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Generalized and Specific Cognitive Performance in Clinical High-Risk Cohorts: A Review Highlighting Potential Vulnerability Markers for Psychosis

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Cognitive deficits are a core feature of established psychotic illnesses. However, the association between cognition and emerging psychosis is less understood. While there is some evidence that cognitive deficits are present prior to the onset of psychosis, findings are not consistent. In this article we provide an overview of the more general cognitive findings available from genetic high-risk studies, retrospective studies, and birth cohort studies. We then focus the review on neuropsychological performance in clinically "at-risk" groups. Overall, general cognitive ability as assessed by established batteries appears to remain relatively intact in these ultra-high risk cohorts and is a poor predictor close to illness onset relative to other vulnerability factors. Further decline may occur with illness progression, more consistent with state relative to trait factors. In addition, most established cognitive tasks involve several relatively discrete cognitive subprocesses, where findings from general batteries of subtests may mask specific deficits. In this context, our review suggests that relatively specific olfactory identification and spatial working memory deficits exist prior to illness onset and may be more potent trait markers for psychosis than cognitively dense tasks such as verbal memory. Suggestions for further research address the importance of standardization of inclusion criteria and the maintenance of basic neuropsychological assessment to allow better comparison of findings across centers. Further, in order to better understand the aetiopathology of cognitive dysfunction in psychosis, more experimental, hypothesis-driven measures of discrete cognitive processes are required. Delineation of the relationship between specific cognitive ability and symptoms from data-driven approaches may improve our understanding of the role of cognition during psychosis onset.

Key words: schizophrenia/high risk/first-episode psychosis/neurodevelopmental/prodrome/cognition

Introduction

Cognitive deficits are viewed as central to the underlying pathophysiology of established psychotic disorders, particularly schizophrenia,[1] with the most consistent findings being problems in attention, memory, and higher-order executive function.[2–4] These deficits are present at the first onset,[5–8] are largely unrelated to positive symptomatology,[9–13] and do not change over time.[9,14] In other studies a proportion of patients appear to undergo a decline in general intellectual function at some point either prior to or around the first onset of psychosis,[15,16] while other findings suggest that deficits improve.[17] These inconsistent findings may be attributed to variability in cohort inclusion criteria, duration of untreated psychosis, and utilization of large cognitive assessment batteries, where measures of performance reflect multiple cognitive subprocesses and summaries of the same may mask intra- and inter-individual heterogeneity. Others have suggested that some cognitive deficits are state dependent and therefore fluctuate with psychopathology,[12] while other deficits reflect a stable, possibly neurodevelopmental, condition.[18] For example, Cornblatt and colleagues[19] suggest that cognitive deficits may be developmentally differentiable, with some deficits specifically predicting psychosis, while others form a more general vulnerability core for psychiatric illness and related disability.[12]

Overall, research to date suggests that at least some deficits are trait-related and are unlikely to be explained by the effects of medication or the accumulation of toxic biopsychosocial sequelae of illness progression. Such deficits may be considered "de facto" biological markers for illness onset, although they may not necessarily occur in people with the illness.

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The Importance of Prediction

Recent studies have emphasized the need for early detection and treatment of the prodrome in order to avoid a full psychotic episode, to weight treatment resources toward those at greater risk for more severe illness, to reduce symptoms, including comorbidity such as depression and substance use,[20–23] and to improve outcome.[24–26] In addition, early detection may shorten the overtly psychotic period, help establish good therapeutic alliance, and improve quality of life and long-term outcome by minimizing severity and disability.[24,27,28] Finally, such paradigms allow the prospective study of the transition process.[21–23]

Overview of Approaches and Rationale for Limits of Current Review

Several approaches address the nature of cognitive deficits prior to illness onset and whether such deficits are predictive of either transition to psychosis or functional outcome. One approach is the genetic high-risk approach, in which cognitive functioning of family members of individuals with psychosis, usually offspring,[29–32] or individuals with psychosis spectrum disorders, eg schizotaxia[33] or schizotypy,[34] is assessed. While this strategy arguably focuses on a core potential biological marker for schizophrenia, sample representativeness of the population who present for first-episode psychosis is limited, as not all people with a genetic risk for schizophrenia develop the illness[35] and as little as 10% of first-episode psychosis cohorts have a positive family history.

However, such approaches do provide clues regarding domains of cognition that may be compromised premorbidly as either a general or potentially more specific vulnerability marker, while recognizing that neither is necessary or sufficient for psychosis onset. Apart from findings on generalized batteries of tests (eg, Wechsler Intelligence Scale for Children [WISC],[36] Rivermead Behavioral Memory Test[37]),[29,38–40] relatively more specific domains of vulnerability include visuo-motor development,[41,42] perceptual problems, conceptual sorting, language processing, and possibly mental tracking, sustained attention, short-term memory, working memory, and verbal recognition and recall.[38,43–48] These deficits are moderate,[49] and in cross-sectional studies they have been reported to be greater in relatives with a higher genetic loading.[50,51] Finally, these cognitive domains remain relatively complex; verbal recognition, for example, could be parsed into relatively discrete subprocesses, including sustained attention, verbal working memory, and efficient storage and retrieval, all or some of which may be differentially compromised.

Another approach to identifying high-risk cohorts is the retrospective study of patients with established psychosis, which also provides clues regarding the nature of more general cognitive deficits many years prior to the onset of illness. Findings suggest compromised general IQ was already present during childhood,[52] though this was minimal and had poor predictive validity. However, significant linear increases in risk for adult schizophrenia across decreasing tertiles of the distributions of general intellectual functioning at the 11- and 15-year assessments have been reported.[53,54] Similar results from other studies suggest low educational achievement is common,[55,56] along with language disturbance.[57] However, as with genetic high-risk studies, these retrospective approaches are limited in that they generally allow no specific, a priori, hypothesis-driven paradigms regarding the nature and timing of onset of cognitive deficits or, indeed, of relatively more specific domains of cognitive function.

