Neuropsychological Test Performance to Enhance Identification of Subjects at Clinical High Risk for Psychosis and to Be Most Promising for Predictive Algorithms for Conversion to Psychosis: A Meta-Analysis

Marta Hauser, PhD[a,b,c]; Jian-Ping Zhang, MD, PhD[a,b,c]; Eva M. Sheridan, MD[a]; Katherine E. Burdick, PhD[d]; Rachel Mogil, BS[b]; John M. Kane, MD[a,b,c,e]; Andrea Auther, PhD[a,b]; Ricardo E. Carrión, PhD[a,b,c]; Barbara A. Cornblatt, PhD[a,b,c]; and Christoph U. Correll, MD[a,b,c,e,*]

ABSTRACT

Objective: To compare neuropsychological performance in people at clinical high risk for psychosis (CHR), healthy controls (HCs), or subjects with first-episode psychosis (FEP).

Data Sources: Systematic PubMed/MEDLINE search through January 2014, without language restrictions, using search terms *prodrome* OR *clinical high-risk* OR *ultra-high risk* AND *cognition* OR individual test names.

Study Selection: Studies reporting neuropsychological data in CHR versus a HC or FEP groups or comparing CHR subjects who converted to psychosis (CHR-P) with CHR subjects who did not convert to psychosis (CHR-NP).

Data Extraction: Two authors independently extracted and compared neurocognitive test data.

Results: A meta-analysis was performed on 60 neuropsychological tests from 9 domains in 32 studies with 21 nonoverlapping samples (CHR = 1,684 patients, HC = 986, FEP = 405). Compared to HCs, people with CHR performed significantly worse in 7 of 9 domains (Hedges *g* effect size [95% confidence limit] = –0.17 [–0.30, –0.04] [attention/vigilance] to –0.42 [–0.64, –0.20] [verbal learning, speed of processing] and –0.43 [–0.68, –0.18] [social cognition]), except reasoning/problem solving and working memory (which separated in longitudinal studies). California Verbal Learning Test (–0.65 [–0.84, –0.46]) and Digit Symbol Test (–0.63 [–0.86, –0.40]) separated groups the most. Compared to FEP subjects, people with CHR performed significantly better in 5 of 6 domains (from 0.29 [0.03, 0.56] [speed of processing] to 0.39 [0.17, 0.62] [attention/vigilance, verbal learning] and –0.40 [0.18, 0.64] [working memory]), except reasoning/problem solving. CHR-P and CHR-NP performed significantly worse than HC (except visual learning, working memory in CHR-NP). Compared to CHR-NP, CHR-P performed significantly worse in 6 of 8 domains (from –0.24 [–0.44, –0.03] [attention/vigilance] to –0.49 [–0.76, –0.22] [verbal learning] and –0.54 [–0.80, –0.27] [visual learning]), without differences in reasoning/problem solving and working memory. Three individual tests (Rey-Osterrieth Complex Figure Test, Verbal Fluency Test/Controlled Oral Word Association Test, and California Verbal Learning Test) discriminated the best between CHR-P and CHR-NP (–0.49 [–0.82, –0.16], –0.45 [–0.86, –0.03], and –0.40 [–0.80, –0.00], respectively).

Conclusions: CHR has mild to moderate globally distributed neuropsychological performance deficits that lie between FEP and HCs. Neuropsychological performance deficits are greater in CHR-P than in CHR-NP, but they overlap, reducing their current utility for risk stratification.

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[a]The Zucker Hillside Hospital, Psychiatry Research, North Shore-Long Island Jewish Health System, Glen Oaks, New York [b]Department of Psychiatry and Molecular Medicine, Hofstra North Shore-LIJ School of Medicine, Hempstead, New York [c]Center of Excellence for Neuroscience, The Feinstein Institute for Medical Research, Manhasset, New York [d]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York [e]Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, Bronx, New York

**Corresponding author:* Christoph U. Correll, MD, Division of Psychiatry Research, The Zucker Hillside Hospital, 75-59 263rd St, Glen Oaks, NY 11004 (ccorrell@northwell.edu).

Given that schizophrenia remains one of the most severe psychiatric disorders that is associated with significant personal and societal suffering and cost, interest has focused on the recognition and prevention of disease in the earliest, prepsychotic illness phases.[1,2] As part of this focus, research criteria for subjects at clinical high risk for psychosis (CHR) or at ultra-high risk for psychosis and those with basic symptoms have been established, which are able to identify up to 36% of individuals who will transition to psychosis within a 3-year follow-up period[3] (differences in clinical criteria and terminology for risk subjects are negligible for the purpose of this article and therefore all are referred to as "CHR"). Although this conversion rate is considerable, leading to inclusion of the associated attenuated psychosis syndrome in section II of the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition *(DSM-5)*,[4] as a specifier for the category "other specified schizophrenia spectrum and other psychotic disorders," this number is considerably less than ideal given the ethical dilemmas associated with a false-positive rate of almost two-thirds of "at-risk" individuals. Thus, the search for other predictors of conversion risk to psychosis has focused on additional, reliably measurable risk markers, such as neuroimaging,[5–8] electrophysiology,[1] and neurocognition,[9–12] with attempts to build sets of clinical and biological correlates into refined prediction models.[13–16]

Cognition is a promising candidate risk marker because cognitive impairments are a hallmark of schizophrenia[17] and are present in the majority of schizophrenia patients.[18] Measurable deficits develop before the onset of (positive) clinical symptoms[19–21] and are present and identifiable during the CHR state. Furthermore, the investigation of cognitive deficits is valuable because evidence exists suggesting cognitive impairments to be even stronger predictors of functional outcomes than positive symptoms in schizophrenia,[22,23] with specific associations

Clinical Points

- Identification strategies for individuals at clinical high risk for psychosis (CHR) are currently too imprecise, stimulating the search for additional risk markers.
- Subjects with CHR differentiated significantly from healthy controls and from individuals with first-episode psychosis, and 3 neuropsychological domains (ie, visual learning, verbal learning, and speed of processing) differentiated CHR subjects who did versus those who did not transition to psychosis.
- Nevertheless, overlapping neuropsychological test performance precludes current recommendations regarding specific tests with utility for clinical care.

between cognitive and functional domains.[24,25] Importantly, in some instances, cognitive deficits appear to be malleable. For example, treatment with antipsychotics can improve cognition, especially in patients with a first episode[26,27] and in combination with psychosocial interventions.[28] Furthermore, cognitive-remediation strategies, especially in conjunction with psychosocial rehabilitation, could have the potential to improve cognition[29] and possibly even enhance functional outcomes in schizophrenia.[28,30–32] Early evidence suggests that cognitive improvement might be easier to attain early in the CHR state versus later in the chronic stage of schizophrenia.[33,34]

Four recent meta-analyses[9–12] reviewed neuropsychological performance in CHR subjects. Giuliano and colleagues[9] included 14 studies published before March 2011, including 1,215 CHR subjects compared to healthy controls (HCs) on a domain level and test level of analysis. Additionally, they compared an unknown number of CHR subjects from 7 publications who converted to psychosis (CHR-P) and those who did not convert (CHR-NP) to HCs. Fusar-Poli and colleagues[10] included 19 studies published before January 2011 with 1,188 CHR subjects, comparing CHR versus HC on a domain level and test level of analysis and 7 studies comparing 598 CHR-P and CHR-NP on a domain level. Bora and colleagues[12] included studies published before April 2013, excluding studies using help-seeking, non-CHR populations as controls, comparing 1,184 CHR subjects from 16 studies with HCs as well as 849 CHR-P and CHR-NP subjects from 9 studies (of which a couple of samples included overlapping subjects), and adding also a control group of 18 studies and 929 subjects at familial high risk for schizophrenia. De Herdt and colleagues' meta-analysis[11] focused only on 9 studies (6 of which overlapped with the ones in the meta-analysis by Bora and colleagues[12]) comparing 583 CHR-P and CHR-NP subjects on 6 of the 7 cognitive domains of the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB).[35] Thus, despite strengths of each of the prior meta-analyses, an updated meta-analysis that pools the maximum available data without considering any overlapping samples and that includes both domain-level and individual test-level results categorized in accordance with professional consensus panels is a relevant addition to the current debate around the potential value of neurocognitive performance assessments in determining risk for psychosis.

Therefore, in this updated meta-analysis, we aimed to substantially increase the number of included subjects and comparisons, address the aforementioned methodological shortcomings, clarify discrepant results of previous meta-analyses, and identify specific neuropsychological tests with the greatest promise to be employed in future prediction models.

METHODS

Search Strategy, Eligibility Criteria, Study Selection, and Data Collection

We performed a literature search in PubMed/MEDLINE through January 2014 without language restrictions, using combinations of the search terms *prodrome* OR *clinical high risk* OR *ultra high risk* AND *cognition* OR *speed of processing* OR *attention* OR *vigilance* OR *memory* OR *learning* OR *reasoning* OR *problem solving* OR *social cognition* OR *intelligence* OR *IQ*. Additionally, we manually searched the reference lists of retrieved articles for additional publications. Studies were included if they (1) were peer reviewed, (2) entailed CHR samples as defined by validated criteria assessed with structured interviews (see Supplementary eTable 1[36–47]), (3) reported neuropsychological test results with statistics that allow for calculation of effect sizes, and (4) entailed 1 or more of the following comparisons: CHR versus HCs, CHR versus first-episode psychosis (FEP) patients, CHR-P versus CHR-NP, or CHR-P or CHR-NP versus HC or versus FEP. We included data for baseline and follow-up assessments if available. If articles reported on overlapping samples for the same tests or domains, only the study with the largest sample was included. Authors were contacted for missing information or to clarify potential overlap between studies. We excluded articles that measured cognition within neuroimaging paradigms, as those studies typically involve selection factors, modifications of the applied neuropsychological tests, and additional stressors of the imaging procedures that could reduce the generalizability of the finding, influence neurocognitive performance, and add variability to the results. Data extraction was performed by authors R.M. and E.M.S. with cross-checking by the first author (M.H.).

Outcomes

Our primary outcome was the baseline neuropsychological performance of CHR subjects compared to HCs on the 7 cognitive domains of the MCCB plus the additional 2 domains current and premorbid IQ (Table 1[48–80]). Secondary outcomes included specific tests, which loaded into the domain scores. Further secondary outcomes included baseline comparisons on domain level and test level between any other included groups as well as comparisons between CHR subjects and HCs at a defined follow-up interval.

