

Cognitive Functioning in Prodromal Psychosis

A Meta-analysis

Paolo Fusar-Poli, MD, PhD; Giacomo Deste, MD; Renata Smieskova, PhD; Stefano Barlati, MD; Alison R. Yung, MD; Oliver Howes, BM, BCh, MA, MRCPsych, PhD, DM; Rolf-Dieter Stieglitz, PhD; Antonio Vita, MD, PhD; Philip McGuire, BSc, MB, ChB, MD, PhD, FRCPSych; Stefan Borgwardt, MD, PhD

Context: A substantial proportion of people at clinical high risk (HR) of psychosis will develop a psychotic disorder over time. Cognitive deficits may predate the onset of psychosis and may be useful as markers of increased vulnerability to illness.

Objective: To quantitatively examine the cognitive functioning in subjects at HR in the literature to date.

Data Sources: Electronic databases were searched until January 2011. All studies reporting cognitive performance in HR subjects were retrieved.

Study Selection: Nineteen studies met the inclusion criteria, comprising a total of 1188 HR subjects and 1029 controls.

Data Extraction: Neurocognitive functioning and social cognition as well as demographic, clinical, and methodological variables were extracted from each publication or obtained directly from its authors.

Data Synthesis: Subjects at HR were impaired relative to controls on tests of general intelligence, executive function, verbal and visual memory, verbal fluency, attention and working memory, and social cognition. Processing speed domain was also affected, although the difference was not statistically significant. Later transition to psychosis was associated with even more marked deficits in the verbal fluency and memory domains. The studies included reported relatively homogeneous findings. There was no publication bias and a sensitivity analysis confirmed the robustness of the core results.

Conclusions: The HR state for psychosis is associated with significant and widespread impairments in neurocognitive functioning and social cognition. Subsequent transition to psychosis is particularly associated with deficits in verbal fluency and memory functioning.

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Author Affiliations:

Department of Psychosis Studies, Institute of Psychiatry, King's College London (Drs Fusar-Poli, Howes, and McGuire), and OASIS prodromal team, South London and Maudsley NHS Foundation Trust (Drs Fusar-Poli and McGuire), London, and University of Manchester, Manchester (Dr Yung), England; Section of Psychiatry, University of Brescia, Brescia, Italy (Drs Deste, Barlati, and Vita); Department of Psychiatry, University of Basel, Basel, Switzerland (Drs Smieskova, Stieglitz, and Borgwardt); and Orygen Youth Health Research Centre, Centre for Youth Mental Health, University of Melbourne, Melbourne, Australia (Dr Yung).

NEUROCOGNITIVE DEFICITS have been identified as a robust feature of schizophrenia since its earliest descriptions^{1,2} and are a central manifestation of the pathophysiology of the disorder.³ The most consistent impairments are in the domains of attention, memory, and executive function and are already evident at the time of the first episode of illness.⁴ Impairments are also observed in social cognition,^{5,6} defined as the mental processes by which humans interpret and respond to others' behavior.⁷ The extent to which these cognitive deficits progress over the course of the disorder is still debated,⁸ with some studies suggesting that there is no change over time but others indicating that deficits get progressively worse.⁹ These inconsistent findings may be explained by the confounding effects of antipsychotic medications and the other features of the disorder, such as persistent psychotic symptoms, institutionalization, and poor physical health.

The effects of these potentially confounding factors can be avoided by studying cognitive function in treatment-naive subjects who have a high clinical risk (HR) of developing psychosis in the near future.¹⁰ These subjects are said to be at HR of psychosis, in particular schizophrenia spectrum psychoses,¹¹ and can be identified if they present with "attenuated" psychotic symptoms, full-blown psychotic symptoms that are brief and self-limiting, or a significant decrease in functioning in the context of a family history of schizophrenia.¹⁰ Subjects at HR can also be defined in terms of "basic symptoms"¹² that include subjective disturbances of cognitive processing and the perception of the self and the world.¹⁰ Neurocognitive studies in HR populations have attempted to establish whether the deficits observed during a first episode of psychosis are already evident during the prodromal phase of the disorder. However, despite several studies in this population, the results have been inconsistent, with some reports of significant alterations but

others finding no significant differences¹³ relative to matched controls, and the profile of the neurocognitive impairments identified has varied across studies. Moreover, a key issue in this field is whether the observed deficits are related to the increased vulnerability to psychosis shared by all HR subjects or are specifically linked to the subsequent onset of psychosis that occurs in a subgroup of this population, in line with structural and functional HR brain abnormalities¹⁴⁻¹⁶ underlying the onset of psychosis. Because it is difficult to predict which HR individuals will go on to develop psychosis on the basis of their presenting clinical features,^{10,17} there is clear clinical need for other markers that could be used to help clinicians identify the subgroup of subjects that will benefit most from preventive interventions. Accurately defining cognitive deficits in HR subjects will also inform the debate about proposals for a new high-risk diagnostic category in the forthcoming DSM-5.¹⁸

To date, the available results in this field have been only summarized in qualitative critical reviews.^{9,19} To our knowledge, the present study is the first that has measured the magnitude of cognitive (neurocognitive or social cognition) impairments in HR subjects using a quantitative meta-analysis. We first sought to examine at a meta-analytical level whether cognitive deficits are evident in HR subjects relative to healthy controls and to define the specific pattern of these cognitive deficits. We then aimed to identify cognitive impairments that specifically predicted the later transition to psychosis, controlling for the potential confounding effect of sociodemographical, methodological, and clinical factors.