A further strategy is to follow large birth cohorts over time, which invariably incorporates early, broad assessment of individuals who eventually develop schizophreniform disorders (eg, the Dunedin Multidisciplinary Health and Development Study[40,58]). However, such approaches are inefficient, particularly regarding the length of follow-up period and the degree of assessment detail that can be applied to test formal hypotheses. Moreover, the number of individuals who are identified with schizophrenia is small relative to the degree of resources invested in screening large numbers of people.[59]

Despite these limitations, general domains of cognition that have been found to be vulnerable early in the development of people who eventually develop schizophrenia include nonverbal and verbal educational achievement and organizational and reading ability.[15,35,60–62] These domains include relatively more specific problems in mathematical and vocabulary skills and in mechanical knowledge.[52,61,62]

More recent approaches of identifying premorbid cohorts have focused on positive symptoms[eg,22] or the German approach of self-recognized ''basic symptoms''[63] (for review[21,64]). Strategies predominantly focus on ''help-seeking'' adolescents, who by definition may already be manifesting established signs of attenuated onset of psychosis, as these state-based criteria are thought to identify an at-risk mental state.[65,66] These approaches reflect a ''close-in'' or ''multiple gate screening'' approach to identifying a high-risk cohort,[67] where an individual must meet a number of criteria to be included in the high-risk group. These incorporate behavioral difficulties in adolescence, in an attempt to improve the accuracy of identifying the high-risk group further. However, inclusion criteria do not yet incorporate factors reflecting cognitive risk specifically.

Studies using this approach have been referred to as ''ultra-high risk'' (UHR) or clinical high-risk studies to differentiate them from traditional genetic high-risk studies that rely on family history as the primary inclusion criterion. The terms ''at-risk mental state'' or ''ultra-high

risk'' do not imply that a full-threshold psychotic illness, such as schizophrenia, is inevitable but suggest that an individual is at increased risk of developing a psychotic disorder by virtue of his or her mental state. These risks arguably reflect a more representative sample of the first-episode cohort than the studies described above that rely solely on genetic risk. All studies described below are summarized in Table 1.

The Personal Assessment and Crisis Evaluation (PACE) Clinic

The Personal Assessment and Crisis Evaluation (PACE) Clinic, established in Melbourne, Australia, in 1994, was the first to specifically target adolescents in a putative prodromal phase.[22] The strategy focuses on individuals in the peak age range of risk for onset of psychotic disorder—adolescents and young adults.[68] In addition, further criteria regarding potential risk factors developed by the PACE Clinic include attenuated psychotic symptoms, self-resolving psychotic symptoms, a trait risk factor (a schizotypal personality disorder in the young person or a family history of a psychotic disorder in a first-degree relative), and functional decline.

Early reports of cognitive ability from this group demonstrated performance profiles intermediate to control and first-episode psychosis cohorts across domains of attention, memory, and executive ability.[69–71] These approaches utilized general neuropsychological assessment protocols (Cognitively Graded Mental Health Research Institute Assessment Protocol for Schizophrenia [COGMAPS][72]). Hypothesis testing concerning relatively more specific cognitive processes was also incorporated into the baseline assessment protocol of this cohort, where it was predicted that olfactory identification (utilizing the University of Pennsylvania Smell Identification Test [UPSIT][73]) deficits, implicating neurodevelopmental compromise of prefrontal (orbitofrontal) neural regions, would be present prior to illness onset. Olfactory identification function of 81 UHR individuals was compared with the functioning of 31 healthy comparison subjects.[74] Twelve of the UHR cohort were diagnosed with a schizophrenia spectrum disorder within 12 months of baseline assessment. Olfactory identification deficits (OID) were specific to the UHR subgroup who developed schizophrenia relative to the healthy comparison group nonpsychotic UHR subgroup, as well as UHR individuals who developed a psychotic disorder that was not within the schizophrenia spectrum (eg, bipolar disorder or substance-induced psychosis). This finding suggests that compromised OID may be a premorbid marker of transition to schizophrenia but is not predictive of psychosis generally. Further, findings of OID have previously been associated with negative symptoms,[71,75] suggesting that reliance on precursors for negative symptoms rather than positive symptoms alone may be a useful focus for inclusion criteria to clinical high-risk paradigms. Current work is underway to confirm the hypotheses that OID in this cohort reflects a neurodevelopmental lag of prefrontal aspects of limbic-prefrontal pathways, that OID is likely to be more associated with emerging negative symptoms and treatment resistance and, further, that OID is likely to reflect stable trait markers.[75,76] Finally, we are working on parsing olfactory identification ability further into sensation, detection, and identification, for example, to examine even more discrete neuropsychological subprocesses that are involved in successful performance on this task.[76]

Utilization of more experimental challenges of relatively specific components of cognition, as measured by the Cambridge Neuropsychological Testing Automated Battery (CANTAB[77]) was reflected in the paradigm reported by Wood and colleagues.[78] Here, working memory (WM) was examined in 38 UHR PACE patients, of whom 9 later developed psychosis. These were compared with 49 healthy control subjects. Both spatial working memory (SWM) and delayed matching-to-sample performance were significantly poorer in the UHR group relative to controls. The subgroup that later developed psychosis also performed more poorly than those who did not, although for the most part these differences were nonsignificant. However, consistent with the olfactory findings above, a significant association between SWM errors and negative symptoms was seen in the later psychotic group. This suggests that the relationship between measures of prefrontal function and negative symptoms may be a useful predictive tool.