Table 1. Cognitive Domains, Included Tests, and Publications

Domain/Test	Study
Attention/vigilance[a]	
Continuous Performance Test (CPT)[a]	Mirzakhanian et al 2013,[48] Frommann et al 2011,[49] Carrión et al 2011,[50] Woodberry et al 2010,[51] 2013,[52] Carr et al 2000,[53] Ozgürdal et al 2009,[54] Becker et al 2010,[55] Lencz et al 2006,[56] Riecher-Rössler et al 2009,[57] Pflueger et al 2007,[58] Pukrop et al 2006,[59] Francey et al 2005[60]
CPT d′ numbers fast/slow	
CPT d′ shapes fast/slow	
CPT figures	
CPT symbols	
CPT 2-, 3-, 4-d′	
CPT false alarm	
CPT missing	
CPT 3/7 hits	
CPT degraded hits	
Stroop Color and Word Test	Jashan et al 2010,[61] Kim et al 2011,[62] Brewer et al 2005,[63] Carr et al 2000,[53] Ozgürdal et al 2009[54]
Digits Forward (WMS-R)	Carrión et al 2011,[50] Lindgren et al 2010,[64] Wood et al 2007,[65]
Digit Span (WAIS-R)	Kim et al 2011,[62] Koutsouleris et al 2012,[66] Lin et al 2013,[67] Lencz et al 2006[56]
Visual Backward Masking	Pukrop et al 2006,[59] 2007[68]
Judgment of Line Orientation	Carrión et al 2011,[50] Lencz et al 2006[56]
Visual Span Forward	Lindgren et al 2010[64]
Attention Memory Index	Stanford et al 2011[69]
Picture Completion (WAIS-R)	Lin et al 2013[67]
TAP (Testbatterie zur Aufmerksamkeitsprufung)	Simon et al 2007[70]
Alertness	
Commission errors	
Omission errors	
Reasoning/problem solving[a]	
Wisconsin Card Sorting Test	Kim et al 2011,[62] Jahshan et al 2010,[61] Pukrop et al 2006,[59] Pflueger et al 2007,[58] Carrión et al 2010,[50] Woodberry et al 2010,[51] Hur et al 2013,[71] Riecher-Rössler et al 2009[57]
Perseveration response	
Perseveration errors	
Tower of Hanoi	Pflueger et al 2007,[58] Riecher-Rössler et al 2009[57]
Ruff Figural Fluency	Carrión et al 2011[50]
Go/no-go (TAP)	Pflueger et al 2007,[58] Riecher-Rössler et al 2009[57]
Similarities (WAIS-R)	Lin et al 2013[67]
Beads Span Test	Broome et al 2012[72]
Speed of processing[a]	
Verbal Fluency Semantic Category[a]	Becker et al 2010,[73] Lindgren et al 2010,[64] Ozgürdal et al 2009,[54] Simon et al 2007[70]
Trail-Making Test A[a]	Lin et al 2013,[67] Kim et al 2011,[62] Frommann et al 2010,[49] Bowie et al 2012,[74] Carrión et al 2010,[50] Lindgren et al 2010,[64] Ozgürdal et al 2009,[54] Koutsouleris et al 2012,[66] Wood et al 2007[65]
Trail-Making Test B	Lin et al 2013,[67] Kim et al 2011,[62] Frommann et al 2010,[49] Carrión et al 2010,[50] Woodberry et al 2010,[51] 2013,[52] Lindgren et al 2010,[64] Bowie et al 2012,[74] Carr et al 2000,[53] Ozgürdal et al 2009,[54] Koutsouleris et al 2012,[66] Simon et al 2007,[70] Pukrop et al 2007[68]
Verbal Fluency Test/Controlled Oral Word Association Test	Becker et al 2010,[73] Frommann et al 2010,[49] Pukrop et al 2006,[59] Woodberry et al 2010,[51] 2013,[52] Kim et al 2011,[62] Carrión et al 2011,[50] Koutsouleris et al 20012,[66] Lin et al 2013,[67] Bowie et al 2012,[74] Wood et al 2007[65]
Digit Symbol Test	Lin et al 2013,[67] Carrión et al 2011,[50] Frommann et al 2010,[49] Koutsouleris et al 2012[66] Wood et al 2007,[65] Pukrop et al 2007[68]
Finger Tapping Test	Carrión et al 2011,[50] Woodberry et al 2010,[51] 2013,[52] Becker et al 2010[55]
Right/Left	
Numerical Attention Test	Jahshan et al 2010[61]
Fine Motor Function Test	Gschwandter et al 2006[75]
Precision	
Tremor	
Grooved Pegboard Test	Carrión et al 2011[50]
Right/Left	
Personal Computer Test (novel computerized task)	Lindgren et al 2010[64]
Choice reaction time	
Simple reaction time	
Bourdon-Wiesma Dual Task Counting Backward	Lindgren et al 2010[64]
Spatial Tapping (difficult)	Lindgren et al 2010[64]
Verbal learning[a]	
Hopkins Verbal Learning Test-Revised[a]	Jahshan et al 2010[61]
California Verbal Learning Test	Becker et al 2010,[55] Carrión et al 2011,[50] Woodberry et al 2010,[51] 2013,[52] Kim et al 2011,[62] Lindgren et al 2010,[64] Hur et al 2013,[71] Pettersson-Yeo et al 2013,[16] Bowie et al 2012,[74] Carr et al 2000,[53] Lencz et al 2006[56]
Immediate recall	
Delayed recall	
Trials 1–5	
Logical memory (WMS-R)	Carrión et al 2011,[50] Woodberry et al 2010,[51] 2013,[52] Lindgren et al 2010,[64] Lin et al 2013,[67] Wood et al 2007,[65] Carr et al 2000,[53] Lencz et al 2006[56]
Delay	
Immediate	
Rey Auditory Verbal Learning Task	Pukrop et al 2006,[59] 2007,[68] Frommann et al 2011,[49] Koutsouleris et al 2012,[66] Lin et al 2013,[67] Wood et al 2007,[65] Ozgürdal et al 2009,[54] Simon et al 2007[70]
Delayed recall	
Immediate recall	
Trials 1–5	

(continued)

Table 1 (continued). Cognitive Domains, Included Tests, and Publications

Domain/Test	Study
Boston Naming Test	Carrión et al 2010,[50] Lencz et al 2006[56]
Verbal Pairs Correct (WMS-R)	Brewer et al 2005,[63] Lin et al 2013[67]
Verbal Memory Index (WMS-R)	Stanford et al 2011,[69] Wood et al 2007[65]
Visual learning[a]	
Rey-Osterrieth Complex Figure Test	Becker et al 2010,[55] Kim et al 2011,[62] Pukrop et al 2007[68]
Immediate recall	
Delayed recall	
Visual Reproduction	Lindgren et al 2010,[64] Lin et al 2013[67]
Working memory[a]	
Letter Number Sequencing (WAIS-III)	Frommann et al 2011,[49] Carrión et al 2011,[50] Woodberry et al 2010,[51] 2013,[52] Simon et al 2007,[70] Jahshan et al 2010,[61] Koutsouleris et al 2012,[66] Bowie et al 2012,[74] Pukrop et al 2007[68]
Digits Backward (WMS-R)	Carrión et al 2010,[50] Lindgren et al 2010,[64] Wood et al 2007[65]
Spatial Working Memory Delayed Response Task	Becker et al 2010,[55] Pukrop et al 2006[59]
Spatial Span Backward	Jahshan et al 2010,[61] Lindgren et al 2010[64]
Arithmetic (WAIS-R)	Stanford et al 2011,[69] Lin et al 2013,[67] Wood et al 2007[65]
Subject Ordered Pointing Task	Frommann et al 2011,[49] Koutsouleris et al 2012[66]
Spatial Location	Kim et al 2011[62]
Working Memory (TAP)	Pflueger et al 2007[58]
False alarm	
Missing	
Social cognition[a]	
False Believe Task	Kim et al 2011,[62] Stanford et al 2011,[69] Hur et al 2013[71]
First order	
Second order	
Strange Story Task	Kim et al 2011,[62] Stanford et al 2011,[69] Hur et al 2013[71]
Reading the Mind in the Eye Test	Couture et al 2008,[76] Stanford et al 2011,[69] Szyli and Kéri 2009[77]
Cartoon Test	Kim et al 2011,[62] Hur et al 2013[71]
Facial Affect Labeling Test	van Rijn et al 2011[78]
Angry	
Fearful	
Happy	
Neutral	
The Awareness of Social Inference Test	Green et al 2012[79]
Abbreviated Trustworthiness Test	Couture et al 2008[76]
Trustworthy	
Untrustworthy	
Facial Emotion Identification Test	Addington et al 2008[80]
Facial Emotion Discrimination Test	Addington et al 2008[80]
Current IQ	
Vocabulary (WAIS-R/WISC-III)	Jahshan et al 2010,[61] Lin et al 2013,[67] Carrión et al 2011,[50] Lindgren et al 2010,[64] Lencz et al 2006,[56] Woodberry et al 2010[51]
Block Design (WAIS-R/WISC-III)	Jahshan et al 2010,[61] Lin et al 2013,[67] Carrión et al 2011,[50] Wood et al 2007,[65] Lencz et al 2006,[56] Woodberry et al 2010[51]
Full scale IQ (WAIS-R/WISC-III)	Stanford et al 2011,[69] Szyli and Kéri 2009,[77] Lencz et al 2006,[56] Woodberry et al 2010[51]
Verbal IQ (WAIS-R/WISC-III)	Stanford et al 2011,[69] Hur et al 2013[71]
Performance IQ (WAIS-R/WISC-III)	Stanford et al 2011,[69] Hur et al 2013[71]
Leistungsprufsystem	Pflueger et al 2007[58]
Mehrfachwortschatztest-A	Pflueger et al 2007,[58] Pukrop et al 2006,[59] Simon et al 2007,[70] Riecher-Rössler et al 2009[57]
Information (WAIS-R/WISC-III)	Lin et al 2013[67]
Quick Test	Broome et al 2012[72]
Premorbid IQ	
Mehrfachwortschatztest-B	Pukrop et al 2007,[68] Frommann et al 2011,[49] Koutsouleris et al 2012[66]
National Adult Reading Test	Becker et al 2010,[55] Lin et al 2013,[67] Brewer et al 2005,[63] Broome et al 2012[72]
Wide Range Achievement Test, Third Edition	Carrión et al 2011,[50] Woodberry et al 2010,[51] Lencz et al 2006[56]

[a]Included in the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) consensus battery.
Abbreviations: TAP = Test of Attentional Performance, WAIS-III = Wechsler Adult Intelligence Scale-Third Edition, WAIS-R = WAIS-Revised, WISC-III = Wechsler Intelligence Scale for Children-Third Edition, WMS-R=Wechsler Memory Scale-Revised.

Classification of Neuropsychological Tests and Domains

Neuropsychological tests were grouped into domains according to the classification of the MATRICS panel,[35,81] including attention/vigilance, speed of processing, verbal learning, visual learning, working memory, reasoning/problem solving, and social cognition. Furthermore, the domains current and premorbid IQ were added. Reported tests that are not part of the MCCB were assigned to domains by the clinical neuropsychologist (K.E.B.) according to their most commonly used function (Table 1).

Meta-Analytic Calculations and Procedures

Analyses of group comparisons and baseline and end point comparisons in longitudinal studies were conducted for any domain level and test level comparisons when ≥ 3

publications reporting data were available (Table 1). If more than 1 test variable was reported for a test, the most commonly used test variable was chosen for data extraction. If several common test variables were reported for the same test, the test variable indicating the most difficult test condition was chosen for analysis on the test level, while the combined mean effect size of all common test variables was included in the domain-level analyses. We chose to take a rigid approach at the test level in order to achieve a detailed picture and took a broader approach on the domain level in order to include as much of the available information as was possible.

Data were analyzed with Comprehensive Meta-Analysis, version 2, of the BioStat software.[82] Pooled effect sizes, Hedges *g*, were calculated using random-effects models[83] from group means and standard deviations, with negative scores reflecting worse performance. Statistics also included the lower and upper 95% confidence limit and I^2 as a measure of heterogeneity across studies ($I^2 \geq 50\%$ is considered significant). When heterogeneity across studies in a meta-analysis was high, meta-regression analysis was attempted to explain the heterogeneity if there were >10 studies in the meta-analysis.[84] Due to inherent heterogeneity among different tests of the same cognitive domain, meta-regression was performed only on test-level meta-analysis. All tests were 2-sided, and α was set at .05 without correction for multiple testing. Finally, publication bias was assessed by inspection of funnel plots by using a nonparametric method, the "trim and fill,"[85] an iterative procedure to assess whether small, extreme included studies and/or potentially unincluded studies biased the true effect size estimate.

RESULTS

Search and Included Articles

The initial database search yielded 305 hits, of which 29 articles met inclusion criteria. Three articles were added through manual cross-searching of references, resulting in a total of 32 articles[48–80] (Supplementary eFigure 1). Of these, 11 articles[42,48,56,60–63,65,74,75,80] reported on overlapping samples, however, including different control groups, comparisons, or neuropsychological tests. Thus, these 11 studies were excluded from the analysis of baseline sample characteristics but were included in the respective meta-analytic calculations (Supplementary eTable 2).

Sample, Neuropsychological Domains, and Tests

The 21 studies of nonoverlapping samples contained 1,684 CHR subjects, 986 HC subjects, and 405 FEP subjects. Five studies[52,55,61,65,74] reported longitudinal cognitive test results. Nine articles[51,55,57,62,63,66–68,72] reported on the comparison between CHR-P and CHR-NP in strictly nonoverlapping samples after a defined follow-up period, including 732 CHR subjects, of whom 221 had converted to psychosis, while 493 had not converted at the end of follow-up.

Information on demographic data, psychopathology, functioning, and medication of the main sample is summarized in Supplementary eTable 2, as are type and frequency of neuropsychological tests. Original publications reported on 60 neuropsychological tests, ranging from reports on a single test to 21 tests in 1 publication, with most data available for the domain attention/vigilance across all comparisons (Tables 2–4).

Neuropsychological Performance of CHR Subjects Versus HCs at Baseline

Subjects with CHR performed significantly worse than HC in all but 2 domains (reasoning/problem solving and working memory), in which differences reached trend level of significance (Table 2). Significant effect sizes ranged from −0.17 (attention/vigilance) to −0.42 and −0.43 (social cognition, speed of processing, verbal learning). On the test-level analysis, CHR subjects showed worse performance than HCs on most tests (9 of 29 tests were not significant). All neuropsychological tests within the domains of verbal and visual learning reflected significantly worse performance of CHR subjects compared to HCs, while performance differed in the tests of the remaining domains. California Verbal Learning Test (CVLT) trials 1–5 (effect size = −0.65) and Digit Symbol Test (effect size = −0.63) showed the most severe deficits compared to HC. Conversely, performance of CHR subjects did not differ from HCs in the only available test of premorbid IQ (Table 2). Heterogeneity across studies was moderate to high in 6 of 9 domains (I^2 = 45.5%–80.1%), with relatively homogeneous findings (I^2 = 5.7%–17.2%) for premorbid and current IQ as well as visual learning (1 test only).

Neuropsychological Performance of CHR Subjects Versus HCs at Baseline and Follow-Up Assessment in Longitudinal Studies

Five studies[52,55,61,65,74] reported on a second neuropsychological assessment after a weighted mean follow-up time of 10.4 months. Baseline results of these 5 studies were comparable to the baseline results of the 21 studies of nonoverlapping samples with only a 1-time assessment described previously, although within longitudinal studies, the domain working memory reached significance for worse performance of CHR subjects compared to HC. At follow-up, CHR subjects still performed worse than HCs in the domains in which they showed lower performance at baseline, without clear trends of change from baseline. However, 4 of the 9 domains were not analyzable at the second assessment due to missing information. The 4 tests that had sufficient data to be analyzed on the test level all reflected worse performance of CHR subjects compared to HCs at the weighted mean follow-up time point (Table 2). Domain score results were more homogeneous (I^2 = 0% each) for baseline and follow-up for all domains, except for attention/vigilance (baseline I^2 = 0%, follow-up I^2 = 47.1%) and current IQ (I^2 > 76.0% each).