METHODS

SELECTION PROCEDURES

Search Strategies

A systematic search strategy was used to identify relevant studies. Three independent researchers (G.D., R.S., and P.F.P.) conducted a two-step literature search. First, a PubMed and Embase search was performed to identify putative studies reporting cognitive functioning in subjects at increased clinical risk (HR) for psychosis. The search was conducted up to January 2011, with no time span specified for date of publication. The following search terms were used: "cognition," "neurocognitive," "psychosis risk," "ultra high risk," "UHR," "prodromal psychosis," "basic symptoms," and "social cognition." In a second step, the reference lists of the articles included in the review were manually checked for any studies not identified by the computerized literature search. There was no language restriction, although all the included articles were in English.

Selection Criteria

Studies were included if they met the following criteria: (1) were reported in an original article in a peer-reviewed journal, (2) had involved subjects at HR for psychosis defined according to established international criteria (see later), and (3) had reported measures of neurocognitive and social cognition performance in both groups. When the inclusion criteria for the HR group were not clearly defined, the study was excluded. Studies of subjects at genetic risk for psychosis (twins and first- or second-degree relatives)²⁰⁻²² or schizotypal personality disorder²³ were not in-

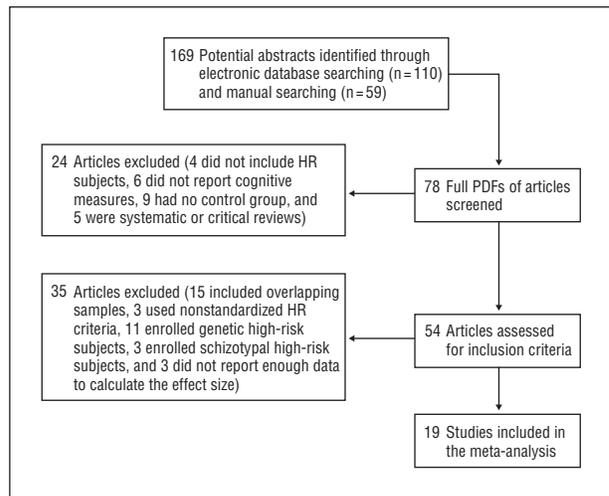


Figure 1. Search strategy used for the inclusion of the studies considered in the current meta-analysis. HR indicates clinical high risk for psychosis.

cluded. When there were two or more studies from the same center, we contacted the authors to clarify whether there was overlap in the respective samples (if several articles dealt with the same population, we selected the article with the largest sample). When studies did not report performance data for each individual task (ie, studies reporting composite scores only), we contacted the respective authors to collect the individual scores.

Recorded Variables

The variables for each article included in the meta-analysis were inclusion criteria for the HR state, psychometric instruments used to assess the psychosis risk (see later), year of publication, sex (proportion of females), mean (SD) age of participants, cognitive tests used, results of tests (mean [SD]), exposure to antipsychotics (proportion of treated HR subjects), and cognitive performance in HR subjects who later developed psychosis (HR-T) and HR subjects who did not develop psychosis (HR-NT). To achieve a high standard of reporting, we adopted Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines²⁴ (**Figure 1**).

Quality Assessment

Although quality assessments can be reliably conducted in meta-analyses of experimental studies, their use in observational research is controversial, with no clear consensus on rating methods or their appropriate use in analysis.²⁵ In the present meta-analysis, we used a simple objective rating system (based on the JAMA meta-analysis²⁶) that coded study quality on a scale of 0 to 10, assigning 2 points for each of the following: a description of the sampling method; the presence of clearly stated inclusion criteria; the assessment of ethnic diversity; the assessment of educational diversity; and a comprehensive description of outcome. Because evidence on the validity of quality ratings in observational research is lacking, we adopted the Meta-analysis of Observational Studies in Epidemiology²⁷ approach of broadly including studies and using sensitivity analysis to determine incremental effects of lower-quality studies.

