support for impaired olfactory identification prior to acute psychosis. The large size of this deficit suggests that the BSIT, although consisting of only 12 of the 40 items of the UPSIT, may demonstrate adequate sensitivity to risk for psychosis and serve as a viable (and more affordable) option for probing this important area of function. In possible contrast to the Brewer study, the pervasiveness of olfactory identification impairment in our CHR sample suggests that, as measured with the BSIT, this impairment may signal broad risk for psychosis rather than specific risk for SCZ.

As olfactory identification is reliant on accurate detection of odors and accurate recognition of verbal odor labels, its impairment may have implications for abnormalities in limbic, ventromedial and orbital prefrontal, and/or temporal lobe development. If the large effect size of this deficit relative to verbal deficits is reliable, neural pathways specific to olfaction are most strongly implicated (e.g., Seidman et al., 1992). This is further supported by post hoc correlational analyses revealing that performance on the BSIT was not correlated with performance on any other domains, including IQ ($p>0.10$ for all domain comparisons). Of note, although not significant after Bonferroni correction for correlations with specific test scores, BSIT score was significantly correlated with the log of perseverative errors on the WCST ($r=-0.272$, $p=0.010$). The possibility of a relationship between olfactory identification and this component of executive functioning may warrant additional study.

4.3. NP performance and progression to severe and psychotic symptoms

The subgroup that later developed "severe and psychotic" symptoms had greater NP impairment at baseline assessment than those who did not, with effect sizes for verbal IQ and verbal memory impairments largely comparable to first episode and established SCZ samples (Mesholam-Gately et al., 2009). Thus, much of the NP impairment associated with SCZ and related disorders may precede the actual onset of psychotic symptoms (Seidman et al., 2010). Impairments in verbal memory may have particular predictive value for later psychosis (Brewer et al., 2005; Lencz et al., 2006; Seidman et al., 2010). However, the incremental value of NP impairments in the context of clinical and familial factors remains to be established (Seidman et al., 2010).

4.4. The role of IQ and attention in NP impairments associated with risk for psychosis

Another issue explored in this study was the potential role of global NP functioning, as indexed by estimated IQ, in NP performance profiles. Level of estimated premorbid IQ did not impact the overall pattern of results. Whereas estimated current IQ had a nearly significant effect on overall profile shape (excluding olfaction), this was for the entire sample, not merely CHR. Relative weaknesses in verbal memory and executive functioning in particular were evident for both CHR and HC at lower IQ, suggesting that these and possibly other specific NP deficits may actually reflect patterns typical of lower global cognition rather than specific risk for psychosis. Consistent with prior literature (e.g., Seidman et al., 2006), low IQ and an apparent discrepancy between current and premorbid IQ estimates are both associated with greater risk of psychosis onset. As neither the degree nor the pattern of overall NP deficits in CHR subjects could be accounted for by attentional impairments, IQ may play a relatively stronger role than attention in risk for psychosis.

4.5. Limitations

Although our study includes several strengths within the emerging literature on CHR samples, including sample size,

demographic comparability between CHR and HC samples, the length of clinical follow-up, and an extensive NP battery, two limitations warrant specific consideration. First, a majority of CHR (73%) were on psychiatric medications at baseline assessment (50% on antipsychotics, 39% on antidepressants, with 45% on two or more psychotropic medications) and participated in a treatment trial during follow-up interval. It is possible that some NP impairments reflect medication effects or that psychopharmacological and psychosocial interventions delayed or prevented symptom progression in some participants (Morrison et al., 2007; Woods et al., 2003). Second, the number of HC with FSIQ below 100 was small, reducing power for the comparison of profile shape by level of IQ and raising the question of ascertainment bias. Recruiting HC fully representative of the larger population from which an at-risk sample is identified remains both a challenge and priority if we are to accurately identify features of risk and emerging illness.

4.6. Conclusion

CHR individuals demonstrated an overall impairment in NP functioning roughly a half standard deviation below HC and a similar NP performance profile, especially when generalized impairment was taken into account. Only a large and specific impairment in olfactory identification approached significance in distinguishing the CHR profile from that of HC. In fact, olfactory identification impairments were uncorrelated with other NP domains, including IQ. Taken together with prior findings, olfactory identification deficits may provide a selectively sensitive early marker of risk for psychosis.

It is notable that the subgroup that developed severe and psychotic symptoms after baseline assessment demonstrated NP impairments already at a level approaching that of fully ill samples. Thus, the bulk of NP impairment measured after illness onset (i.e., in first episode samples), at least within some cognitive domains, may already be present before the full expression of a psychotic disorder. That said, the presence of relative verbal memory impairments at both high and low levels of IQ and the size of verbal memory impairments in those who later developed psychotic-level symptoms support prior studies suggesting that greater verbal memory deficit may have incremental value in predicting the rate or onset of later psychosis.

Although the NP data in this study are cross-sectional, they speak to the potential nature of progressive impairment in NP functioning at some point over the onset of psychosis. Specifically, the effect size of executive function impairments in CHR, even those with Later Psychotic-level symptoms, is smaller than those typically found for related tasks in first episode and chronic SCZ. Additional impairment within this domain may occur between prodromal and first episode stages of illness. Given the active development of executive function during late adolescence and early adulthood, this domain may be most vulnerable to derailment by progression to illness onset or at least one of the last domains impacted. Measurement of various components of executive functions over time is needed to truly assess progressive and differential impairment over time within this domain.

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Contributors

All authors have made significant scientific contributions to this manuscript. Kristen A. Woodberry contributed to the conceptualization of this neuropsychological study, secured part of its funding, conducted statistical analyses, and wrote the first and final draft of the manuscript. Larry J. Seidman and Anthony J. Giuliano both contributed to the conceptualization and implementation of the study, secured funding to support their advisory roles, and provided major editing of the manuscript. Mary B. Verdi contributed to the conceptualization and implementation of the study and the editing of the manuscript. William L. Cook and William R. McFarlane contributed to the conceptualization and implementation of the study, secured funding for the larger randomized controlled trial from which this study was derived, and contributed to editing of the manuscript.

Conflict of interest

None of the authors have any actual or potential conflicts of interest to disclose.

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