Table 2. Neuropsychological Performance in Subjects at Clinical High Risk for Psychosis (CHR) Versus Healthy Controls and Versus Patients With First-Episode Psychosis (FEP)

	CHR vs Healthy Controls						CHR Versus FEP					
Cognitive Test/Domain[a]	No. of Studies	n	Hedges g[b]	95% CL	*P*	I^2 (%)	No. of Studies	n	Hedges g[b]	95% CL	*P*	I^2 (%)
Attention/vigilance	***14***	***2,038***	***−0.171***	***−0.299, −0.043***	***.009***	***45.79***	***7***	***906***	***0.398***	***0.138, 0.658***	***.003***	***70.58***
LT studies: baseline	***5***	***316***	***−0.323***	***−0.558, −0.089***	***.007***	***0***						
LT studies: f/u at 10.4 mo	***5***	***308***	***−0.341***	***−0.674, −0.007***	***.045***	***47.08***						
CPT numbers	5	938	−0.308	−0.451, −0.166	<.0001	11.95						
CPT shapes	5	787	−0.225	−0.372, −0.079	.003	0 (55.50)						
LT studies: baseline	3	206	−0.334	−0.631, −0.037	.027	0						
LT studies: f/u at 11.7 mo	3	205	−0.462	−0.931, −0.010	.045	55.5						
Stroop Color and Word Test	3	306	−0.260	−0.896, 0.377	.424	85.83	3	216	0.273	−0.033, 0.580	.081	16.33
Digits Forward	3	364	−0.288	−0.495, −0.080	.007	0						
Digit Span	4	445	−0.048	−0.245, 0.149	.632	0						
Reasoning/problem solving	***8***	***969***	***−0.243***	***−0.490, 0.004***	***.054***	***70.55***	***3***	***441***	***0.081***	***−0.261, 0.423***	***.642***	***66.05***
WCST preservation response	4	389	−0.059	−0.509, 0.391	.796	80.22						
WCST preservation errors	3	421	−0.446	−0.647, −0.245	<.0001	0	3	441	0.081	−0.261, 0.423	.642	66.05
Speed of processing	***12***	***1,664***	***−0.427***	***−0.612, −0.242***	***<.0001***	***67.82 (0)***	***5***	***527***	***0.294***	***0.029, 0.560***	***.030***	***54.86***
LT studies: baseline	***5***	***313***	***−0.410***	***−0.646, −0.175***	***.001***	***0***						
LT studies: f/u at 10.4 mo	***5***	***312***	***−0.446***	***−0.683, −0.209***	***<.0001***	***0***						
Verbal Fluency Test/COWAT	8	1,274	−0.351	−0.636, −0.067	.015	81.72	4	557	0.253	0.043, 0.463	.018	31.85
LT studies: baseline	3	212	−0.343	−0.654, −0.031	.031	0						
LT studies: f/u at 9.8 mo	3	210	−0.496	−0.890, −0.101	.014	43.38						
Verbal Fluency Semantic Category							3	343	0.522	−0.005, 1.049	.052	82.00
Trail-Making Test A	6	936	−0.368	−0.510, −0.227	<.0001	7.70						
Trail-Making Test B	8	1,170	−0.492	−0.656, −0.327	<.0001	42.82	3	343	0.322	−0.165, 0.808	.195	79.56
Digit Symbol Test	5	868	−0.630	−0.856, −0.404	<.0001	55.36						
Finger Tapping Test Left	3	371	−0.030	−0.321, 0.262	.843	38.60						
Finger Tapping Test Right	3	371	−0.054	−0.266, 0.159	.621	0						
Verbal learning	***11***	***1,132***	***−0.419***	***−0.638, −0.201***	***<.0001***	***67.40 (0)***	***6***	***655***	***0.394***	***0.172, 0.617***	***.001***	***44.19***
LT studies: baseline	***5***	***315***	***−0.426***	***−0.660, −0.192***	***<.0001***	***0***						
LT studies: f/u at 10.4 mo	***5***	***303***	***−0.280***	***−0.525, −0.036***	***.024***	***0***						
CVLT immediate recall	4	323	−0.552	−1.009, −0.095	.018	72.81						
CVLT delayed recall	5	530	−0.417	−0.752, −0.081	.015	69.11						
CVLT trials 1–5	4	484	−0.650	−0.838, −0.463	<.0001	0						
LT studies: baseline	3	211	−0.400	−0.692, −0.108	.007	0						
LT studies: f/u at 11.7 mo	3	199	−0.482	−0.796, −0.169	.003	0						
Logical Memory	4	576	−0.396	−0.717, −0.074	.016	70.64						
RAVLT delayed recall	3	497	−0.440	−0.731, −0.149	.003	50.87						
RAVLT trials 1–5	4	629	−0.537	−0.823, −0.252	<.0001	60.75						
Visual learning	***5***	***520***	***−0.268***	***−0.470, −0.103***	***.002***	***5.76***						
ROCFT	3	262	−0.355	−0.669, −0.040	.027	31.81						
Working memory	***10***	***1,512***	***−0.242***	***−0.490, 0.005***	***.054***	***80.10***	***3***	***418***	***0.411***	***0.181, 0.642***	***<.0001***	***19.15***
LT studies: baseline	***5***	***320***	***−0.265***	***−0.496, −0.035***	***.024***	***0***						
LT studies: f/u at 10.4 mo	***5***	***308***	***−0.603***	***−0.848, −0.358***	***.000***	***0***						
Letter Number Sequencing	6	888	−0.373	−0.571, −0.175	<.0001	38.21(0)						
LT studies: baseline	3	231	−0.256	−0.555, 0.043	.093	16.19						
LT studies: f/u at 8.2 mo	3	223	−0.058	−0.846, −0.271	<.0001	0						
Digits Backward	3	374	−0.275	−0.612, 0.061	.109	55.08						
SOPT	3	497	−0.513	−1.112, 0.087	.094	88.12						
Social cognition	***8***	***755***	***−0.431***	***−0.683, −0.179***	***.001***	***62.84***						
False Believe Task	3	241	−0.533	−0.904, −0.162	.005	43.15						
Strange Story Task	3	294	−0.276	−0.511, −0.041	.021	0						
Eye Test	3	292	−0.323	−0.957, 0.312	.319	84.09						
Current IQ	***9***	***1,059***	***−0.210***	***−0.347, −0.073***	***.003***	***12.82***	***3***	***418***	***0.307***	***0.106, 0.508***	***.003***	***0***
LT studies: baseline	***3***	***185***	***−0.866***	***−1.565, −0.167***	***.015***	***76.82***						
LT studies: f/u at 10.4 mo	***3***	***185***	***−0.699***	***−1.375, −0.023***	***.043***	***76.16***						
Vocabulary	5	730	−0.396	−0.634, −0.159	.001	50.91						
Block Design	4	433	−0.569	−1.054, −0.083	.022	78.04						
Premorbid IQ	***7***	***1,260***	***−0.251***	***−0.391, −0.112***	***<.0001***	***17.19***						
MWT-B	3	497	−0.391	−0.672, 0.033	.076	66.91						

[a]Bold/italic type indicates cognitive domains. [b]Hedges g = effect size. Negative effect size indicates greater impairment.

Abbreviations: CL = confidence limits, COWAT = Controlled Oral Word Association Test, CPT = Continuous Performance Test, CVLT = California Verbal Learning Test, f/u = follow-up, LT = longitudinal, MWT-B = Mehrfachwortschatztest-B, RAVLT = Rey Auditory Verbal Learning Test, ROCFT = Rey-Osterrieth Complex Figure Test, SOPT = Subject Ordered Pointing Task, WCST = Wisconsin Card Sorting Test.

Table 3. Neuropsychological Performance[a] in Subjects at Clinical High Risk for Psychosis (CHR) Who Converted to Psychosis (CHR-P) and Those Who Did Not Convert to Psychosis (CHR-NP) Versus Healthy Controls

	CHR-P vs Healthy Controls						CHR-NP vs Healthy Controls					
Cognitive Test/Domain[b]	No. of Studies	n	Hedges g^c	95% CL	*P*	I^2 (%)	No. of Studies	n	Hedges g^c	95% CL	*P*	I^2 (%)
Attention/vigilance	***8***	***483***	***−0.415***	***−0.712, −0.118***	***.006***	***57.60***	***8***	***611***	***−0.213***	***−0.375, −0.052***	***.010***	***0***
CPT shapes	4	205	−0.386	−0.688, −0.084	.012	0	4	287	−0.287	−0.522, −0.053	.016	0
Digit Span	4	238	−0.431	−0.846, −0.017	.042	51.87	4	301	−0.227	−0.615, 0.160	.251	63.07
Reasoning/problem solving	***5***	***328***	***−0.499***	***−0.731, −0.267***	***<.0001***	***0***	***5***	***420***	***−0.340***	***−0.591, −0.090***	***.008***	***38.13***
WCST preservation errors	3	182	−0.308	−1.089, −0.474	.440	81.91	3	229	−0.292	−0.771, −0.187	.233	69.13
Speed of processing	***7***	***429***	***−0.802***	***−1.022, −0.583***	***<.0001***	***0***	***7***	***528***	***−0.345***	***−0.534, −0.157***	***<.0001***	***0***
Verbal Fluency Test	6	371	−0.621	−1.042, −0.200	.004	71.79	6	442	−0.244	−0.537, 0.049	.103	57.68
Trail-Making Test A	5	321	−0.617	−0.946, −0.288	<.0001	46.61	5	362	−0.356	−0.640, −0.072	.014	44.82
Trail-Making Test B	3	171	−0.876	−1.700, −0.052	.037	83.18	3	228	−0.374	−0.918, 0.170	.177	75.26
Digit Symbol Test	3	222	−0.974	−1.253, −0.695	<.0001	0	3	245	−0.476	−0.737, −0.215	<.0001	1.83
Verbal learning	***7***	***400***	***−0.869***	***−1.218, −0.520***	***<.0001***	***58.50***	***7***	***489***	***−0.542***	***−0.896, −0.187***	***.003***	***66.47***
CVLT	3	126	−1.433	−1.845, −1.022	<.0001	0	3	183	−0.673	−1.110, −0.235	.003	49.33
Logical Memory	3	174	−0.873	−1.394, −0.351	.001	57.66	3	236	−0.422	−1.010, 0.167	.160	79.45
RAVLT	3	213	−0.719	−1.335, −0.102	.022	78.36	3	222	−0.421	−0.850, 0.008	.055	60.35
Visual learning	***4***	***240***	***−0.749***	***−1.063, −0.436***	***<.0001***	***21.93***	***4***	***285***	***−0.159***	***−0.391, 0.072***	***.178***	***0***
ROCFT	3	165	−0.751	−1.263, −0.239	.004	49.70	3	199	−0.172	−0.448, 0.105	.225	0
Working memory	***6***	***344***	***−0.632***	***−0.892, −0.372***	***<.0001***	***23.71***	***6***	***427***	***−0.308***	***−0.647, 0.030***	***.074***	***65.35***
Letter Number Sequencing	4	224	−0.627	−0.969, −0.286	<.0001	29.39	4	276	−0.288	−0.689, 0.113	.159	63.62
Social cognition	***…***	***…***	***…***	***…***	***…***	***…***	***…***	***…***	***…***	***…***	***…***	***…***
Current IQ	***3***	***174***	***−0.716***	***−1.040, −0.391***	***<.0001***	***0***	***3***	***236***	***−0.609***	***−0.879, −0.340***	***<.0001***	***3.32***
Premorbid IQ	***6***	***406***	***−0.747***	***−1.007, −0.487***	***<.0001***	***8.32***	***6***	***424***	***−0.299***	***−0.491, −0.106***	***.002***	***0***

[a]Weighted means. [b]Bold/italic type indicates cognitive domains. [c]Hedges *g* = effect size. Negative effect size indicates greater impairment.
Abbreviations: CL = confidence limits, CPT = Continuous Performance Test, CVLT = California Verbal Learning Test, RAVLT = Rey Auditory Verbal Learning Test, ROCFT = Rey-Osterrieth Complex Figure Test, WCST = Wisconsin Card Sorting Test.
Symbol: … = data not available.

Neuropsychological Performance of CHR Subjects Versus FEP Subjects

At the domain level, CHR subjects performed significantly better than FEP subjects in 5 domains and showed no significant difference in performance in reasoning/problem solving, while there was insufficient data in the domains visual learning, social cognition, and premorbid IQ (Table 2). The only individual test that showed significantly better performance in the CHR group was the Verbal Fluency Test/Controlled Oral Word Association Test (COWAT) (Table 2). Results for current IQ ($I^2 = 0\%$) and working memory ($I^2 = 19.2\%$) were rather homogeneous, while results for verbal learning, attention/vigilance, reasoning/problem solving, and speed of processing were more heterogeneous ($I^2 = 44.2\%–70.6\%$).

Neuropsychological Performance of CHR-P and CHR-NP Subjects Versus HCs

Subjects with CHR-P showed worse performance than HCs in all domains. Likewise, CHR-NP showed worse performance in all domains, except for visual learning and working memory. Similarly, on the test level, all but 1 test (Wisconsin Card Sorting Test perseveration errors) revealed worse performance of CHR-P compared to HCs. Conversely, CHR-NP and HC performed similarly well on the majority of tests, with CHR-NP subjects showing worse performance in Continuous Performance Test shapes, Trail-Making Test A, Digit Symbol Test, and CVLT. The domain and tests of social cognition could not be analyzed due to insufficient data (Table 3). Except for attention/vigilance in CHR-P, verbal learning in CHR-P and CHR-NP, and working memory in CHR-NP, results for the other domains were homogeneous ($I^2 = 0\%–38.1\%$). However, most individual test results were heterogeneous.