REVIEW OF INCLUSION AND TRANSITION CRITERIA USED WITH STUDIES

A detailed discussion of the inclusion and assessment criteria used with studies is fully provided in a complementary publi-

cation by our group.¹⁰ In summary, there are two main forms of diagnostic criteria used to define HR features, the ultra high risk (UHR) and the basic symptoms (BS), and most centers worldwide have adopted one of these. Because the UHR and BS criteria relate to complementary sets of clinical features, there is an increasing tendency for centers to use both when assessing HR subjects.²⁸ In a recent work¹⁷ by our group, we demonstrated that the transition risks to psychosis are comparable across different UHR inclusion criteria (ie, Structured Interview for Prodromal Syndromes vs Comprehensive Assessment of At-Risk Mental States), while higher rates were observed in studies using the BS criteria. Overall, we showed that HR is associated with a consistent increased risk of developing a psychotic episode over time (18% [95% CI, 12 to 25] after 6 months of follow-up, 22% [95% CI, 17 to 28] after 1 year, 29% [95% CI, 2 to 36] after two years, and 36% [95% CI, 30 to 43] after 3 years).¹⁷ In a subsequent meta-analytical work, we further showed that 73% of the HR-T will develop *International Classification of Diseases/DSM* schizophrenia spectrum psychotic disorders and 11% of them, an affective psychotic disorder (risk ratio, 5.4).¹¹

STATISTICAL ANALYSIS

Data were entered into an electronic database and analyzed with a quantitative meta-analytical approach using Comprehensive Meta-Analysis Software version 2 (Biostat, Inc).²⁹ The software uses the same computational algorithms used by the Cochrane collaborators to weight studies by the inverse variance method.²⁹ The primary outcome was the neurocognitive performance (mean [SD]) in HR subjects as compared with controls. The different neurocognitive tasks were grouped in cognitive domains on the basis of the criteria developed by the MATRICS conference^{30,31} and then discussed by us, according to the indications of the articles included: (1) verbal fluency, (2) verbal memory, (3) working memory, (4) visual memory, (5) executive functioning, (6) attention, and (7) processing speed. The individual tests included in each neurocognitive domain are detailed in the eTable (<http://www.archgenpsychiatry.com>). To better clarify the pattern of putative neurocognitive deficits, we also analyzed each measure for each cognitive domain separately, when sufficient data were available to calculate the effect in at least 3 studies for each cognitive test. Further, we analyzed the domain of general intelligence by using the total scores of the Wechsler Adult Intelligence Scale. As a second cognitive outcome, we analyzed the domain of social cognition, which refers to the mental operations underlying social behavior, such as the interpretation of another person's intentions or emotions.⁶ The social cognition domain comprised HR studies addressing emotional processing, social perception and knowledge, theory of mind, and attributional bias.⁶ To compute the overall cognitive impairment, the different neurocognitive domains were averaged together within each individual study and combined with the social cognition domain. A final meta-analysis compared cognitive performance between HR-T and HR-NT across studies using a baseline cognitive assessment with longitudinal follow-up of transition outcomes.

The effect size was estimated by calculating the Hedges' unbiased g , with negative values reflecting worse performances in the HR subjects as compared with healthy controls and in HR-T as compared with HR-NT. The Hedges' g is obtained with the difference between the means of the patient and control groups divided by the standard deviation and weighted for sample size, to correct for bias from small sample sizes.³² This metric is normally computed by using the square root of the mean square error from the analysis of

variance testing for differences between the two groups, as indicated by the formula:

$$g = M1 - M2/S_{\text{pooled}}$$

where

$$S = \sqrt{\sum (X - M)^2 / (N - 1)}$$

and

$$S_{\text{pooled}} = \sqrt{MS_{\text{within}}}$$

where X is the raw score, M is the mean, and N is the number of cases.³²

To determine whether categorical factors modified the cognitive performance in HR subjects, subgroup analyses were performed.²⁶ The influence of continuous moderator variables was tested using meta-regression analyses. The slope of meta-regression (β coefficient: direct [+] or inverse [-]) of the regression line indicates the strength of a relationship between moderator and outcome. To limit the risk of false-positive (type I) errors arising from multiple comparisons, we adjusted $P < .05$ by dividing α by the number of meta-regressions.

Heterogeneity among study point estimates was assessed with Q statistics²⁶ with magnitude of heterogeneity being evaluated with the I^2 index.³³ For homogeneous data, we calculated the global effect size, using a fixed-effects model. In the absence of significant heterogeneity, the use of a fixed-effects model is legitimate and may provide greater statistical power than the random-effects model.³⁴ For heterogeneous data, we used random-effects models, which are more conservative than fixed-effects models and appear to better address heterogeneity between studies and study populations, allowing for greater flexibility in parsing effect size variability.³⁵ The possibility of a small study bias, such as publication bias, in the present study was examined by visually inspecting funnel plots and applying the regression intercept of Egger.³⁶ In this way, we assessed whether there was a tendency for selective publication of studies based on the nature and direction of their results. In addition, we used the fail-safe procedure³⁷ to generate the number of unpublished studies that would be needed to move estimates to a nonsignificant threshold. To assess the robustness of the results, we performed sensitivity analyses by sequentially removing each study and rerunning the analysis. We also conducted a separate analysis excluding studies with quality ratings in the lowest third to determine if potential methodological weaknesses influenced meta-analytic estimates.