In the largest study of UHR cohorts conducted to date, Brewer and colleagues[79] examined 98 UHR young people, of whom 34 later developed psychosis, compared with 37 healthy controls. A striking finding was the overall lack of clinically significant cognitive impairment in the UHR group, suggesting that global cognitive deficits found after psychosis onset may not be key features of premorbid vulnerability. However, UHR subjects did have significantly lower Performance IQ than the comparison subjects, along with lower premorbid functioning and aspects of visual and verbal learning. Further impairments specific to the UHR patients who developed psychosis were also found in the visual reproduction subtest and the verbal memory index of the Wechsler Memory Scale—Revised (WMS-R).[80] This last impairment was completely explained by lower Logical Memory scores, with no deficit in Paired Associated Learning. No other memory, attentional, or executive tasks discriminated between any of the groups, and there were no differences in performance related to different psychotic diagnoses. The findings suggest that visuo-spatial processing impairment and some prefrontally mediated, rather than medial-temporal-mediated, memory deficits were apparent before the full expression of psychotic illness. Cognitive performance on more complex tasks requiring rapid

Table 1. Description of Clinical High Risk Studies by Programs: Method, Cognition Results, and Main Conclusions

Program Investigators	N	Age	Clinical High-Risk Subject Group: Diagnostic and Risk Characteristics	Follow-up Duration/Transition Rate	Cognitive Assessments	Cognitive Battery Raw Scores	Main Findings
PACE (Yung et al. 1996)							
Brewer et al. 1996 (Abs)[69]	UHR = 17 CTL = 22	N/A	N/A	Baseline only	COGMAPS UPSIT	N/A	Deficits in olfactory identification
Brewer et al. 1998 (Abs)[70]	UHR = 65 CTL = 24	N/A	N/A	18/12 follow-up / 21 (32%) UHR-P	COGMAPS UPSIT	N/A	Deficits in Current IQ, attention, memory, and executive function, and olfactory identification at baseline; Mental arithmetic poorer in UHR-P compared to UHR-NP
Brewer et al. 2003[74]	UHR = 81 CTL = 31	19.9 (4.1) P 20.4 (3.2) NP 21.1 (3.9) 14–30 years	Attenuated = 48.1% BLIPS = 11.1% T&S = 13.6% Attenuated/BLIP = 1.2% Attenuated/T&S = 11.1% BLIPS/T&S = 12.3% All 3 = 2.5% Remaining 10 UHR-P not Scz: Dep with psychotic features (n = 2); Schizaff-Dep (n = 1); Bipolar (n = 3); Psychotic disorder NOS (n = 3); Substance-induced psychosis (n = 1)	18/12 follow-up / 22 (27.2%) UHR-P, of whom 12 developed Scz	NART UPSIT	NART IQ: UHR-P = 99.9 (Scz) = 96.8 (Spectrum) = 103.6 UHR-NP = 100.5 CTL = 108.5 UPSIT: UHR-P = 31.2 (Scz) = 29.8 (Spectrum) = 32.9 UHR-NP = 32.2 CTL = 33.4	Deficit in olfactory identification in UHR-P
Wood et al. 2003[78]	UHR = 38 CTL = 49	18.3 (3.2) P 19.7 (2.8) NP 20.3 (2.7) 14–30 years	Attenuated = 36.8% BLIPS = 2.6% T&S = 26.3% Attenuated/BLIPS = 2.6% Attenuated/T&S = 31.6%	12-24/12 follow-up / 9 (23.7%) UHR-P	NART CANTAB	NART IQ: UHR-P = 92.8 UHR-NP = 101.7 CTL = 100.3	UHR impaired on Spatial Span, SWM, and DMTS; NS trend for UHR-P poorer on SWM; WM linked to negative symptoms in UHR group generally
Brewer et al. 2005[79]	UHR = 98 CTL = 37	19.4 (4.0) P 20.0 (3.6) NP 20.7 (4.3) 15–29 years	Attenuated = 44.9% BLIPS = 13.3% T&S = 15.3% Attenuated/BLIPS = 1.0% Attenuated/T&S = 11.2% BLIPS/T&S = 11.2% All 3 = 3.1% Remaining 16 UHR-P not Scz: Dep with psychotic features (n = 5); Schizaff (n = 1); Bipolar (n = 4); Psychotic disorder NOS (n = 3); Substance-induced psychosis (n = 1); Brief psychotic disorder (n = 2)	12/12 → follow-up / 34 (34.7%) UHR-P WMS-R Vis Rep	NART 7 Subtest WAIS-R WMS-R VMI 3-trial RAVLT Trails A & B COWAT Stroop[118]	NART IQ: UHR-P = 99.3 UHR-NP = 100.4 CTL = 108.1 WAIS-R VIQ: UHR-P = 99.2 UHR-NP = 98.5 CTL = 103.8 WAIS-R PIQ: UHR-P = 100.6 UHR-NP = 102.4 CTL = 111.6 WMS-R Vis Rep Raw: UHR-P = 32.1 UHR-NP = 35.3 CTL = 36.0	UHR deficits: VIQ, Block Design, Vis Rep UHR-P deficits: VMI (Logical Memory), Vis Rep UHR-NP deficits: Digit Symbol UHR did not improve in IQ between premorbid and current as did CTL

Table 1. Continued

Program Investigators	N	Age	Clinical High-Risk Subject Group: Diagnostic and Risk Characteristics	Follow-up Duration/Transition Rate	Cognitive Assessments	Cognitive Battery Raw Scores	Main Findings
			UHR-NP: Dep (n = 4); GAD (n = 2); OCD (n = 1); Social phobia (n = 2); Dysthymia (n = 2); Adjustment disorder (n = 1); PTSD (n = 1)			WMS-R VMI: UHR-P = 82.2 UHR-NP = 91.1 CTL = 96.7 RAVLT 3-trials: UHR-P = 9.6 UHR-NP = 9.6 CTL = 9.6 Trails A/B Seconds: UHR-P = 26.8/70.3 UHR-NP = 28.0/70.8 CTL = 23.4/61.0 COWAT: UHR-P = 35.4 UHR-NP = 37.2 CTL = 33.7 Stroop interference D/B: UHR-P = 0.46 UHR-NP = 0.49 CTL = 0.46	
Francey et al. 2005[81]	UHR = 70 CTL = 51	20.9 P 19.9 NP 23.3 14–30 years	Attenuated = 42.9% BLIPS = 15.7% T&S = 14.3% Attenuated/BLIPS = 14.3% Attenuated/T&S = 12.9% Remaining 12 UHR-P not Scz: Dep with psychotic features (n = 3); Schizaff (n = 1); Bipolar (n = 3); Psychotic disorder NOS (n = 3); Substance-induced psychosis (n = 1); Brief psychotic disorder (n = 1) UHR-NP: None (n = 28) Dep (n = 4); GAD (n = 1); Panic disorder (n = 2); Social phobia (n = 1); Dysthymia (n = 4); Adjustment disorder (n = 1)	12/12 follow-up / 20 (28.6%) UHR-P (n = 21 UHR received low-dose neuroleptics and therapy)	NART CPT-IP	NART IQ N/A CPT-IP Raw Scores N/A	UHR CPT deficits compared to CTL; however, of those who developed psychosis, there were no differences to those who did not develop psychosis.
Koutsouradis et al. 2005[86]	UHR = 16 CTL = 17	N/A	N/A	12-18/12 follow-up / 7 (43.8%) UHR-P	COGMAPS	N/A	Visual reproduction, verbal fluency, and Trails B all showed significant declines over the transition to psychosis, while cognitive performance for UHR-NP group remained stable or improved