Neuropsychological Performance of CHR-P Versus CHR-NP Subjects

Subjects with CHR-P showed worse performance than CHR-NP in the domains attention/vigilance, speed of processing, verbal and visual learning, and current and premorbid IQ. Effect sizes for the significant comparisons ranged from −0.23 for attention/vigilance to −0.54 for visual learning. Conversely, CHR-P and CHR-NP did not differ significantly from one another in the domains of reasoning/problem solving and working memory. At the test level, performance varied between tests in the domains of attention/vigilance, speed of processing, and verbal learning, despite the overall significant difference at the domain level. The 3 individual tests with the highest discriminatory power (ie, significant effect size ≥ −0.40) between CHR-P and CHR-NP were the Rey-Osterrieth Complex Figure Test (ROCFT), Verbal Fluency Test/COWAT, and the CVLT.

Conversely, the only available test for the premorbid IQ domain, the National Adult Reading Test, was not significantly different by group, despite the significant difference at the domain level. Despite nonsignificant results at the domain level for working memory, individual task-level performance on the Letter Number Sequencing Test showed a significant difference between converters and nonconverters (Table 4). Heterogeneity of the domain scores was low ($I^2 = 0\%–26.6\%$), and only 2 of the individual tests (Digit Span, Verbal Fluency Test/COWAT) had $I^2 > 50\%$.

Table 4. Neuropsychological Performance in Subjects at Clinical High Risk for Psychosis Who Developed Psychosis Versus Those Who Did Not Develop Psychosis

Cognitive Test/Domain[a]	No. of Studies	n	Hedges g[b]	95% CL	P	I^2 (%)
Attention/vigilance	***9***	***580***	***−0.235***	***−0.439, −0.031***	***.024***	***26.57***
CPT shapes	4	208	0.198	−0.103, 0.498	.197	0
Digit Span	4	249	−0.316	−0.901, 0.269	.290	75.14
Reasoning/problem solving	***7***	***400***	***−0.076***	***−0.274, 0.122***	***.451***	***0***
WCST preservation errors	4	234	0.053	−0.216, 0.323	.698	0
Speed of processing	***7***	***428***	***−0.397***	***−0.610, −0.184***	***<.0001***	***0***
Verbal Fluency Test/COWAT	6	375	−0.451	−0.865, −0.037	.033	74.30
Trail-Making Test A	5	293	−0.188	−0.419, 0.043	.110	0
Trail-Making Test B	3	197	−0.272	0.572, 0.027	.074	0
Digit Symbol Test	3	255	−0.333	−0.583, −0.082	.009	0
Verbal learning	***7***	***400***	***−0.488***	***−0.755, −0.222***	***<.0001***	***25.91***
CVLT	3	139	−0.406	−0.806, −0.006	.046	14.51
Logical Memory	3	192	−0.339	−0.670, −0.008	.045	11.98
RAVLT	3	213	−0.273	−0.626, 0.081	.131	18.34
Visual learning	***4***	***244***	***−0.535***	***−0.797, −0.274***	***<.0001***	***0***
ROCFT delayed recall	3	157	−0.497	−0.827, −0.167	.003	0
Working memory	***7***	***436***	***−0.159***	***−0.352, 0.034***	***.107***	***0***
Letter Number Sequencing	4	218	−0.302	0.583, −0.022	.035	0
Social cognition	...	...	...	...	...	...
Current IQ	***5***	***273***	***−0.302***	***−0.559, −0.044***	***.022***	***0***
Premorbid IQ	***7***	***384***	***−0.228***	***−0.452, −0.005***	***.045***	***0***
National Adult Reading Test	3	167	−0.185	−0.504, 0.133	.255	0

[a]Bold/italic type indicates cognitive domains. [b]Hedges g = effect size. Negative effect size indicates greater impairment.
Abbreviations: CL = confidence limits, COWAT = Controlled Oral Word Association Test, CPT = Continuous Performance Test, CVLT = California Verbal Learning Test, RAVLT = Rey Auditory Verbal Learning Test, ROCFT = Rey-Osterrieth Complex Figure Test, WCST = Wisconsin Card Sorting Test.
Symbol: ... = data not available.

Publication Bias

Of 128 analyses, 70 (54.7%) had no evidence of a significant publication bias as assessed by the funnel plot inspection. Although 52 (40.6%) showed evidence of publication bias, adjusting for the potential bias using the "trim-and-fill" method did not significantly alter the results. There were only 6 results (4.7%) where adjusting for a potential publication bias resulted in a change from a significant to a nonsignificant finding regarding pooled effect sizes. These were CVLT in the CHR-P versus CHR-NP and CHR-NP versus HC comparisons, logical memory in the CHR-P versus CHR-NP comparison, Rey Auditory Verbal Learning Test 1–5 in the CHR-P versus HC comparison, social cognition domain in the CHR versus HC comparison, and premorbid IQ in the CHR-NP versus CHR-P comparison.

DISCUSSION

The investigation of risk markers to support validated clinical risk symptom constellations in the early identification of individuals at CHR for the transition to frank psychosis has become a growing, fruitful area. Cognition plays an important role because of its predictive value for an individual's functioning and prognosis, its malleability, and its psychometric reliability.[22–32] Recent meta-analyses[9–12] have confirmed various cognitive impairments in CHR individuals; however, additional data and specifications are provided in this updated meta-analysis.

Summary of Findings

The main findings from this currently largest meta-analysis of neuropsychological performance in CHR subjects are (1) CHR subjects compared to HCs performed significantly worse in 7 of 9 domains (except for reasoning/problem solving and working memory, which significantly separated CHR from HC subjects in the subset of longitudinal studies), with significant effect sizes ranging from −0.17 (attention/vigilance) to −0.42 and −0.43 (verbal learning, speed of processing, social cognition); (2) individual tests revealing the most severe impairment were the CVLT trials 1–5 (effect size = −0.65) and Digit Symbol Test (effect size = −0.63); (3) CHR subjects compared to FEP subjects performed significantly better in 5 of 6 examined domains (except for reasoning/problem solving), with significant effect sizes ranging from 0.29 (speed of processing) to 0.40 and 0.41 (verbal learning, attention/vigilance, working memory); (4) both CHR-P and CHR-NP subjects performed significantly worse than HCs, except for visual learning and working memory in CHR-NP; (5) CHR-P compared to CHR-NP subjects performed significantly worse in 6 of 8 domains (except for reasoning/problem solving and working memory), with significant effect sizes ranging from −0.24 (attention/vigilance) to −0.54 (visual learning); and (6) the 3 individual tests with the highest discriminatory power (ie, effect size ≥ −0.40) between CHR-P and CHR-NP were the ROCFT, Verbal Fluency Test/COWAT, and the CVLT.

Cross-Sectional Comparisons to HCs (domain level)

To predict "true" risk for psychosis, a neuropsychological test or domain needs to differentiate between subjects in a clinically defined risk state of psychosis and HCs. According to our results, all assessed domains except for reasoning/problem solving and working memory (although even those showed a strong trend and significance in a subset of studies, respectively) served to differentiate between those 2 groups. This finding is mostly consistent with 3 previous meta-analyses,[9,10,12] despite some differences in the choice of domains and the classification of individual tests into specific domains. For those domains that overlap between the meta-analyses, our results do validate that CHR subjects perform significantly worse on tests that measure the domains of attention/vigilance, verbal learning, visual learning, working memory, social cognition, and current IQ, adding data of 496 subjects to the previous findings of Fusar-Poli et al[10] and 469 to Giuliano et al.[9] A comparison with the number of subjects

in the publication by Bora et al[12] is complicated by the fact that these authors allowed for sample overlap in their overall subjects count, while we excluded overlapping samples from the main sample description and only included them in meta-analytic calculations when such samples added data not otherwise available (ie, additional comparison groups or neuropsychological tests). While our data suggested only a strong trend toward significant differences in the working memory of CHR subjects compared to HCs in the whole study sample, it reached significance in the subset of longitudinal studies, which is in line with all 3 previous meta-analyses[9,10,12] that found significant performance impairments in CHR subjects in working memory. On the other hand, while we identified impairments in performance in the speed of processing of CHR subjects, which is in line with the results of Giuliano and colleagues[9] as well as Bora and colleagues,[12] the data of Fusar-Poli and colleagues[10] showed only a trend for a difference in this area.

Cross-Sectional Comparisons to HCs (test level)

Direct comparison of meta-analytic results is complicated by different test assignments into domains, calling for a test-level analysis. The importance of an additional test-level analysis is furthermore highlighted by the fact that a variety of tests did not show significant differences between groups, despite domain-level group differences. For example, while the Continuous Performance Test and the Digits Forward Test both differentiated between CHR and HC subjects in the domain of attention/vigilance, the Stroop Color Word Test and Digit Span Test did not. At the same time, this level of analysis helps to compare the results across publications. While the Continuous Performance Test did and Digit Span Test did not differentiate between CHR and HC individuals in our sample, both tests differentiated subjects in the meta-analyses by Giuliano and colleagues,[9] Fusar-Poli and colleagues,[10] and Bora and colleagues.[12] Nevertheless, generally, test-level results were consistent across the meta-analyses.

Analyses of Longitudinal Data

Our meta-analysis is the first that takes follow-up data into account. Although they were sparse, we were able to analyze follow-up data for the domains attention/vigilance, speed of processing, verbal learning, working memory, and current IQ and the tests Continuous Performance Test shapes, CVLT, Verbal Fluency Test/COWAT, and Letter Number Sequencing Test at a mean second assessment time point of 8–12 months. Despite that the sample at follow-up naturally strongly differed from the baseline sample due to the considerably lower number of studies and subjects, all of our follow-up results resembled the differences found at baseline. Interestingly, despite conversion in a subgroup of subjects at follow-up, there was no clear change in effect sizes over this interval. These results point to the relative stability of cognition as a potential additional risk marker, as well as to the validity of our results. Likewise, these findings again underscore the significance of comparable test categorizations into domains for the interpretation across publications, as pointed out in an early qualitative review[86] of cognitive performance in CHR subjects.

Comparison of CHR-P and CHR-NP (domain level and test level)

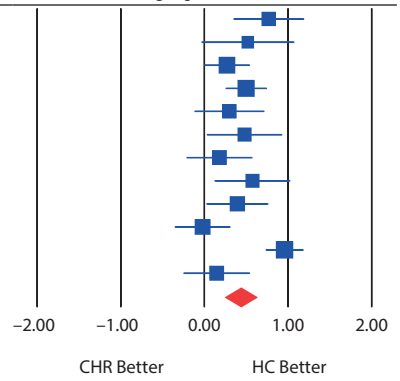
As the CHR group contains an unknown amount of individuals who are at true risk for psychosis as well as false positives, comparing the CHR-P and CHR-NP groups is of greatest importance. Ideally, a domain or test should reflect a difference in performance between CHR-P and CHR-NP as well as between CHR-P and HC, while the same domain or test should not show significantly different results between CHR-NP and HC, ie, it should have specificity for true positives (Figure 1). While several domains and tests showed a significant difference between all 3 groups (CHR-P vs CHR-NP, CHR-P vs HC, and CHR-NP vs HC), 1 domain and 4 tests fulfilled the proposed requirement of specificity in our data set. Thus, although 3 previous meta-analyses[10–12] reported on a comparison between CHR-P and CHR-NP and 1 meta-analysis[9] reported on the comparison of CHR-P/CHR-NP with HC (but not on the comparison of CHR-P vs CHR-NP), our results add greater specificity by including all these comparisons in 1 meta-analysis.