RESULTS

RETRIEVED STUDIES

The combined search strategies yielded a total of 78 PDFs, of which after a complete full text analysis, 24 were excluded. All authors of studies reporting composite scores were contacted to obtain raw data of individual tasks. Three studies did not provide enough data and were excluded. Nineteen studies published between 2005 and January 2011 met the inclusion criteria (Figure 1). The overall database comprised 1188 HR subjects (mean [SD] age = 20 [3.37] years; age range, 15.2-27.2 years; 44% female) and 1029 controls (mean [SD] age = 21 [3.16] years; age range, 15.9-25.5 years; 45% female) (**Table**), well matched with respect to age and sex (t test $P > .05$). Within the 1188 HR subjects, 23% had been treated with antipsychotic medication while 73% fulfilled the UHR criteria; 19%, the UHR and BS criteria; and 8%, the BS criteria.

Table. Studies of Subjects at HR for Psychosis Included in the Meta-analysis

Source (Year)	HR Group	HR Subjects			Controls			Cognitive Domain
		No.	% Female	Age, y, Mean (SD)	No.	% Female	Age, y, Mean (SD)	
Brewer et al ³⁸ (2005) ^a	UHR	98	48	19.7 (3.9)	37	24	20.7 (4.3)	GI, EF, PS, ViM, VM, VF, WM, AT
Silverstein et al ³⁹ (2006)	UHR	70	34	17.4 (3.6)	24	25	20.7 (4.4)	PS
Simon et al ⁴⁰ (2007)	UHR, BS	69	42	20.5 (5.2)	49	20	21.8 (4.9)	AT, EF, PS, VF, VM, WM
Pflueger et al ⁴¹ (2007) ^b	UHR	60	43	27.2 (8.7)	51	45	23.4 (4.9)	EF, WM, AT, PS
Broome et al ⁴² (2007) ^c	UHR	35	47	24.2 (4.3)	23	40	24.9 (3.0)	GI, WM, VF, ViM, PS
Addington et al ⁴³ (2008)	UHR	86	43	19.2 (2.6)	55	40	21.2 (6.1)	SC
Chung et al ⁴⁴ (2008)	UHR	33	42	20.9 (3.2)	36	44	22.0 (2.5)	GI, EF, VF, WM, ViM, VM, PS, SC
Szily and Kéri ⁴⁵ (2009)	UHR, BS	26	58	22.0 (8.7)	50	62	21.1 (6.3)	GI, SC
Korver et al ⁴⁶ (2010) ^d	UHR, BS	63	34	19.6 (3.3)	30	50	19.8 (3.4)	GI, VM, VF, AT, PS, ViM
Seidman et al ⁴⁷ (2010)	UHR	167	36	18.2 (4.9)	109	56	18.8 (4.5)	GI, EF, PS, WM, AT, VF
An et al ⁴⁸ (2010)	UHR	24	42	20.0 (3.9)	39	59	19.7 (3.5)	SC
Ilonen et al ⁴⁹ (2010)	UHR	22	91	15.7 (1.8)	187	63	15.5 (1.7)	GI, EF, PS, WM
Woodberry et al ⁵⁰ (2010)	UHR	73	51	16.5 (2.7)	34	47	16.2 (2.5)	GI, AT, VM, WM, VF, EF, PS
Lindgren et al ⁵¹ (2010)	UHR	62	79	16.6 (0.9)	72	78	16.4 (1.5)	VF, PS, VM, ViM, WM, AT, EF
Magaud et al ⁵² (2010)	UHR	77	23	21.0 (3.4)	61	24	19.6 (3.3)	VF
van Rijn et al ⁵³ (2011)	UHR, BS	36	31	15.2 (2.1)	21	43	15.9 (1.4)	GI, SC, EF, PS
Green et al ⁵ (2011)	UHR	50	28	18.3 (3.1)	34	44	19.0 (2.8)	SC
Koutsouleris et al ⁵⁴ (2011)	UHR	48	33	24.7 (5.8)	30	40	26.0 (2.7)	GI, PS, WM, VM, VF
Frommann et al ⁵⁵ (2011) ^e	BS	89	40	25.3 (6.4)	87	44	25.5 (4.4)	GI, VM, WM, PS, VF, AT

Abbreviations: AT, attention; BS, basic symptoms; EF, executive function; GI, general intelligence; HR, clinical high risk; PS, processing speed; SC, social cognition; UHR, ultra high risk; VF, verbal fluency; ViM, visual memory; VM, verbal memory; WM, working memory.