Table 1. Continued

Program Investigators	N	Age	Clinical High-Risk Subject Group: Diagnostic and Risk Characteristics	Follow-up Duration/Transition Rate	Cognitive Assessments	Cognitive Battery Raw Scores	Main Findings
RAP							
Lencz et al. 2005[12]	CHR = 38 CTL = 39	16.5 (2.2) 15.8 (2.6)	n = 23 (60.5%) neuroleptic-free	6/12 → follow-up / 12 (31.6%) CHR-P	WRAT-III WISC-III/WAIS-R Vocab Block Design Digit Span WMS-R Log Mem I/II Vis Rep I/II CVLT WCST COWAT TRAILS A/B Ruff Figural Fluency[119] Letter-Number Span CPT-IP Finger Tap[120] Groove Pegboard[121] Line Judgment[122] Boston Naming Test[123]	WRAT IQ: UHR = 101.0 CTL = 108.0 WAIS-R FSIQ (Prorated): UHR = 97.5 CTL = 110.0 Further individual scores not reported Cognitive Domains: (*z*-score deficits compared to CTL): Verbal Memory $z = 1.8$ Executive/WM $z = 1.6$ Language z = 1.3 Motor $z = 1.2$ Attention $z = 1.0$ Visuo-spatial $z = 0.75$ Verbal Memory: CHR-P z = 2.8 CHR-NP z = 1.2 CPT Raw Scores N/A	CHR impaired on global cognition, along with verbal memory and executive function/working memory, while visuo-spatial relatively spared; CHR-P had lower verbal memory at baseline.
Smith et al. 2006[94]	CHR = 8 CTL = 10	16.3 (2.6) 16.6 (2.9)	Comorbidity: Anxiety (n = 4); Dep (n = 2); ADHD (n = 2) 10 low-risk CTL (1 year extra education).	Baseline only	WISC-III/ WAIS-R Vocab Block Design Computerized SWM task	Prorated IQ: CHR = 108.0 CTL = 111.9	SWM deficits in CHR but not on a non-WM-demanding spatial control task.
PRIME							
Hawkins et al. 2004[98]	CHR = 36 CTL = comparable published norms from Test Manuals and Goldberg's[124] discordant twin samples	19.8 (4.7) 16–45 years	Not reported	Not reported	WAIS-R 4 subtest CPT-IP 450 Letter/Number Sequencing Dot location Trails A/B Stroop	WAIS-R Vocab SS: UHR = 10.8 Norm = 10.0 WAIS-R Info SS: UHR = 9.8 Norm = 10.0	UHR poorer on digit symbol, Vocab, CPT, Letter/Number Sequencing, Dot Location, Trails B, CVLT, COWAT, and Figural Fluency; normal on Trails A, WMS-R Vis Rep I/II, and CVLT Total Recall.

Table 1. Continued

Program Investigators	N	Age	Clinical High-Risk Subject Group: Diagnostic and Risk Characteristics	Follow-up Duration/Transition Rate	Cognitive Assessments	Cognitive Battery Raw Scores	Main Findings
					Finger tapping CVLT WMS-R Vis Rep I/II COWAT Ruff Figural Fluency	WAIS-R Block Design SS: UHR = 9.8 Norm = 10.0 WAIS-R Digit Symbol SS: UHR = 8.9 Norm = 10.0 WMS-R Vis Rep I Raw Score: UHR = 33.0 Norm = 34.0 WMS-R Vis Rep II Raw Score: UHR = 31.9 Norm = 31.5 CVLT: UHR = 50.5 Norm = 55.9 Trails A/B Seconds: UHR = 28.6/76.5 Norm = 26.6/54.3 COWAT: UHR = 32.5 Norm = 43.7 Stroop: UHR = 39.8 Norm = 49.8 Letter/Number Sequencing: UHR = 13.8 Norm = 15.7 Dot Location: UHR = 0.63 Norm = 1.27 Ruff Figural Fluency: UHR = 83.7 Norm = 107.5 CPT 450 D': UHR = 1.2 Norm = 0.8	
FEPSY							
Gschwandtner et al. 2003[99]	CHR = 32 CTL = 32	26.5 (8.8) 25.5 (4.4)	Not reported	Baseline only	WCST Twr of Hanoi[125] TAP CPT	WCST Perseverations (%): CHR = 26.6 CTL = 15.6	UHR higher perseveration and prolonged reaction times in Twr of Hanoi; GoNoGo, WM, and CPT reaction also deficit.