When we searched for specific result constellations on the domain level, CHR-P showed poorer visual learning performance than HC and CHR-NP, while CHR-NP did not differ from HC in this domain. The only test with sufficient data to be analyzed on a test level within this domain, the ROCFT, followed the same pattern. This finding is in line with the meta-analysis conducted by De Herdt and colleagues[11] and Bora and colleagues,[12] who also found poorer visual learning performance in CHR-P compared to CHR-NP. That we were able to add 149 subjects to the analysis by De Herdt and colleagues[11] (again, a comparison of subjects to Giuliano and colleagues[9] and Bora and colleagues[12] is not possible because both meta-analyses allowed for overlapping samples in their overall subject count) and that we were able to compare the performance between CHR-NP and HCs strengthens the validity of the results and suggests that the ROCFT and visual learning are promising candidates for the identification of true risk for psychosis in CHR individuals. Of note, Giuliano and colleagues[9] also found that, compared to HCs, CHR-P but not CHR-NP subjects had poorer visual-spatial performance (measured with the ROCFT and additional tests). Furthermore, the same performance pattern was shown by 3 additional tests: (1) the Verbal Fluency Test/COWAT as part of speed of processing, (2) the Logical Memory Test as part of the domain of verbal learning, and (3) the Letter Number Sequencing Test as part of working memory. De Herdt and colleagues[11] did not analyze data on the test level. Therefore, we can compare our results to theirs only on a domain level. Doing so indicates that our data are consistent with one of their findings, ie, regarding significant differences between CHR-P and CHR-NP on working memory. However, our 2 other results regarding processing speed and verbal learning are not reflected in the meta-analysis by De Herdt and colleagues.[11] Nevertheless,

Figure 1. Forest Plots of Visual Learning Performance in Different Groups

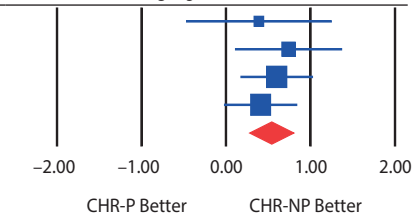
A. Visual Learning in CHR Patients Versus HCs

Study	Outcome	Hedges *g*	95 % CL Lower Limit	95 % CL Upper Limit	*P* Value	Total Subjects
Becker et al[73] 2010	Verbal Fluency Semantic Category	0.770	0.341	1.199	.000	89
Becker et al[55] 2010	Verbal Fluency Test	0.520	−0.042	1.082	.070	57
Carrión et al[50] 2011	Combined	0.270	−0.011	0.551	.060	207
Frommann et al[49] 2011	Combined	0.500	0.246	0.754	.000	292
Gschwandtner et al[75] 2006	Combined	0.300	−0.126	0.726	.167	82
Jahshan et al[61] 2010	Numerical Attention Test	0.480	0.023	0.937	.040	77
Kim et al[62] 2011	Combined	0.180	−0.221	0.581	.379	94
Koutsouleris et al[66] 2012	Combined	0.575	0.114	1.036	.015	78
Lin et al[67] 2013	Combined	0.395	0.017	0.773	.040	140
Lindgren et al[64] 2010	Combined	−0.021	−0.361	0.318	.902	134
Pukrop et al[59] 2006	Verbal Fluency Test	0.960	0.726	1.194	.000	307
Woodberry et a[151] 2010	Combined	0.148	−0.258	0.553	.476	107
		0.427	0.242	0.612	.000	1,664



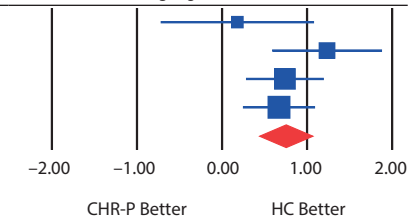
B. Visual Learning in CHR-P Patients Versus CHR-NP Patients

Study	Outcome	Hedges *g*	95% CL Lower Limit	95% CL Upper Limit	*P* Value	Total Subjects
Becker et al[55] 2010	ROCFT delayed recall	0.390	−0.472	1.252	.375	25
Kim et al[62] 2011	Combined	0.740	0.107	1.373	.022	49
Lin et al[67] 2013	Visual Reproduction	0.600	0.171	1.029	.006	87
Pukrop et al[68] 2007	ROCFT delayed recall	0.410	−0.023	0.843	.064	83
		0.535	0.274	0.797	.000	244



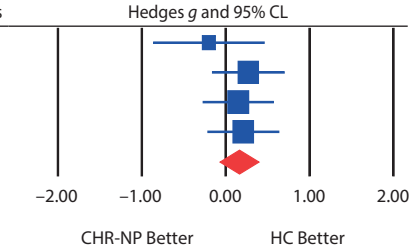
C. Visual Learning in CHR-P Patients Versus HCs

Study	Outcome	Hedges *g*	95% CL Lower Limit	95% CL Upper Limit	*P* Value	Total Subjects
Becker et al[55] 2010	ROCFT delayed recall	0.180	−0.721	1.081	.695	19
Kim et al[62] 2011	Combined	1.235	0.589	1.881	.000	58
Lin et al[67] 2013	Visual Reproduction	0.740	0.283	1.197	.002	75
Pukrop et al[68] 2007	ROCFT delayed recall	0.670	0.246	1.094	.002	88
		0.749	0.436	1.063	.000	240



D. Visual Learning in CHR-NP Patients Versus HCs

Study	Outcome	Hedges *g*	95% CL Lower Limit	95% CL Upper Limit	*P* Value	Total Subjects
Becker et al[55] 2010	ROCFT	-0.200	−0.865	0.465	.555	35
Kim et al[62] 2011	Combined	0.270	−0.163	0.703	.222	81
Lin et al[67] 2013	Visual Reproduction	0.150	−0.274	0.574	.488	86
Pukrop et al[68] 2007	ROCFT delayed recall	0.210	−0.219	0.639	.337	83
		0.159	−0.072	0.391	0.178	285



Abbreviations: CHR = clinical high risk for psychosis, CHR-P = CHR patients who converted to psychosis, CHR-NP = CHR patients who did not convert to psychosis, CL = confidence limit, HC = healthy control, ROCFT = Rey-Osterrieth Complex Figure Test.

as many tests contribute to a domain-level analysis, this discrepancy does not necessarily contradict our findings, because different tests may have contributed to the results of De Herdt and colleagues.[11] Furthermore, our analysis validates Bora and colleagues' recent findings[12] by confirming significant differences in the Letter Number Sequencing Test (which Bora and colleagues,[12] however, categorized into a different domain than in our analysis) and by also confirming differences in the Letter Fluency Test (the "fluency" domain in Bora and colleagues' analysis[12]). For the remaining domains, our findings validate the results of Fusar-Poli and colleagues' analysis[10] by adding 134 CHR subjects to the analysis. An exception is the significant difference between CHR-P and CHR-NP in the Digit Symbol Test as part of the speed of processing domain, in addition to the Verbal Fluency Test/COWAT. While Fusar-Poli and colleagues[10] did not find a significant difference in speed of processing between CHR-P and CHR-NP in their meta-analysis, our differences found on the test level in the Digit Symbol Test may become relevant for future abbreviated cognitive test tools with utility for psychosis prediction. Interestingly, the tests and domain that differentiated CHR-P from CHR-NP also showed significant differences in the larger comparison of CHR versus HC. However, one needs to keep in mind that results will be influenced by the fact that subjects with CHR-NP can still be at true risk for psychosis although they have not yet converted to psychosis during the study follow-up, indicating that longer follow-up periods are needed. Of note, current data were still insufficient to analyze the domain of social cognition for the comparison of CHR-P versus CHR-NP.

Cross-Sectional Comparison With FEP (domain level and test level)

To our knowledge, our meta-analysis is the first to also compare CHR with FEP individuals. Sufficient data were available to compare the 2 groups on 5 major domains and tests. Results indicate that CHR subjects had significantly worse neuropsychological performance compared to HCs but also significantly better neuropsychological performance than FEP individuals in the domains of attention/vigilance, speed of processing, verbal learning, working memory, and current IQ. Thus, the cognitive findings resemble the clinical status in that CHR subjects are in-between HCs and FEP. However, since likely the majority of CHR subjects will not convert to psychosis, one cannot conclude from these cross-sectional findings that performance worsens during the transition from CHR to FEP status. Prospective neuropsychological data in patients converting to psychosis prior to and after conversion, ideally unconfounded by initiation of antipsychotic treatment, would be needed to answer this question. Interestingly, CHR and FEP subjects did show comparable performance on all of the assessed tests on a test-level analysis. Although this finding could suggest these tests as potentially useful tools of risk assessment, data currently either lack another comparison group for the tests or show comparable performance not only between CHR and FEP subjects but also between CHR-P and CHR-NP, CHR-P and HC, or CHR-NP and HC, indicating that these tests may not have sufficient specificity as risk assessment tools. Nevertheless, one needs to consider that due to the relatively modest effect sizes of cognitive domain and test differences, there is still a great overlap between CHR-P and CHR-NP, so that cognitive risk markers of risk for psychosis will most likely not be useful clinically in isolation,[12] and their utility in more complex risk prediction models with other clinical and putative biomarkers will need to be tested further.

Limitations

Limitations of this meta-analysis include certain aspects inherent in the publications that were included for analysis. These pertain to variations in the sampling frame, defining criteria of CHR (ie, CHR/ultra-high risk criteria, basic symptom criteria, nonspecific risk criteria), and utilized neuropsychological tests. Furthermore, although the number of studies is growing, there is still a considerable lack of data on comparisons between CHR converters, CHR nonconverters, and FEP individuals, particularly with regard to overlapping tests that can be gathered for a meta-analytic procedure. Additionally, since the outcome in the meta-analyzed studies was psychosis, which includes schizophrenia-spectrum and affective-spectrum disorders,[87] we cannot exclude that the lack of predictive value of specific neuropsychological impairment for conversion to psychosis is because some psychotic disorders are more related to cognitive impairment than others. Therefore, future studies should report neuropsychological test results separately for subjects converting to schizophrenia-spectrum and affective-spectrum disorders. Ideally, such studies would be large enough to have sufficient power to compare these subgroups. Alternatively, a complementary, dimensional, rather than categorical, approach could be taken. This way, one would test how cognitive performance scores relate to symptom severity on the various symptom scales from the Structured Interview for Prodromal Syndromes/Comprehensive Assessment of At-Risk Mental States and how the symptom severity and their associated cognitive performance impairments differentiate between psychotic disorders. At least when constructing predictive models of transition to psychosis,[2] this approach has already been taken,[2] yet so far, all psychotic disorders have been lumped together. Further, we did not perform meta-regression and subgroup analyses, as has been done previously.[9,10,12] We believe that creating a combined performance score across all different tests and domains is artificial and loses sensitivity, especially as different studies provided only a subset of data and tests, resulting in potentially spurious or pseudospecific results of meta-regression and moderator analyses. This points to the need of future studies to use comprehensive neurocognitive assessments that are similar across studies, allowing for more meaningful pooling. On the other hand, conducting meta-regression analyses for each domain or the most promising tests is prohibitive. Last, the analyses we were able to perform with regard to comparisons between CHR converters and nonconverters, although informative, were

based on cross-sectional data only. The inclusion of such data from longitudinal studies of these separate groups will be an invaluable further step, as will be the consistent use of a consensus-based classification system of neuropsychological tests and domains that goes beyond the still limited number of tests that we were able to categorize according to the MATRICS consensus.

CONCLUSION

In summary, results from this most inclusive meta-analysis of neuropsychological performance in the CHR state for psychosis, which carefully avoided the analysis of overlapping samples, confirm the presence of broad impairments in performance in CHR individuals. The current meta-analysis extends existing knowledge by suggesting that the domains of visual learning and verbal learning, as well as, possibly, speed of processing, are particularly promising risk markers for true risk for psychosis. At the test level, the ROCFT, Verbal Fluency Test/COWAT, and CVLT represent the most reliable predictors of conversion. These particular domain scores or individual tests should be examined as potential candidates for complex risk prediction models and be included in longitudinal studies.

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Potential conflicts of interest: **Dr Hauser** has been a consultant to Otsuka. **Dr Burdick** has served as an advisory board member for Dainippon Sumitomo and Takeda, Lundbeck. **Dr Kane** has been a consultant to Alkermes, Forum, Forest, Genentech, Janssen, Teva, AstraZeneca, Janssen, Pfizer, Eli Lilly, Bristol-Myers Squibb, Dainippon Sumitomo/Sepracor/Sunovion, Johnson & Johnson, Otsuka, Vanda, Proteus, Takeda, Targacept, IntraCellular Therapies, Merck, Lundbeck, Novartis, Roche, Rules-Based Medicine, and Sunovion; has received honoraria for lectures from Genentech, Lundbeck, Otsuka, Eli Lilly, Esai, Boehringer-Ingelheim, Bristol-Myers Squibb, and Janssen; has received grant support from The National Institute of Mental Health (NIMH); and is a stock shareholder in MedAvante and Vanguard Research Group. **Dr Correll** has been a consultant and/or advisor to or has received honoraria from AbbVie, Actavis, Actelion, Alexza; Alkermes, Bristol-Myers Squibb, Cephalon, Eli Lilly, Genentech, Gerson Lehrman Group, IntraCellular Therapies, Janssen/Johnson & Johnson, Lundbeck, MedAvante, Medscape, Merck, Otsuka, Pfizer, ProPhase, Reviva, Roche, Sunovion, Supernus, Takeda, Teva, and Vanda; has received grant support from American Academy of Child and Adolescent Psychiatry, NIMH, Thrasher Foundation, Bristol-Myers Squibb, Janssen/Johnson & Johnson, Novo Nordisk A/S, Otsuka, and Takeda; and has given expert testimony on behalf of Janssen. **Drs Zhang**, **Sheridan**, **Auther**, **Carrión**, and **Cornblatt** and **Ms Mogil** declare no conflict of interest.

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Supplementary material: See accompanying pages.