^aAttention reported in Francey et al.⁵⁶

^bHigh-risk subjects who later developed psychosis vs HR subjects who did not develop a psychotic disorder reported in Riecher-Rössler et al⁵⁷; PS reported in Gschwandtner et al.⁵⁸

^cVerbal fluency, PS, and ViM reported in Broome et al⁵⁹ and Fusar-Poli et al.⁶⁰

^dVisual memory and subjects at HR who later developed psychosis vs HR subjects who did not develop a psychotic disorder reported in Becker et al.⁶¹

^eSubjects at HR who later developed psychosis vs HR subjects who did not develop a psychotic disorder reported in Pukrop et al.⁶²

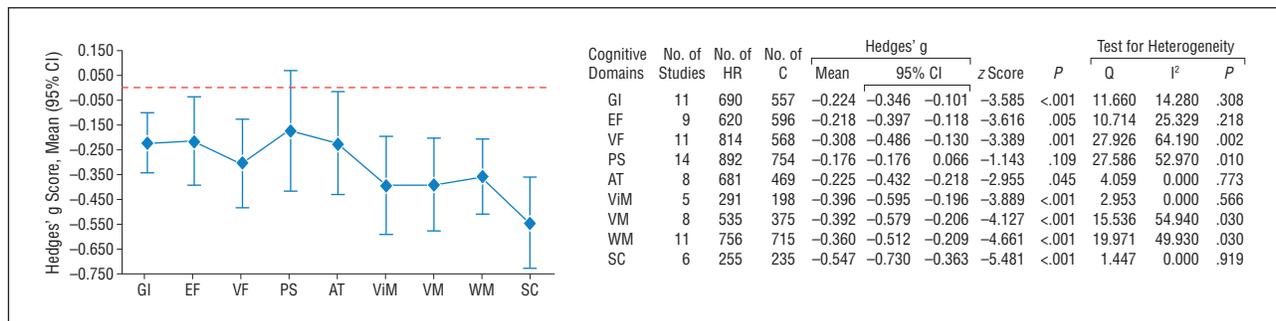


Figure 2. Cognitive functioning in subjects at clinical high risk (HR) for psychosis compared with controls (C) across the neurocognitive and social cognition (SC) domains. Hedges' g scores (mean and 95% CI) across domains are given (negative values indicate worse performance in the HR subjects compared with the C group). The dotted red line (Hedges' g=0) indicates no significant difference as compared with C. AT indicates attention; EF, executive functioning; GI, general intelligence; PS, processing speed; VF, verbal fluency; ViM, visual memory; VM, verbal memory; and WM, working memory.

COGNITIVE ALTERATIONS ASSOCIATED WITH VULNERABILITY TO PSYCHOSIS

General Intelligence

There was a significant impairment in general intelligence of HR subjects compared with controls (number of studies=11; number of HR subjects=690; number of control subjects=557) (**Figure 2**).

Neurocognitive Functioning

Across all the neurocognitive domains, there was consistent evidence indicating an overall impairment in HR sub-

jects compared with controls (Hedges' g=-0.344; 95% CI, -0.428 to -0.260; z=-8.003; P<.001). There was no heterogeneity across these findings (Q=2.123; P=.87). Vulnerability to psychosis was associated with neurocognitive deficits in executive function, verbal fluency, attention, visual and verbal memory, and working memory (Figure 2), while no significant differences with respect to controls were found in the domain of processing speed (but see later for specific alterations in the individual processing speed tasks). The greatest impairment in magnitude was observed in the visual and verbal memory domains.

To provide a better neurocognitive profile of these impairments, the effect sizes of the individual cognitive tasks and the relative sample sizes were additionally summa-