Table 1. Continued

Program Investigators	N	Age	Clinical High-Risk Subject Group: Diagnostic and Risk Characteristics	Follow-up Duration/Transition Rate	Cognitive Assessments	Cognitive Battery Raw Scores	Main Findings
						Twr of Hanoi (seconds): CHR = 468 CTL = 299 TAP GoNoGo R/T (ms): CHR = 585 CTL = 488 TAP WM R/T (ms): CHR = 784 CTL = 550 TAP WM (missed): CHR = 4.0 CTL = 1.3 CPT R Time (ms): CHR = 494 CTL = 399	
Gschwandtner et al. 2005[100]	CHR = 40 CTL = 42	27.4 (9.1) 25.9 (5.2)	Not reported	Baseline only	WCST Twr of Hanoi TAP CPT	Verbal IQ: CHR = 105.2 CTL = 119.0 Nonverbal IQ: CHR = 111.1 CTL = 118.8 WCST Perseverations: CHR = –0.08 CTL = 0.23 WCST Perseverative Error: CHR = –0.13 CTL = 0.31 Twr of Hanoi (moves): CHR = –0.05 CTL = –0.09 TAP WM False Alarm: CHR = –0.34 CTL = 0.34 TAP WM Missing: CHR = –0.44 CTL = 0.39 TAP GoNoGo False Alarm: CHR = –0.24 CTL = 0.13	UHR deficits in sustained attention, WM, and perseveration.

Table 1. Continued

Program Investigators	N	Age	Clinical High-Risk Subject Group: Diagnostic and Risk Characteristics	Follow-up Duration/Transition Rate	Cognitive Assessments	Cognitive Battery Raw Scores	Main Findings
						TAP GoNoGo Missing: CHR = –0.38 CTL = 0.12 CPT Missing: CHR = –0.32 CTL = 0.34 CPT False Alarm: CHR = –0.39 CTL = 0.38	
PAS							
Silverstein et al. 2006[107]	UHR = 70 CTL = 24	17.4 (3.6) 20.7 (4.4)	Trait = GAF drop of 30 points (n = 11); Attenuated (n = 38); BLIPS (n = 21)	18-24/12 follow-up / 49 assessed, of whom 24 (49.0%) UHR-P	NART Computerized Perceptual Organization Task		No differences between UHR and CTL
Schall et al. 2003[109]	UHR = 103	N/A		12-36/12 follow-up / 62 (55.3%) of original UHR (n = 112) UHR-P	WCST Stroop Trails B Verbal Recall	N/A	UHR higher error rates on WCST, Stroop, and Trails B; UHR-P poorer in Verbal Memory at baseline
CARE							
Shafer et al. 2003	UHR = 27 CTL = 17	N/A	N/A	Baseline only	CPT-IP	N/A	UHR attentional deficits intermediate to CTL and FEP
University of Drebecen							
Bartok et al. 2005[24]	CHR = 11	25.0 (5.0) 19–40 years		12/12 follow-up / 9 (81.82%) CHR-P	CANTAB		CHR impaired on PAL, SRM, RVP, and SWM compared to CTL; No difference between UHR-P and UHR-NP
FETZ							
Hambrecht et al. 2002[112]	CHR = 29 CTL = 29	23.1 (4.4) 24.0 (3.0) 15–31 years	Not reported	15/12 follow-up / 5 (9.8%) of larger cohort (n = 51), 29 of which received cognitive assessment	Matched by Verbal IQ, measured by 37 series of 4 nonwords, and 1 word has to be identified Visual BM CPT- IP SWM (DR) Task RAVLT	Visual BM (% hits): UHR = 84.7 CTL = 86.9 Attention (% hits): UHR = 72.7 CTL = 81.5	Self perceived deficits in perception, cognition, and stress reactivity; CHR worse on verbal recall, verbal fluency, attention, and visual memory, though only fluency after Bonferroni corrections; CTL had higher premorbid IQ

Table 1. Continued

Program Investigators	N	Age	Clinical High-Risk Subject Group: Diagnostic and Risk Characteristics	Follow-up Duration/Transition Rate	Cognitive Assessments	Cognitive Battery Raw Scores	Main Findings
					COWAT (+ category) Rey Figure WCST Perseverative Errors;	RAVLT: UHR = 11.2 CTL = 12.1 Recognition: UHR = 14.0 CTL = 14.1 COWAT: UHR = 17.6 CTL = 21.6 Visual Recall (Rey copy less delay): UHR = 12.4 CTL = 8.9 WCST (% perseveration): UHR = 11.4 CTL = 10.8	

Note: Abbreviations—Abs: Abstract; ADHD: Attention Deficit Hyperactivity Disorder; BLIPS: Brief Limited Intermittent Psychotic Symptoms[22]; BM: Backward Masking; CANTAB: Cambridge Neuropsychological Testing Automated Battery[77]; CARE: Cognitive Assessment and Risk Evaluation Program, University of California, San Diego; CHR: Clinical High Risk; CHR-NP: Clinical High Risk-Non Psychotic; CHR-P: Clinical High Risk-Psychotic; COGMAPS: Cognitively Graded Mental Health Research Institute Assessment Protocol for Schizophrenia[72]; COWAT: Controlled Oral Word Association Test[87]; CPT-IP: Continuous Performance Test, Identical Pairs version[126]; CTL: Control Group; CVLT: California Verbal Learning Test[127]; Dep: Depression; DR: Delayed Response (CANTAB); DMTS: Delayed Matching to Sample; FEP: First-Episode Psychosis; FEPSY: Früherkennung von Psychosen, Basel, Germany; FETZ: Früherkennungs- und Therapiezentrum für psychotische Krisen; FSIQ: Full Scale Intelligence Quotient; GAD: Generalised Anxiety Disorder; GAF: Global Assessment Form; Log Mem: Logical Memory subtest from the WMS-R[80]; ms: milliseconds; N/A: Not available; NART: National Adult Reading Test[128]; NOS: Not otherwise specified; NS: Non-significant; OCD: Obessessive Compulsive Disorder; PACE: Personal Assessment and Crisis Evaluation Clinic, Melbourne, Australia; PAS: Psychological Assistance Service, Newcastle, Australia; PAL: Paired Associate Learning (WMS-R); PIQ: Performance IQ (WAIS); PRIME: Prevention through Risk Identification, Management, and Education Clinic, Yale University; PTSD: Post Traumatic Stress Disorder; R: Revised; RAP: Recognition and Prevention Program, New York; RAVLT: Rey Auditory Verbal Learning Test[129,130]; R/T: Reaction Time; RVP: Rapid Visual Processing (CANTAB); Scz: Schizophrenia; Schizaff: Schizo Affective Disorder; SRM: Spatial Recognition Memory (CANTAB); SS: Scaled Score; SWM: Spatial Working Memory (CANTAB); TAP: Testbattreie zur Aufmerksamkeitsprufung[103]; T&S: Trait/State; Twr: Tower; UHR: Ultra-High Risk; UHR-NP: Ultra-High Risk—Nonpsychotic; UHR-P: Ultra-High Risk—Psychotic transition; UPSIT: University of Pennsylvania Smell Identification Test[73]; Vis Rep: Visual Reproduction subtest (WMS-R); VIQ: Verbal IQ (WAIS)[131]; VMI: Verbal Memory Index (WMS-R); WAIS: Wechsler Adult Intelligence Scale[131]; WAIS-R: Wechsler Adult Intelligence Scale-Revised; WCST: Wisconsin Card Sorting Test[102]; WISC: Wechsler Intelligence Scale for Children[36]; WM: Working Memory; WMS-R: Wechsler Memory Scale—Revised[80]; WRAT: Wide Range Achievement Test[132]