REFERENCES

1. Correll CU, Hauser M, Auther AM, et al. Research in people with psychosis risk syndrome: a review of the current evidence and future directions. *J Child Psychol Psychiatry*. 2010;51(4):390–431.
2. Fusar-Poli P, Borgwardt S, Bechdolf A, et al. The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA Psychiatry*. 2013;70(1):107–120.
3. Fusar-Poli P, Bonoldi I, Yung AR, et al. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. *Arch Gen Psychiatry*. 2012;69(3):220–229.
4. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*. Fifth Edition. Washington, DC: American Psychiatric Association; 2013.
5. Fusar-Poli P, Perez J, Broome M, et al. Neurofunctional correlates of vulnerability to psychosis: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2007;31(4):465–484.
6. Fusar-Poli P, Borgwardt S, Crescini A, et al. Neuroanatomy of vulnerability to psychosis: a voxel-based meta-analysis. *Neurosci Biobehav Rev*. 2011;35(5):1175–1185.
7. Fusar-Poli P, Radua J, McGuire P, et al. Neuroanatomical maps of psychosis onset: voxel-wise meta-analysis of antipsychotic-naive VBM studies. *Schizophr Bull*. 2012;38(6):1297–1307.
8. Smieskova R, Fusar-Poli P, Allen P, et al. Neuroimaging predictors of transition to psychosis—a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2010;34(8):1207–1222.
9. Giuliano AJ, Li H, Mesholam-Gately RI, et al. Neurocognition in the psychosis risk syndrome: a quantitative and qualitative review. *Curr Pharm Des*. 2012;18(4):399–415.
10. Fusar-Poli P, Deste G, Smieskova R, et al. Cognitive functioning in prodromal psychosis: a meta-analysis. *Arch Gen Psychiatry*. 2012;69(6):562–571.
11. De Herdt A, Wampers M, Vancampfort D, et al. Neurocognition in clinical high-risk young adults who did or did not convert to a first schizophrenic psychosis: a meta-analysis. *Schizophr Res*. 2013;149(1–3):48–55.
12. Bora E, Lin A, Wood SJ, et al. Cognitive deficits in youth with familial and clinical high-risk to psychosis: a systematic review and meta-analysis. *Acta Psychiatr Scand*. 2014;130(1):1–15.
13. Cannon TD, Cadenhead K, Cornblatt B, et al. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Arch Gen Psychiatry*. 2008;65(1):28–37.
14. Ruhrmann S, Schultze-Lutter F, Salokangas RK, et al. Prediction of psychosis in adolescents and young adults at high-risk: results from the prospective European prediction of psychosis study. *Arch Gen Psychiatry*. 2010;67(3):241–251.
15. Yung AR, Phillips LJ, Yuen HP, et al. Risk factors for psychosis in an ultra high-risk group: psychopathology and clinical features. *Schizophr Res*. 2004;67(2–3):131–142.
16. Pettersson-Yeo W, Benetti S, Marquand AF, et al. Using genetic, cognitive and multi-modal neuroimaging data to identify ultra-high-risk and first-episode psychosis at the individual level. *Psychol Med*. 2013;43(12):2547–2562.
17. Conn PJ, Tamminga C, Schoepp DD, et al. Schizophrenia: moving beyond monoamine antagonists. *Mol Interv*. 2008;8(2):99–107.
18. Palmer BW, Dawes SE, Heaton RK. What do we know about neuropsychological aspects of schizophrenia? *Neuropsychol Rev*. 2009;19(3):365–384.
19. Cornblatt B, Obuchowski M, Roberts S, et al. Cognitive and behavioral precursors of schizophrenia. *Dev Psychopathol*. 1999;11(3):487–508.
20. Heaton RK, Gladsjo JA, Palmer BW, et al. Stability and course of neuropsychological deficits in schizophrenia. *Arch Gen Psychiatry*. 2001;58(1):24–32.
21. Schuepbach D, Keshavan MS, Kmiec JA, et al. Negative symptom resolution and improvements in specific cognitive deficits after acute treatment in first-episode schizophrenia. *Schizophr Res*. 2002;53(3):249–261.
22. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? *Am J Psychiatry*. 1996;153(3):321–330.
23. Green MF. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *J Clin Psychiatry*. 2006;67(10):e12.
24. Stip E. Cognition, schizophrenia and the effect of antipsychotics [in French]. *Encephale*. 2006;32(3 pt 1):341–350.
25. Bowie CR, Harvey PD. Communication abnormalities predict functional outcomes in chronic schizophrenia: differential associations with social and adaptive functions. *Schizophr Res*. 2008;103(1–3):240–247.
26. Bilder RM, Goldman RS, Volavka J, et al. Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 2002;159(6):1018–1028.
27. Harvey PD, Keefe RS. Studies of cognitive change in patients with schizophrenia following novel antipsychotic treatment. *Am J Psychiatry*. 2001;158(2):176–184.
28. Harvey PD, Bowie CR. Cognitive enhancement in schizophrenia: pharmacological and cognitive remediation approaches. *Psychiatr Clin North Am*. 2012;35(3):683–698.
29. Wykes T, Huddy V, Cellard C, et al. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. *Am J Psychiatry*. 2011;168(5):472–485.
30. Genevsky A, Garrett CT, Alexander PP, et al. Cognitive training in schizophrenia: a neuroscience-based approach. *Dialogues Clin Neurosci*. 2010;12(3):416–421.
31. Medalia A, Saperstein AM. Does cognitive remediation for schizophrenia improve functional outcomes? *Curr Opin Psychiatry*. 2013;26(2):151–157.
32. Kluwe-Schiavon B, Sanvicente-Vieira B, Kristensen CH, et al. Executive functions rehabilitation for schizophrenia: a critical systematic review. *J Psychiatr Res*. 2013;47(1):91–104.

33. Cornblatt BA, Lencz T, Smith CW, et al. The schizophrenia prodrome revisited: a neurodevelopmental perspective. *Schizophr Bull*. 2003;29(4):633–651.
34. Rauchensteiner S, Kawohl W, Ozgurdal S, et al. Test-performance after cognitive training in persons at risk mental state of schizophrenia and patients with schizophrenia. *Psychiatry Res*. 2011;185(3):334–339.
35. Green MF, Nuechterlein KH, Gold JM, et al. Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICS conference to select cognitive domains and test criteria. *Biol Psychiatry*. 2004;56(5):301–307.
36. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Third Edition, Text Revision. Washington, DC: American Psychiatric Association; 1987.
37. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
38. Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychol Rep*. 1962;10(3):799–812.
39. Andreasen NC. *Comprehensive Assessment of Symptoms and History (CASH)*. Iowa City, IA: Department of Psychiatry, University of Iowa College of Medicine; 1987.
40. Yung AR, Yuen HP, McGorry PD, et al. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Aust N Z J Psychiatry*. 2005;39(11–12):964–971.
41. Miller TJ, McGlashan TH, Rosen JL, et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr Bull*. 2003;29(4):703–715.
42. Riecher-Rössler A, Aston J, Ventura J, et al. The Basel Screening Instrument for Psychosis (BSIP): development, structure, reliability and validity [in German]. *Fortschr Neurol Psychiatr*. 2008;76(4):207–216.
43. Lukoff D, Liberman RP, Nuechterlein KH. Symptom monitoring in the rehabilitation of schizophrenic patients. *Schizophr Bull*. 1986;12(4):578–602.
44. Ventura J, Green MF, Shaner A, et al. Training and quality assurance with the Brief Psychiatric Rating Scale: "the drift busters." *Int J Methods Psychiatr Res*. 1993;3:221–244.
45. Maurer K, Häfner H. Early diagnosis of schizophrenia [in German]. *MMW Fortschr Med*. 2007;149(13):36–38.
46. Huber G, Gross G. The concept of basic symptoms in schizophrenic and schizoaffective psychoses. *Recenti Prog Med*. 1989;80(12):646–652.
47. Schultze-Lutter F, Addington J, Rurhmann S, et al. *Schizophrenia Proneness Instrument, Adult Version (SPI-A)*. Rome, Italy: Giovanni Fioriti Editore srl; 2007.
48. Mirzakhanian H, Singh F, Seeber K, et al. A developmental look at the attentional system in the at risk and first episode of psychosis: age related changes in attention along the psychosis spectrum. *Cogn Neuropsychiatry*. 2013;18(1–2):26–43.
49. Frommann I, Pukrop R, Brinkmeyer J, et al. Neuropsychological profiles in different at-risk states of psychosis: executive control impairment in the early—and additional memory dysfunction in the late—prodromal state. *Schizophr Bull*. 2011;37(4):861–873.
50. Carrión RE, Goldberg TE, McLaughlin D, et al. Impact of neurocognition on social and role functioning in individuals at clinical high-risk for psychosis. *Am J Psychiatry*. 2011;168(8):806–813.
51. Woodberry KA, Seidman LJ, Giuliano AJ, et al. Neuropsychological profiles in individuals at clinical high-risk for psychosis: relationship to psychosis and intelligence. *Schizophr Res*. 2010;123(2–3):188–198.
52. Woodberry KA, McFarlane WR, Giuliano AJ, et al. Change in neuropsychological functioning over one year in youth at clinical high-risk for psychosis. *Schizophr Res*. 2013;146(1–3):87–94.
53. Carr V, Halpin S, Lau N, et al. A risk factor screening and assessment protocol for schizophrenia and related psychosis. *Aust N Z J Psychiatry*. 2000;34(34 suppl):S170–S180.
54. Ozgürdal S, Littmann E, Hauser M, et al. Neurocognitive performances in participants of at-risk mental state for schizophrenia and in first-episode patients. *J Clin Exp Neuropsychol*. 2009;31(4):392–401.
55. Becker HE, Nieman DH, Wiltink S, et al. Neurocognitive functioning before and after the first psychotic episode: does psychosis result in cognitive deterioration? *Psychol Med*. 2010b;40(10):1599–1606.
56. Lencz T, Smith CW, McLaughlin D, et al. Generalized and specific neurocognitive deficits in prodromal schizophrenia. *Biol Psychiatry*. 2006;59(9):863–871.
57. Riecher-Rössler A, Pflueger MO, Aston J, et al. Efficacy of using cognitive status in predicting psychosis: a 7-year follow-up. *Biol Psychiatry*. 2009;66(11):1023–1030.
58. Pflueger MO, Gschwandtner U, Stieglitz RD, et al. Neuropsychological deficits in individuals with an at risk mental state for psychosis—working memory as a potential trait marker. *Schizophr Res*. 2007;97(1–3):14–24.
59. Pukrop R, Schultze-Lutter F, Ruhrmann S, et al. Neurocognitive functioning in subjects at risk for a first episode of psychosis compared with first- and multiple-episode schizophrenia. *J Clin Exp Neuropsychol*. 2006;28(8):1388–1407.
60. Francey SM, Jackson HJ, Phillips LJ, et al. Sustained attention in young people at high-risk of psychosis does not predict transition to psychosis. *Schizophr Res*. 2005;79(1):127–136.
61. Jahshan C, Heaton RK, Golshan S, et al. Course of neurocognitive deficits in the prodrome and first episode of schizophrenia. *Neuropsychology*. 2010;24(1):109–120.
62. Kim HS, Shin NY, Jang JH, et al. Social cognition and neurocognition as predictors of conversion to psychosis in individuals at ultra-high-risk. *Schizophr Res*. 2011;130(1–3):170–175.
63. Brewer WJ, Francey SM, Wood SJ, et al. Memory impairments identified in people at ultra-high-risk for psychosis who later develop first-episode psychosis. *Am J Psychiatry*. 2005;162(1):71–78.
64. Lindgren M, Manninen M, Laajasalo T, et al. The relationship between psychotic-like symptoms and neurocognitive performance in a general adolescent psychiatric sample. *Schizophr Res*. 2010;123(1):77–85.
65. Wood SJ, Brewer WJ, Koutsouradis P, et al. Cognitive decline following psychosis onset: data from the PACE clinic. *Br J Psychiatry suppl*. 2007;51:s52–s57.
66. Koutsouleris N, Davatzikos C, Bottlender R, et al. Early recognition and disease prediction in the at-risk mental states for psychosis using neurocognitive pattern classification. *Schizophr Bull*. 2012;38(6):1200–1215.
67. Lin A, Yung AR, Nelson B, et al. Neurocognitive predictors of transition to psychosis: medium- to long-term findings from a sample at ultra-high-risk for psychosis. *Psychol Med*. 2013;43(11):2349–2360.
68. Pukrop R, Ruhrmann S, Schultze-Lutter F, et al. Neurocognitive indicators for a conversion to psychosis: comparison of patients in a potentially initial prodromal state who did or did not convert to a psychosis. *Schizophr Res*. 2007;92(1–3):116–125.
69. Stanford AD, Messinger J, Malaspina D, et al. Theory of Mind in patients at clinical high-risk for psychosis. *Schizophr Res*. 2011;131(1–3):11–17.
70. Simon AE, Cattapan-Ludewig K, Zmilacher S, et al. Cognitive functioning in the schizophrenia prodrome. *Schizophr Bull*. 2007;33(3):761–771.
71. Hur JW, Byun MS, Shin NY, et al. General intellectual functioning as a buffer against theory-of-mind deficits in individuals at ultra-high-risk for psychosis. *Schizophr Res*. 2013;149(1–3):83–87.
72. Broome MR, Day F, Valli I, et al. Delusional ideation, manic symptomatology and working memory in a cohort at clinical high-risk for psychosis: a longitudinal study. *Eur Psychiatry*. 2012;27(4):258–263.
73. Becker HE, Nieman DH, Dingemans PM, et al. Verbal fluency as a possible predictor for psychosis. *Eur Psychiatry*. 2010a;25(2):105–110.
74. Bowie CR, McLaughlin D, Carrión RE, et al. Cognitive changes following antidepressant or antipsychotic treatment in adolescents at clinical risk for psychosis. *Schizophr Res*. 2012;137(1–3):110–117.
75. Gschwandtner U, Pflüger M, Aston J, et al. Fine motor function and neuropsychological deficits in individuals at risk for schizophrenia. *Eur Arch Psychiatry Clin Neurosci*. 2006;256(4):201–206.
76. Couture SM, Penn DL, Addington J, et al. Assessment of social judgments and complex mental states in the early phases of psychosis. *Schizophr Res*. 2008;100(1–3):237–241.
77. Szily E, Kéri S. Anomalous subjective experience and psychosis risk in young depressed patients. *Psychopathology*. 2009;42(4):229–235.
78. van Rijn S, Schothorst P, Wout M, et al. Affective dysfunctions in adolescents at risk for psychosis: emotion awareness and social functioning. *Psychiatry Res*. 2011;187(1–2):100–105.
79. Green MF, Bearden CE, Cannon TD, et al. Social cognition in schizophrenia, part 1: performance across phase of illness. *Schizophr Bull*. 2012;38(4):854–864.
80. Addington J, Addington D. Social and cognitive functioning in psychosis. *Schizophr Res*. 2008;99(1–3):176–181.
81. Nuechterlein KH, Green MF, Kern RS, et al. The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. *Am J Psychiatry*. 2008;165(2):203–213.
82. Borenstein M, Rothstein H. *Comprehensive Meta-Analysis: A Computer Program for Research Synthesis*. Englewood, NJ: Biostat; 1999.
83. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177–188.
84. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration Web site. http://handbook.cochrane.org/. Updated March 2011.
85. Duval SJ, Tweedie RL. A non-parametric "trim and fill" method of assessing publication bias in meta-analysis. *J Am Stat Assoc*. 2000;95(409):89–98.
86. Pukrop R, Klosterkötter J. Neurocognitive indicators of clinical high-risk states for psychosis: a critical review of the evidence. *Neurotox Res*. 2010;18(3–4):272–286.
87. Fusar-Poli P, Bechdolf A, Taylor MJ, et al. At risk for schizophrenic or affective psychoses? a meta-analysis of *DSM/ICD* diagnostic outcomes in individuals at high clinical risk. *Schizophr Bull*. 2013;39(4):923–932.