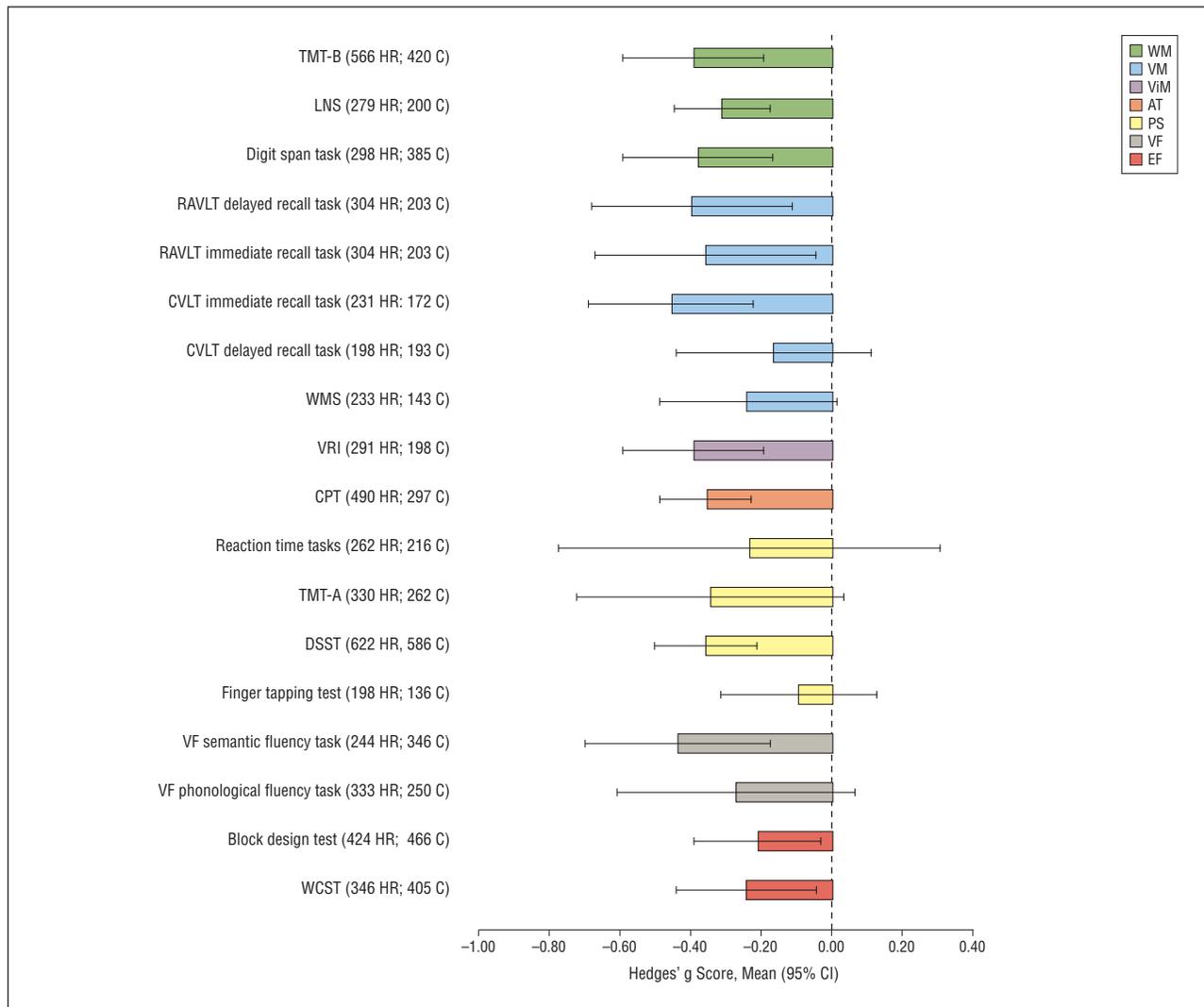


Figure 3. Neurocognitive profiles of individual tasks in subjects at clinical high risk (HR) for psychosis compared with controls (C). Hedges' g scores (mean and 95% CI) across cognitive tasks are given (negative values indicate worse performance in the HR subjects compared with the C group, while 0 indicates no difference). AT indicates attention; CPT, Continuous Performance Test (d'); CVLT, California Verbal Learning Test; DSST, Digit Symbol Substitution Test; EF, executive functioning; LNS, Letter Number Sequencing task; PS, processing speed; RAVLT, Rey Auditory Verbal Learning Test; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; VF, verbal fluency; ViM, visual memory; VM, verbal memory; VRI, Visual Reproduction Index (Wechsler Memory Scale visual reproduction and Rey complex figures); WCST, Wisconsin Card Sorting Test (perseverative errors); WM, working memory; and WMS, Wechsler Memory Scale (verbal recall). See the eTable (<http://www.archgenpsychiatry.com>) for further details on the clustering of each task into the cognitive domains.

rized in **Figure 3**. This analysis confirmed that there were deficits in all neurocognitive tasks indexing working memory, attention, visual memory, and executive function. Conversely, within the verbal memory domain, HR subjects were significantly impaired on the California Verbal Learning Test immediate recall but not delayed recall tasks and while within the verbal fluency domain, they were impaired on the semantic but not phonological verbal fluency tasks. All neurocognitive tasks addressing processing speed except the Digit Symbol Substitution Test showed no significant differences between HR subjects and controls. Finally, we found that HR subjects were best distinguished from controls on the performance of the Digit Symbol Substitution Test, Letter Number Sequencing task, and Continuous Performance Test, as these tasks showed the smallest confidence intervals.

Social Cognition

There was a statistically significant impairment in the social cognition domain of HR subjects compared with controls (number of studies=6; 255 HR subjects; 235 control subjects) (Figure 2).

COGNITIVE ALTERATIONS ASSOCIATED WITH TRANSITION TO PSYCHOSIS

A further meta-analysis was performed across the studies (7 studies^{38,47,50,54,57,61,62}; 598 HR subjects; 378 controls; Table) reporting baseline neurocognitive functioning in HR-T (n=233) compared with HR-NT (n=365). The mean (SD) follow-up time for later conversion to psychosis was 19 (7.3) months. General intelligence was significantly lower in HR-T compared with HR-NT. Subjects at HR who later devel-

oped psychosis showed poorer neurocognitive functioning in verbal fluency, verbal and visual memory, and working memory compared with HR-NT (**Figure 4**). Not enough data were available to analyze social cognition regarding transition to psychosis.