registration and efficient recall may be compromised before the development of psychosis; however, further examination of the subprocesses involved in performance of these tasks is required.

These findings contrast with those of Francey and colleagues,[81] who examined attention with the Continuous Performance Test, Identical Pairs version (CPT-IP)[82] in 70 UHR patients relative to 51 normal control subjects and 32 first-episode psychosis (FEP) patients. While the UHR group exhibited performance deficits relative to the comparison group (similar to the FEP group), those who developed psychosis did not differ from those who did not. These results suggest that sustained attention was an indicator of vulnerability for psychosis but did not predict transition. Consistent with this notion, impaired performance on the CPT-IP has been found in people with schizophrenia, their first-degree relatives, and people with schizophrenia spectrum personality disorders.[83–85]

In a small longitudinal study of 16 UHR patients (7 of whom developed psychosis), Koutsouradis and colleagues[86] found that visual reproduction scores from the WMS-R, verbal fluency (Controlled Oral Word Association Test [COWAT][87]), and Trail Making Test Form B[88] all showed significant declines over the transition to psychosis, while cognitive performance for the nonpsychotic UHR group remained stable or improved. These data indicate that the onset of psychotic disorder is associated with additional impairment in visuo-spatial and executive abilities.

As highlighted in the approach of genetic high-risk cohorts above, use of subtests from IQ and memory batteries arguably involve a number of cognitive subdomains or elements; in the case of the Logical Memory subtest from the WMS-R, sustained attention, strategic processing, verbal working memory, and retrieval are relatively more discrete cognitive processes that may be challenged for successful performance.[89,90] Experimental paradigms that parse these processes more clearly to determine the relative weighting that each process holds for successful performance are recommended. Results from such experimental paradigms that utilize nonstandardized tasks also need to be reported in the context of more general IQ and memory batteries in order to allow standardized comparability of patient cohorts across centers. Further, this approach acknowledges that variation in general IQ summaries (premorbid and current), which in the normal population are usually also related to memory ability, no doubt mask individual performance differences on subtests of general batteries or, further, confound performance on experimental cognitive tasks that are designed to challenge parsed components of subtests/indexes such as "verbal memory."

In summary, the findings from the PACE UHR group are consistent with findings from the genetic high-risk paradigms. Results from large batteries of standardized tests indicate that UHR patients perform at a level that is intermediate to that displayed by FEP and control samples. In addition, decomposing generalized tests of cognitive function into relatively more specific cognitive abilities such as olfactory identification and spatial working memory may be useful trait markers specific to the schizophrenia diagnosis per se, although further longitudinal follow-up of this cohort is required. It is feasible that potential trait markers, such as deficits in sustained attention, are confounds within assessments that utilize generalized or more neuropsychologically "blunt" cognitive batteries, and this should be considered in future experimental designs.

Recognition and Prevention (RAP) Program

The Recognition and Prevention (RAP) Program further elaborated the PACE ultra-high risk criteria for identifying young people thought to be at high risk of psychosis.[19] Adolescents between the ages of 12 and 22 (with a primary focus on ages 14–18) are recruited to this program if they are seeking treatment for attenuated positive psychotic symptoms (referred to as the clinical high risk—positive group [CHR-P]) or if they display specific combinations of cognitive, academic, and social impairments and disorganization/odd behavior. This second cohort is referred to as the clinical high risk—negative group (CHR-N). It is hypothesized that the developmental course of schizophrenia follows a progression from CHR-N to CHR-P to "schizophrenia-like psychosis" (essentially schizophreniform/brief psychotic disorder) to schizophrenia. The transition rate from CHR-P status to psychotic disorder, using both the PACE and Prevention through Risk Identification, Management, and Education (PRIME; see below) clinics' definitions of psychosis, was 26.5% (9 of 34 patients) within 6 months,[91] a rate similar to the 6-month transition rate in the PACE Clinic.[66] The transition rate to schizophrenia in the schizophrenia-like psychosis group was 33%.[92] This approach of further refining and characterizing subclasses of CHR states facilitates the implementation of more specific hypothesis-driven experimental paradigms, particularly in the interests of predicting relatively discrete or parsed cognitive processes that may be differentially related to CHR subclasses.