Supplementary material follows this article.

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Supplementary Material

Article Title: Neuropsychological Test Performance to Enhance Identification of Subjects at Clinical High Risk for Psychosis and Be Most Promising for Predictive Algorithms for Conversion to Psychosis: A Meta-Analysis

Authors: Marta Hauser, PhD; Jian-Ping Zhang, MD, PhD; Eva M. Sheridan, MD; Katherine E. Burdick, PhD; Rachel Mogil, BS; John M. Kane, MD; Andrea Auther, PhD; Ricardo E. Carrión, PhD; Barbara A. Cornblatt, PhD; and Christoph U. Correll, MD

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List of Supplementary Material for the article

1. eTable 1 Most Commonly Used Clinical Risk Criteria and Assessment tools
2. eTable 2 Baseline Characteristics of Included Studies and Samples
3. eFigure 1 Literature Search

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplemental Material - Tables and Figures

Supplemental eTable 1. Most commonly used clinical risk criteria and assessment tools

Risk group	Clinical risk criteria	Applied interview / Diagnostic manual
Ultra high risk (UHR)/ Clinical high risk (CHR) group	*APS (Attenuated Positive Symptoms) / APSS (Attenuated Positive Symptom Syndrome):* Attenuated psychotic-like symptoms with subthreshold intensity or frequency. *BLIPS (Brief Limited Intermittent Psychotic Symptoms / BIPS (Brief Intermittent Psychotic Symptoms):* Psychotic symptoms that last for less than 1 week and resolve spontaneously. *Trait and state risk factors / GRDS (Genetic Risk and Deterioration Syndrome:* Individuals with a 1st or 2nd degree relative with a psychotic disorder or with schizotypal personality disorder **plus** a significant reduction in functioning (30 points on the GAF) in the past month	- DSM III-R (APA, 1987) [36] - DSM IV (APA, 1994) [37] - BPRS: Brief Psychiatric Rating Scale (Overall et al. 1962 [38]) **plus** CASH: Comprehensive Assessment of Symptoms and History (Andreasen et al. 1987 [39]) - CAARMS: Comprehensive Assessment of At-Risk Mental States (Yung et al. 2005 [40]) - SIPS (Structured Interview for Prodromal Symptoms) and SOPS (Scale of Prodromal Symptoms) (Miller et al. 2003 [41]) - Basel Screening Instrument for Psychosis (BSIP, Riecher-Rossler et al. 2008 [42]) **in combination**

Risk group	Clinical risk criteria	Applied interview / Diagnostic manual
		with BPRS: Brief Psychiatric Rating Scale (version Lukoff et al. 1986 [43], Ventura et al. 1993 [44])
Basic symptom (BS) group	*COPER (cognitive-perceptual basic symptoms):* Presence of 1 out of 10 basic symptoms (thought interference, thought perseveration, thought pressure, thought blockages, disturbances of receptive speech, decreased ability to discriminate between ideas/perception or fantasy/true memories, unstable ideas of reference, derealisation, visual or acoustic perceptual disturbances) with sufficient severity and duration *COGDIS (cognitive disturbances):* Presence of 2 out of 9 basic symptoms (inability to divide attention, thought interference, thought pressure, thought blockages, disturbances of receptive speech, disturbances of expressive speech, unstable ideas of reference, disturbances of abstract thinking, captivation of attention by details of the visual field) with sufficient severity and duration.	- Early Recognition Inventory* (ERIraos, Maurer & Hafner 2007 [45]) * if additional frequency and duration criteria were available - Bonn Scale for Assessment of Basic Symptoms* (BSABS, Huber et al. 1989 [46], revised BSABS-P, Schultze-Lutter & Klosterkoetter, unpublished) * if additional frequency and duration criteria were available - Schizophrenia Proneness Instrument - Adult Version (SPIA-A, Schultze-Lutter et al. 2007 [47])

DSM III/IV= Diagnostic and Statistical Manual of Mental Disorders III/IV

Supplemental eTable 2. Baseline characteristics of included studies and samples

Author Country Design Follow-up duration	Groups	n	Mean age (SD)	% male	Education (years)	Risk criteria	Illness severity (BPRS or PANSS total score)	Functioning (GAF)	Treatment (%)	Neuropsychological Tests[1]	Frequency of Assessment
Carr et al. 2000 [53] Australia Cross-sectional NA	CHR FE	60 56	17.6 19.4	61.7 55.4	10.3 11.0	CHR	-	56.5 51.3		CPT, SCWT, COWAT, WCST, ROCFT, TMT-A and B, CVLT, Logical Memory, Verbal Paired Associates, Digit Span Test, Digit-Symbol Test, NART	baseline
Brewer et al. 2005* [63] Australia Prospective At least 12 months	CHR CHR-P CHR- NP HC	98 34 64 37	19.7 (3.9) 19.4 (4.0) 20.0 (3.6) 20.7 (4.3)	52.0 44.1 56.3 75.5	11.2 (1.8) 11.1 (1.5) 11.2 (1.9) 12.5 (1.2)	CHR	BPRS: 19.0 (8.2) BPRS: 19.9 (6.6) BPRS: 18.5 (9.0) BPRS: -	62.6 (14.6) 55.6 (14.4) 66.3 (13.4) -	-	SCWT, Verbal Pairs Correct, NART	Baseline
Francey et al. 2005# [60] Australia Prospective 12 months	CHR CHR-P CHR- NP HC FE	70 20 50 51 32	20.2 20.9 19.9 21.4 23.3	52.9 40.0 58.0 37.3 75.0	- 11.3 11.0 12.8 11.5	CHR	BPRS: - BPRS: 20.1 BPRS: 17.8 BPRS: - BPRS: 19.8	- 55.9 68.3 - -	- - - - AP: 79.0 MS: 21.0 AntiCh: 14.0 None: 10.0	CPT	baseline
Pukrop et al. 2006# [59] Germany Cross-sectional NA	CHR HC FE	128 179 86	24.4 29.2 29.8	63.3 44.7 60.5	11.8 (1.6) 12.5 (1.2) 11.3 (1.8)	CHR, BS	PANSS: 12.9 (4.1) PANSS: - PANSS: 19.0 (6.0) (positive sub-score only)	-	AP: 0 AP: 0 AP: 35.0	CPT, Visual Backward Masking, WCST, Verbal Fluency Test, RAVLT, SWM, MWT-A and B	baseline
Gschwandter et al. 2006 [75] Switzerland Cross-sectional NA	CHR HC	40 41	27.4 (9.1) 25.9 (5.2)	50.0 52.4	-	CHR, CUR	-	-	AP: 0 ANX: 37.5	Fine Motor Function Test	baseline
Lencz et al. 2006 [56]	CHR	32	16.2 (2.1)	56.3	10.2 (2.2)	CHR	-	-	AP: 31.3	CPT, Digit Span,	baseline

Author Country Design Follow-up duration	Groups	n	Mean age (SD)	% male	Education (years)	Risk criteria	Illness severity (BPRS or PANSS total score)	Functioning (GAF)	Treatment (%)	Neuropsychological Tests[1]	Frequency of Assessment
USA Prospective At least 6 months	CHR-P CHR-NP HC	12 20 39	16.8 15.9 15.8 (2.7)	83.3 40.0 62.0	- - 9.9 (2.6)				AD: 18.8 ST: 3.1	Judgment of Line Orientation, CVLT, Logical Memory, Boston Naming Test, Vocabulary, Block Design, Full Scale IQ, WRAT-III	
Pukrop et al. 2007^# [68] Germany Cross-sectional NA	CHR CHR-P CHR-NP HC	83 44 39 44	24.0 (5.4) 23.2 (5.4) 24.9 (5.3) 25.1 (3.2)	67.5 70.5 64.1 70.5	11.7 (1.6) 11.3 (1.7) 12.1 (1.5) 12.7 (1.0)	CHR, BS	PANNS: 12.9 (4.3) PANSS: 14.1 (4.5) PANSS: 11.6 (3.8) PANSS: - (positive subscore only)	-	-	Visual Backward Masking, TMT-B, Digit-Symbol Test, RAVLT, ROCFT, LNS	baseline
Simon et al. 2007* [70] Switzerland Cross-sectional NA	CHR HC FE	69 49 43	20.5 (5.2) 21.8 (4.9) 22.2 (6.1)	58.0 80.0 69.8	-	CHR, BS	-	-	none none AP: 37	TAP, Verbal Fluency Semantic Category, TMT-B, RAVLT, LNS, MWT-A	baseline
Pfluger et al. 2007*# [58] Switzerland Cross-sectional NA	CHR HC	60 51	27.2 (8.7) 23.4 (4.9)	56.7 54.9	-	CHR, CUR	-	-	AP: 6.7 AD: 23.3	CPT, Tower of Hanoi, TAP (Go/No-go, working memory), Leistungsprufsystem, MWT-A	baseline
Wood et al. 2007^# [65] Australia Prospective At least 12 months	CHR CHR-P CHR-NP HC	16 7 9 17	19.4 (3.4) 17.3 (2.8) 21.0 (3.1) 19.7 (2.4)	62.5 71.4 55.6 82.4	-	CHR	BPRS: 22.5 (12.6) BPRS: 15.1 (5.4) BPRS: 28.3 (13.7) -	-	AP: 0 AP: 0 AP: 6.3 NR	Digits Forward, TMT-A, COWAT, Digit Symbol Test, Logical Memory, RAVLT, Verbal Memory Index, Digits Backwards, Arithmetic, Block Design	Baseline, at least 12 months
Addington et al. 2008* [80] USA Cross-sectional NA	CHR HC FE	86 55 50	19.2 (2.6) 21.2 (6.1) 25.6 (8.0)	57.0 60.0 60.0	-	CHR	PANSS: 12.6 (2.8) PANSS: - PANSS: 11.6 (5.4) (positive sub-score only)	-	-		
Couture et al. 2008 [76]	CHR	88	18.9 (4.6)	57.0	-	CHR	PANSS: 12.4 (2.7)	-	-	RME, Abbreviated	baseline

Author Country Design Follow-up duration	Groups	n	Mean age (SD)	% male	Education (years)	Risk criteria	Illness severity (BPRS or PANSS total score)	Functioning (GAF)	Treatment (%)	Neuropsychological Tests[1]	Frequency of Assessment
USA Cross-sectional NA	HC	41	23.0 (5.9)	93.0			PANSS: - (positive sub-score only)			Trustworthiness Test	
Szily and Keri et al. 2009*# [77] Hungary Cross-sectional NA	CHR HC	26 50	22.0 (8.7) 21.1 (6.3)	42.0 38.0	11.3 (7.1) 10.9 (5.2)	CHR , BS	-	-	-	RME	baseline
Ozgurdal et al. 2009 [54] Germany Cross-sectional NA	CHR FE	54 37	24.7 (5.1) 28.3 (6.3)	63.0 73.0		CHR, BS	PANSS: 15.0 (2.5) PANSS: 16.9 (3.8) (positive sub-score only)	-	AP: 31.5 AP: 24.3	CPT, SCWT, Verbal Fluency Semantic Category, TMT-A and B, RAVLT,	baseline
Riecher-Rossler et al. 2009 [57] Switzerland Prospective Up to 7 years	CHR CHR-P CHR-NP	53 21 32	26.3 (8.6) 26.5 (6.8) 26.2 (9.7)	60.4 66.7 56.3	10.6 (2.7) 10.4 (2.4) 10.7 (2.9)	CHR, CUR	BPRS: 39.6 (9.1) BPRS: 42.4 (9.8) BPRS: 37.8 (8.3)	-	AP: 7.5 AD: 26.4 AP: 14.3 AD: 33.3 AP: 3.1 AD: 21.9	CPT, WCST, Tower of Hanoi, TAP (Go/No-go), MWT-A	baseline
Becker et al. 2010^# [73] Netherlands Prospective 24 months	CHR CHR-P CHR-NP HC FE	47 18 29 42 69	20.9 (3.6) 21.3 (3.6) 20.3 (3.6) 20.5 (3.2) 21.2 (2.8)	69.7 69.0 70.0 71.0 80.0	-	CHR, BS	PANSS: 12.4 (2.7) PANSS: 12.3 (2.5) PANSS: 12.4 (2.9) PANSS: - PANSS: 12.9 (5.4)	-	- AP: 33.3 AD: 11.1 ANX: 11.1 AP: 20.7 AD: 6.9 - AP: 100.0	Verbal Fluency Semantic Category	baseline
Becker et al. 2010*^# [55] Netherlands Prospective 18 months	CHR CHR-P CHR-NP HC	41 17 24 17	19.9 (3.6) 20.8 (4.4) 19.2 19.4 (3.8)	70.7 76.5 66.7 52.1	-	CHR, BS	-	47.8 (10.3) 44.9 (7.6) 49.8 (11.5) 86.0 (6.5)	-	CPT, Verbal Fluency Semantic Category, Verbal Fluency Test, Finger Tapping, CVLT, ROCFT, SWM, NART	baseline, 18 months
Lindgren et al. 2010*# [64] Finland Cross-sectional NA	CHR HC	62 72	16.6 (0.9) 16.4 (1.5)	21.0 22.2	-	CHR	-	38.1 (12.0) -	-	Digits Forward, Visual Span Forward, Verbal Fluency Semantic Category, TMT-A and B, PC Test, Bourdon-	baseline