EFFECT OF MODERATORS

Meta-regressions showed no significant modulating effect of publication year on the cognitive functioning in HR subjects ($\beta = -0.015$; 95% CI, -0.069 to 0.041 ; $z = -0.516$; $P = .61$). Age of participants had a small albeit significant effect on the cognitive performance of HR subjects, with older subjects performing worse than younger subjects ($\beta = -0.025$; 95% CI, -0.034 to -0.011 ; $z = 3.818$; $P < .001$). Exposure to antipsychotic medication did not influence the cognitive functioning in HR subjects (exposed: Hedges' $g = -0.389$; 95% CI, -0.506 to -0.271 ; nonexposed: Hedges' $g = -0.318$; 95% CI, -0.501 to -0.135 ; exposed vs nonexposed: $Q = 1.130$; $P = .57$). Cognitive impairments appeared less marked in studies using the BS approach (Hedges' $g = -0.227$; 95% CI, -0.470 to 0.0016), intermediate in studies adopting the UHR approach (Hedges' $g = -0.357$; 95% CI, -0.453 to -0.262), and more pronounced in studies combining the two approaches (Hedges' $g = -0.410$; 95% CI, -0.694 to -0.125), although these group differences were statistically nonsignificant ($Q = 1.166$; $P = .56$). Finally, there was a trend-level significance effect of sex on cognitive performance in the HR subjects, with females performing relatively better than males (females: Hedges' $g = -0.208$; 95% CI, -0.307 to -0.109 ; males: Hedges' $g = -0.366$; 95% CI, -0.411 to -0.321 ; $Q = 4.858$; $P = .053$).

HETEROGENEITY, PUBLICATION BIAS, AND SENSITIVITY ANALYSIS

Visual inspection of funnel plots revealed no obvious evidence of publication bias within the whole database, and quantitative evaluation of publication bias, as measured by the Egger intercept, was nonsignificant ($P = .18$). The fail-safe procedure estimated that 285 unpublished studies would be needed to bring the overall meta-analytic estimate to the nonsignificant threshold. According to the criteria set by Higgins and Thompson,⁶³ the heterogeneity across the included studies was statistically nonsignificant ($Q = 14.198$; $P = .84$). Sensitivity analysis confirmed the results were robust because no study affected the meta-analytic estimate by more than 5%. Removing studies with quality ratings in the lowest 30% influenced the meta-analytic estimate by only 7%.

COMMENT

To our knowledge, this is the first comprehensive meta-analysis of cognitive functioning in subjects at HR for psychosis. We found strong evidence for a consistent impairment of performance in at-risk groups across different centers and HR inclusion criteria. Compared with controls, HR subjects showed deficits in the general intelligence, attention, executive function, verbal fluency, work-

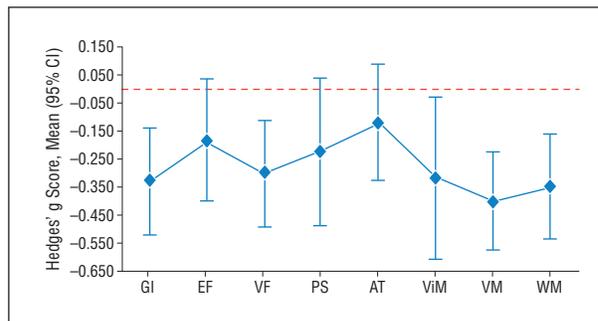


Figure 4. Cognitive functioning in clinical high-risk subjects who later developed psychosis (HR-T) compared with HR subjects who did not develop a psychotic disorder (HR-NT). Hedges' g scores (mean and 95% CI) across cognitive domains are given (negative values indicate worse performance in HR subjects who later developed psychosis compared with HR subjects who did not develop a psychotic disorder). The dotted red line (Hedges' $g = 0$) indicates no significant difference between HR-T and HR-NT. AT indicates attention; EF, executive functioning; GI, general intelligence; PS, processing speed; VF, verbal fluency; VIM, visual memory; VM, verbal memory; WM, working memory.

ing memory, and verbal and visual memory domains, while no differences were observed in the processing speed domain. Age and sex influenced cognitive performance of the HR subjects. Over and above these findings, we showed that subsequent transition to psychosis was characterized by additional impairments in verbal fluency, visual and verbal memory, and working memory.