A further advantage of the RAP program is that it has focused specifically on cognitive impairments that may precede the onset of acute psychosis.[12,92,93] Lencz and colleagues[12] examined the performance on a neuropsychological battery of 38 clinical HR patients and 39 age- and sex-matched healthy controls. Clinical follow-up of at least 6 months duration was available on 33 patients, of whom 12 had developed nonaffective psychotic disorders. Similar to the findings of Brewer et al.[79] discussed above, the CHR patients showed significant impairments of global intelligence, although these

were not large enough to be clinically meaningful. Furthermore, measures of verbal memory and executive functioning/working memory were generally more impaired, while visuo-spatial functioning was relatively spared. High-risk patients who later developed psychosis had significantly lower verbal memory scores at baseline compared with those patients who did not. These findings suggest that verbal memory deficits (assessed using non-hippocampal specific tasks, such as story recall and list learning) might be an important risk factor for the development of schizophrenia spectrum psychotic disorders, possibly implicating prefrontal-hippocampal neurodevelopmental abnormality.

In a small study of spatial working memory in this CHR cohort (using the Delayed Response Task), Smith et al.[94] compared 8 patients with 10 controls matched for age, gender, education, IQ, and socioeconomic status. Consistent with findings from the PACE clinic,[78] the CHR group was impaired on this task. This task is a good example of attempts to parse more generalized cognitive abilities into subcomponent processes; however, the lack of accompanying general IQ or memory data limits the comparability of this cohort to those of other centers. There is also no context for determining the functional significance of the results.

Prevention through Risk Identification, Management, and Education (PRIME) Clinic

The ultra-high-risk concept and 'close-in' strategy has also been adopted at Yale University's Prevention through Risk Identification, Management, and Education (PRIME) Clinic, which began in 1997. Young people between 12 and 45 years old who are thought to be experiencing the onset phase of a first psychotic episode are recruited to the clinic. The PRIME group has coined the term Criteria of Prodromal Syndromes, or COPS, to describe its intake criteria, which are very similar to the ultra-high risk criteria developed earlier at PACE. The PRIME group has also developed a semistructured interview, originally influenced by the Comprehensive Assessment of At-Risk Mental States (CAARMS)[95] from the PACE clinic and the Positive and Negative Syndrome Scale (PANSS),[96] called the Structured Interview for Prodromal Syndromes (SIPS).[97] Although it has been suggested that this approach is the most specific and methodologically stringent in the field so far,[64] the high number of refusers (86%) and the severity of symptoms in those who participate in the research indicate that the sample is more ill (although not more likely to become psychotic) than samples from other centers. Only 1 study of cognition has been reported by this group,[98] which assessed 36 UHR patients on a broad neuropsychological battery. Although there was no control group (comparisons were with population norms), the results suggest that the UHR group were performing below population norms.

Früherkennung von Psychosen (FEPSY)

The Basel Early Detection of Psychosis Study was initiated in 1999 and has yet to report the operationalization of the at-risk state. In 2 overlapping reports,[99,100] data from 32 UHR and 32 control subjects (increased to 40 and 42 in the later paper) were reported. In the earlier (smaller subgroup) study, UHR patients performed significantly worse on measures of executive function (Wisconsin Card Sorting Test [WCST][101,102]), CPT (but it is unclear whether this is the CPT-IP), and Testbatterie zur Aufmerksamkeitsprufung (TAP,[103] a test of working memory). However, no transition rates are given (even in the later paper), and the members of the UHR group are much older than those seen by PACE, PRIME, or RAP (average age). In the later study, data were no longer reported as means, and instead *z*-scores were presented, making direct comparison difficult. However, it appears that the results from the former study were maintained. Utilization of tasks such as the WCST traditionally may reflect "prefrontal" functioning; however, the number of cognitive subprocesses required to perform this task suggests that it remains a relatively blunt probe of prefrontal functioning, particularly as hippocampal integrity may also be challenged during performance on this task.[104]

Psychological Assistance Service (PAS)

In 1997 the Psychological Assistance Service (PAS) opened in Newcastle, Australia, as a clinical service for the assessment and treatment of young people at high risk of psychosis and those experiencing a first psychotic episode. The high-risk criteria are based on those of PACE but also allow inclusion if a young person has a second-degree relative with a history of psychotic disorder in conjunction with a significant decline in functioning.[105] The transition rate to psychosis after a 12-month period was 50%.[106]

In a further study,[107] 70 UHR patients were compared with FEP patients and 24 comparable, subjects using an adapted task with known sensitivity to perceptual organization deficits in schizophrenia (adapted from[108]) and whose scores have predicted long-term outcome and disorganized symptomatology. There was no difference between the groups on this task. The data were found to be consistent with the notion that preattentive processes in schizophrenia are not impaired and that perceptual organization problems are not a general feature of the UHR group. A further unpublished study reporting data from a larger cognitive battery suggests that conversion to schizophrenia was predicted by impairments in verbal memory and executive function.[109]

Cognitive Assessment and Risk Evaluation (CARE) Program

The Cognitive Assessment and Risk Evaluation (CARE) program at the University of California, San Diego, was established in 2000, and only preliminary information is available.[110] However, the criteria used are comparable to other UHR studies, and the research includes a control group. Unpublished data from this study generally support the findings of Francey and colleagues[81]—that UHR patients have some impairment of attentional processing intermediate to controls and first-episode psychosis patients.

University of Debrecen

Bartok and colleagues[24] assessed young Hungarian adults referred to an outpatient clinic of the Department of Psychiatry at the University of Debrecen. They were referred for secondary care by general practitioners after help-seeking for nonspecific emotional or behavioral abnormalities. All had specific, isolated, mild, nonaffective psychotic symptoms and were diagnosed as being in the pre-psychotic phase following International Classification of Diseases ICD-10 based psychiatric interview (9 developed psychosis by the 12-month follow-up). However, this cohort is not adequately characterized by objective measures of psychosis threshold or entry criteria. Results from baseline assessment utilizing the CANTAB suggested that prepsychotic patients had deficits in attentional, frontal, and prefrontal cognitive function, when compared with CANTAB normative data from the United Kingdom (n = 3000), although examination of a local control group would be useful in extending our understanding of these findings.