Author Country Design Follow-up duration	Groups	n	Mean age (SD)	% male	Education (years)	Risk criteria	Illness severity (BPRS or PANSS total score)	Functioning (GAF)	Treatment (%)	Neuropsychological Tests[1]	Frequency of Assessment
										Wiesma Dual Task Counting Backwards, Spatial Tapping, CVLT, Logical Memory, Visual Reproduction, Digits Backward, Spatial Span Backwards, Vocabulary	
Woodberry et al. 2010*^# [51] USA Prospective 12 months	CHR CHR-P CHR-NP HC	73 13 55 34	16.5 (2.7) 16.7 (2.4) 16.4 (2.4) 16.2 (2.5)	49.0 38.5 51.0 53.0	-	CHR	-	-	-	CPT, WCST, TMT-B, Verbal Fluency Test, Finger Tapping Test, CVLT, Logical Memory, LNS, Vocabulary, Block Design, Full Scale IQ, WRAT-III	baseline
Jahshan et al. 2010# [61] USA Prospective 6 months	CHR HC FE	46 29 18	18.7 (4.2) 19.0 (5.2) 20.1 (5.7)	58.3 48.3 85.0	11.2 (2.8) 11.9 (4.4) 11.4 (2.8)	CHR	BPRS: 15.6 (9.6) BPRS: - BPRS: 20.4 (7.2)	52.1 (9.6) - 42.5 (9.5)	AP: 20.8 - AP: 70.0	WCST, Numerical Attention Test, HVLT-R, LNS, Spatial Span Backward, Vocabulary, Block Design,	baseline, 6 months
Carrión et al. 2011# [50] USA Cross-sectional NA	CHR HC	127 80	16.1 (2.1) 16.0 (2.8)	67.0 45.0	9.9 (2.1) 10.2 (2.8)	CHR	-	-	-	CPT, Digits Forward, Judgment of Line Orientation, WCST, Ruff Figural Fluency, TMT-A and B, Verbal Fluency Test, Digit Symbol Test, Finger Tapping Test, Grooved Pegboard Test, CVLT, Logical Memory, Boston Naming Test, LNS, Digits Backward, Vocabulary, Block	baseline

Author Country Design Follow-up duration	Groups	n	Mean age (SD)	% male	Education (years)	Risk criteria	Illness severity (BPRS or PANSS total score)	Functioning (GAF)	Treatment (%)	Neuropsychological Tests[1]	Frequency of Assessment
										Design, WRAT-III	
Green et al. 2011* [79] USA Cross-sectional NA	CHR	50	18.3 (3.1)	72.0	-	CHR	-	-	AP: 34.0 AD: 30.0 MS: 10.0 ANX: 6.0 ST: 2.0 None: 20.0	TASIT	baseline
	HC	34	19.0 (2.9)	66.0	12.5 (2.0)				-		
	FE	81	22.0 (4.2)	75.0	-				AP: 100.0 AntiCh: 14.8		
Van Rijn et al. 2011*# [78] Netherlands Cross-sectional NA	CHR	36	15.2 (2.1)	69.4	-	CHR, BS	-	59.3 (13.5)	AP: 19.4 AD/MS: 13.9 ANX: 5.6 ST: 5.6	Facial Affect Labeling Test	baseline
	HC	21	15.9 (1.2)	57.1				91.3 (7.1)	None: 100.0		
Frommann et al. 2011*# [49] Germany Cross-sectional NA	CHR	205	25.5 (6.2)	62.9	-	CHR, BS	PANSS: 10.8 (3.6) (positive sub-score only)	59.0 (11.3)	AP: 4.4 AD: 16.1 ANX: 4.4 Other: 2.9 None: 76.1	CPT, TMT-A and B, Verbal Fluency Test, Digit-Symbol Test, RAVLT, LNS, Subject Ordered Pointing Test, MWT-B	baseline
	HC	87	25.5 (4.4)	56.3			PANSS: -	-	-		
Koutsouleris et al. 2011*^# [66] Germany Prospective 4 years	CHR CHR-P CHR-NP HC	48 15 20 30	247 (5.8) 22.8 (3.8) 25.8 (6.8) 26.0 (2.7)	67.7 73,3 70.0 60.0	12.0 (1.2) 11.9 (1.1) 11.9 (1.2) 12.4 (1.2)	CHR, BS	PANSS: 62.6 (18.7) PANSS: 65.5 (20.5) PANSS: 52.9 (11.8) PANSS: -	58.6 (10.8) 59.9 (14.2) 58.6 (10.9) -	-	Digit Span, TMT-A and B, Verbal Fluency Test, Digit-Symbol Test, RAVLT, LNS, Subject Ordered Pointing Task, MWT-B	baseline
Stanford et al. 2011 [69] USA Cross-sectional NA	CHR HC	63 24	19.6 (3.6) 21.0 (3.6)	79.4 62.5	-	CHR	-	43.6 (7.3) 80.6 (8.7)	-	Attention Memory Index, Verbal Memory Index, Arithmetic, False Believe Task, Strange Story Task, RME, Full	baseline

Author Country Design Follow-up duration	Groups	n	Mean age (SD)	% male	Education (years)	Risk criteria	Illness severity (BPRS or PANSS total score)	Functioning (GAF)	Treatment (%)	Neuropsychological Tests[1]	Frequency of Assessment
										Scale IQ, Verbal IQ, Performance IQ,	
Kim et al. 2011^# [62] Korea Prospective Up to 5.2 years	CHR CHR-P CHR-NP HC	49 13 36 45	21.1 (3.9) 21.0 (4.8) 21.2 (3.6) 22.7 (3.5)	61.2 69.2 58.3 62.2	12.7 (2.0) 12.7 (1.9) 12.6 (2.0) 14.3 (1.6)	CHR	PANSS: 54.3 (11.1) PANSS: 55.9 (12.5) PANSS: 53.7 (10.7) PANSS: -	54.8 (8.0) 54.0 (8.4) 55.1 (7.9) -	AP: 6.1	SCWT, Digit Span, WCST, TMT-A and B, COWAT, CVLT, ROCFT, Spatial Location, False Belief Task, Strange Story Task, Cartoon Test	baseline
Bowie et al. 2012 [74] USA Prospective 6 months	CHR HC	53 17	16.2 (1.9) 16.4 (2.3)	75.5 52.9	9.8 (1.9) 10.7 (2.3)	CHR	-	-	None at study entry	TMT-A and B, Verbal Fluency Test, CVLT, LNS,	baseline, 6 months
Broome et al. 2012 [72] UK Prospective 24 months	CHR CHR-P CHR-NP	28 5 23	24.4 (4.2) 24.0 (3.8) 24.5 (4.3)	NR	-	CHR	PANSS: 51.9 (14.2) PANSS: 52.7 (19.7) PANSS: 51.7 (13.3)	56.2 (12.2) 48.8 (21.3) 57.8 (9.2)	-	Beads Span Test, Quick Test, NART	baseline
Pettersson-Yeo et al. 2013 [16] UK Cross-sectional NA	CHR HC FE	19 19 15	22.4 (3.4) 23.3 (3.4) 23.3 (3.7)	47.4 47.4 60.0	-	CHR	PANSS : 52.5 (9.3) PANSS : - PANSS : 54.4 (15.1)	-	-	CVLT	baseline
Lin et al. 2013# [67] Australia Prospective Up to 15 years	CHR CHR-P CHR-NP HC	325 81 244 66	19.1 (3.3) 19.6 (3.4) 19.0 (3.3) 20.8 (4.4)	47.1 49.4 46.3 59.1	-	CHR	BPRS: 6.4 (3.4) BPRS: 8.7 (5.0) BPRS: 5.7 (2.3) BPRS: - (positive sub-score only)	65.3 (15.6) 55.6 (18.0) 68.7 (13.2) -	AP: 19.4 MS: 7.4 AP: 24.7 MS :2.5 AP: 17.6 MS: 9.0 -	Digit Span, Picture Completion, Similarities, TMT-A and B, COWAT, Digit-Symbol Test, Logical Memory, RAVLT, Verbal Pairs Correct, Visual Reproduction, Arithmetic, Vocabulary, Block Design, Information, NART,	baseline
Woodberry et al. 2013	CHR	53	16.0 (2.4)	49.0	-	CHR	-	-	-	CPT, WCST, TMT-B,	baseline, 12

Author Country Design Follow-up duration	Groups	n	Mean age (SD)	% male	Education (years)	Risk criteria	Illness severity (BPRS or PANSS total score)	Functioning (GAF)	Treatment (%)	Neuropsychological Tests[1]	Frequency of Assessment
[52] USA Prospective 12 months	HC	32	16.3 (2.6)	50.0						Verbal Fluency Test, Finger Tapping Test, CVLT, Logical Memory, LNS,	months
Mirzakhanian et al. 2013 [48] USA Prospective Up to 12 months	CHR HC FE	109 102 90	19.1 (4.1) 20.8 (4.6) 20.9 (5.4)	57.8 46.0 74.4	11.4 (2.7) 13.1 (4.2) 12.1 (3.4)	CHR	BPRS: 15.6 (6.5) BPRS: - BPRS: 17.7 (8.3)	50.1 (10.2) - 42.4 (8.2)	-	CPT	baseline
Hur et al. 2013 [71] Korea Cross-sectional NA	CHR HC	55 58	22.0 (3.3) 23.1 (3.0)	67.3 50.0	-	CHR	PANSS: 57.2 (12.3) PANSS: -	-	-	WCST, CVLT, False Belief Task, Strange Story Task, Cartoon Test, Verbal IQ, Performance IQ	baseline
<u>Summary for non-overlapping CHRvsHC</u>											
21 studies 9 countries 15 cross-sectional 6 prospective	CHR	1684	20.5 (3.4)	59.2	11.3 (1.0)	CHR: 21 BS: 8 CUR: 1	PANSS: 56.7 (4.4) BPRS: 15.6 (9.6) PANSS (pos. score): 12.8 (1.7) BPRS (pos. score): 6.4 (3.4)	53.5 (8.2)	AP: 14.2 AD: 15.4 MS: 5.6 ANX: 2.8 ST: 2.5	60 Tests and Test-batteries	19 baseline cognitive assessment only 2 f/u cognitive assessment
	CHR-P	139	20.2 (2.3)	61.4	12.3 (0.6)		PANSS: 60.7 (6.8) BPRS (pos. score): 8.7 (5.0)	53.6 (6.3)			
	CHR-NP	379	20.3 (3.5)	58.5	12.3 (0.5)		PANSS: 53.3 (0.7) BPRS (pos. score): 5.7 (2.3)	58.1 (8.0) 86.0 (5.4)			
	HC	986 405	21.2 (3.7) 23.3 (3.8)	55.4 69.8	12.1 (1.3) 11.2 (0.2)		PANSS/BPRS: -	46.9 (6.2)	AP: 48.3		
	FE						PANSS: 54.4 (15.1) BPRS: 42.5 (9.5) PANSS (pos. score): 18.0 (1.5)		AntiCh: 14.8		

* included in Fusar-Poli et al. 2012; ^included in deHerdt et al. 2013, #included in Bora et al. 2014

[1] Tests listed were used in this analysis. Original publications may contain more tests that have been not used for analysis due to the overlap of samples and are not thus included in this table.

AP=Antipsychotics; AD=Antidepressants; MS=Mood Stabilizers; AntiCh=Anticholinergics; ANX=Anxiolytics; COWAT=Controlled Oral Word Association; CPT=Continuous Performance Test; CUR=Combination of Unspecific Risk Symptoms; CVLT=California Verbal Learning Test; HVLT-R= Hopkins Verbal Learning Test Revised; LNS=Letter Number Sequencing; MWT-A and B=Mehrfachwortschatztest A and B; NART=National Adult Reading Test; RAVLT= Ray Auditory Verbal Learning Test; RME=Reading the Mind in the Eye Test; ROCFT=Rey Osterrieth Complex Figures Test; SCWT=Stroop Color and Word Test; ST=Stimulants; SWM= Spatial Working Memory Delayed response Task; TAP=Testbatterie zur Aufmerksamkeitsprufung; TASIT= Awareness of Social Inference Test ; TMT-A and B=Trail Making Test A and B; WCST=Wisconsin Card Sorting Test; WRAT-III=Wide Range Achievement Test 3rd Edition

Supplemental eFigure 1. Literature Search