Basic Symptoms: An Alternative Approach to Clinical High Risk

The German approach to early detection and intervention in schizophrenia follows the long-standing observation that cognitive, affective, and social disturbances often occur years before the first psychotic episode and are often recognized by the person affected at this early stage. For example, social deficits appeared as early as 2–4 years before the first hospital admission and, thus, in the prodromal phase about a year before the onset of the first psychotic symptom.[111] A new instrument to assess basic symptoms was recently developed—the Schizophrenia Prediction Instrument, Adult version (SPI-A). Preliminary results have indicated that 25 of 147 individuals (17%) who have reported experiencing at least 1 basic symptom developed schizophrenia within an average of 12 months of assessment (SD = 7.6; range 2–33)[21]. Although preliminary, this result reveals that the basic symptom approach is compatible with short follow-up intervals.

As 20% of individuals who report experiencing basic symptoms do not also report experiencing subthreshold psychotic symptoms, it is suggested that basic symptoms either describe an additional at-risk group to that identified using ultra-high risk criteria or—more likely—that basic symptoms occur earlier in the course of the illness.[21]

Früherkennungs- und Therapiezentrum für psychotische Krisen (FETZ)

Hambrecht and colleagues[112] examined the role of subjective and objective neuropsychological deficits in 29 basic symptoms patients and compared them with 29 healthy control subjects. These groups differed significantly in premorbid IQ, and the basic symptoms patients performed poorly on attention, verbal memory (free recall), verbal fluency, and visual memory tasks. No differences were found in visual backward masking, spatial working memory, verbal recognition memory, and WCST performance. However, when Bonferroni adjustments were made, verbal fluency was the only task indicating significant deficit. None of the cognitive variables were predictive.

General Discussion

Overall, clinical high-risk studies using the "close-in" approach are still in their infancy. No center has been operating for more than 12 years, and only the PACE clinic has published more than 2 studies. Nevertheless, early indications are that, depending on the matching characteristics of comparison groups and of the generalized test batteries utilized, CHR cohorts perform relatively normally, though intermediate in performance to normal controls and patients with first-episode psychosis. Further, they demonstrate specific areas of cognitive impairment prior to psychosis onset, where more discrete functions such as olfactory identification and spatial working memory may have predictive value. While some measures of verbal memory are also useful, they are neuropsychologically complex, and it is only those measures that require prefrontal processes for successful performance that appear to be predictive.

Comparison between centers is limited by the variability in the operationalization of inclusion criteria, although most use criteria based on those originally PACE criteria. Further refined characterization of clinical risk profiles can only advance our understanding of this transition period (eg, RAP and PAS). In contrast, characterization based on cognitive profiles is in its infancy, and no center has yet formally incorporated cognitive vulnerability into its inclusion criteria. Transition rates differ, as does the composition of sample subgroups based on clinical characteristics. Age at intake varies greatly between the UHR and the basic symptoms approach, although not in the expected direction (the mean age of the basic symptoms patients tends to be 8

or 9 years older than that of UHR patients). This has implications for interpretation, where a confounding factor that has not been adequately addressed to date concerns the likely incomplete maturation of executive function that parallels prefrontal development.[76] Further, both the UHR and basic symptoms approaches rely on help-seeking people rather than a whole population, epidemiological approach. This limits the generalizability of the findings and makes comparison with genetic- and population-risk approaches difficult.

Genetic and birth cohort studies imply that cognitive abnormalities are present from early development, but the data reported here demonstrate that they are much more consequences of illness stage and progression relative to other vulnerability factors. Importantly, most UHR patients perform normally in many domains. Several studies have found that some schizophrenia patients can be characterized as neuropsychologically normal.[113–115] However, others have suggested that, when examined more closely, such patients have either previously performed at a higher level and have thus deteriorated to average, normal, or functional IQ[89,116] or they have isolated subtle impairments in executive and sensorimotor function against a background of normal performance on a wide range of other tasks.[117] In either case, this suggests that in the UHR population, vulnerability may only be unmasked by high demand tasks, not routine tests. Finally, vulnerability does not always progress, so the key is to prevent vulnerability from progressing to transition and further deterioration (from early change to full decompensation).

Conclusions and Future Directions

High-risk research has revealed promising cognitive indicators of the future development of psychosis in the context of generally normal function. Future work needs to address the inconsistencies in intake criteria and to engage in longitudinal studies at predefined intervals. Furthermore, specific research hypotheses need to be generated that address core vulnerability markers, particularly those that involve parsing more complex cognitive processes into relatively discrete elements. General batteries are neuropsychologically dense, though they hold the advantage of obtaining reliable IQ measures or memory indexes, whereas experimental approaches that allow task performance on subtests of such batteries to be parsed into even more basic psychological processes allow refined appreciation of the neural abnormalities underlying the at-risk mental state.[89] Likewise, popular tasks such as the WCST and the Rey-Osterreith Complex Figure, which reflect more general domains of executive ability and which provide gross indications of ability in relatively broad cognitive domains, can also be parsed into subprocesses. As they stand, such tasks reflect relatively gross challenges of cognitive ability, where they could be supplemented by computerized tasks that parse subprocesses more clearly. The CANTAB and Delayed Response Paradigms represent superior experimental examples in this regard. In addition to reporting patient mean performance on cognitive tasks, more sophisticated analysis of potential subgroups of patients based on cognitive profiling is recommended, as normal performance in some patients may mask significant deficits in subgroups. Moreover, characterization of general current and premorbid cognitive IQs via utilization of reliable and valid test batteries such as the Wechsler scales should remain a standard approach. This not only affords a reliable point of comparison across centers but also provides a functional context for reports of nonstandardized experimental results of ''parsed'' cognitive processes, which are likely confounded by more general intellectual ability. Incorporation of matched control groups, particularly with regard to measures of premorbid IQ (including years of education) reflects superior experimental design, relative to reliance on published norms of popular neuropsychological tasks. Finally, as has historically occurred with symptom ratings, the use of cluster analysis and factor analytic techniques focused on cognitive scores to characterize potential subgroups of subjects would be useful. Cognitive profiles can then be more meaningfully associated with clinical profiles for the purpose of incorporating the same into inclusion criteria for clinical high risk for psychosis.

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