Because this meta-analysis was well powered, characterized by low heterogeneity across studies, and not undermined by significant publication bias, we conclude that cognitive impairment distinguishes HR patients from healthy comparison subjects. According to the criteria established by Cohen, the magnitude of the observed cognitive impairments in the HR subjects was small to moderate. This finding is in line with studies comparing HR subjects and subjects with a first episode of illness, showing that cognitive deficits in subjects at risk for psychosis are less marked than those observed during the first episode of illness.⁵⁹ Moreover, meta-analyses of genetic high-risk samples revealed neurocognitive deficits in unaffected adolescents⁶⁴ and adult first-degree relatives, with similar effect sizes.⁶⁵ Our results indicate that vulnerability to psychosis is associated with significant cognitive impairment. Although the majority of HR subjects will not develop a psychotic episode over time,¹⁷ these findings are of great interest for preventive interventions in psychosis. Cognitive deficits in HR subjects may account for the presenting symptoms and problems, which are often more of a concern to subjects than their long-term risk of transition.⁶⁶ Cognitive dysfunction has been associated with a range of crucial outcomes in psychotic disorders including relapse rates, time spent in the hospital, levels of symptoms, social functioning, vocational functioning (ie, work or education), treatment resistance, and independent living/residential status.⁶⁷ Because most of these outcomes have been found to be already impaired during the prepsychotic phase,⁶⁶ preventive interventions may aim at remediating cognitive impairments and reducing poor functional outcomes.¹⁰ The impaired cognitive functioning in HR subjects is also in line with underlying anomalies in the brain function,¹⁴ structure,⁶⁸ and neurochemistry.^{69,70}

Although we found a statistically significant lower general intelligence in HR subjects compared with matched controls, the magnitude of neurocognitive impairments in the HR subjects was not the same across all the examined domains. The extent of HR neurocognitive deficits varied from attention, executive function, verbal fluency, working memory, and verbal and visual memory, with the latter domains being the most impaired. Conversely, no significant differences between HR subjects and controls were elicited in the processing speed domain. To better clarify the specific neurocognitive profile of vulnerability to psychosis, we individually analyzed the single neurocognitive tasks clustered in each cognitive domain. We confirmed that most tasks addressing processing speed (except the Digit Symbol Substitution Test) uncovered no significant neurocognitive deficits. This result is not surprising as previous meta-analyses in schizophrenia indicated that across different measures of processing speed, the Digit Symbol Substitution Test coding yields the largest impairments.⁷¹ Additional evidence shows the processing speed, as measured by the Digit Symbol Substitution Test, is particularly good in capturing the neurocognitive dysfunction during the early phases of psychosis.⁷² Of interest, there were selective deficits across different neurocognitive tasks. Thus, HR subjects were significantly impaired on the California Verbal Learning Test immediate recall but not delayed recall task and in the semantic but not phonological verbal fluency tasks. When considering the smallest confidence intervals, our meta-analysis indicated that the HR subjects were best distinguished from controls on the performance of the Digit Symbol Substitution Test, Letter Number Sequencing task, and Continuous Performance Test.

Our secondary aim was to clarify the cognitive alterations associated with later transition to psychosis. We thus conducted a sub-meta-analysis of HR-T vs HR-NT. We found that baseline neurocognitive impairments in general intelligence, verbal fluency, verbal and visual memory, and working memory were associated with the onset of psychosis within 19 months of baseline assessment. These findings are in line with recent evidence indicating that most HR subjects develop psychosis within the first two years after baseline assessment.¹⁷ The association between neurocognitive deficits and onset of psychotic episode also suggests possible targets for cognitive remediation strategies. Cognitive Enhancement Therapy has been shown to exert neurobiological protective effects in early psychosis that are associated with improved long-term outcomes⁷³ and may thus be considered as a new potential clinical intervention in the HR population. This finding is also of great relevance to improve the predictive value of current psychopathological HR criteria.¹⁷ In this scenario, some studies have already shown that prediction of transitions in HR cohorts could be improved by a stronger weighting of neurocognitive tests in a stepwise risk assessment.⁵⁷ With these predictors in an integrated model for predicting transition to psychosis, the overall predictive accuracy was about 80% with a good sensitivity and specificity.⁵⁷ More recent studies used multivariate neurocognitive pattern classification to facilitate the HR diagnosis and the individualized prediction of illness transition.⁵⁴

Over the past years, a number of studies have investigated social cognition in HR subjects, in addition to the

earlier-mentioned traditional neurocognitive measures.^{6,74} Despite the different methods used across studies, at the meta-analytical level, we found a significant impairment in social cognition of HR subjects as compared with controls. Furthermore, the magnitude of such a deficit exceeded any of the examined neurocognitive domains. This is in line with a large body of research indicating that traditional neurocognitive measures do not account for the total variance in functional outcome of psychosis.⁷ In comparison with basic neurocognitive assessments, measures of social cognition have been shown to be better predictors of functional and psychosocial outcomes in established disease.⁷ Impairments in social cognition associated with established psychosis range from deficits in theory of mind,⁷⁵ which assesses one's ability to comprehend the intentions of others; deficits in social perception and social knowledge,⁷⁶ both of which refer to the ability to use social cues (eg, gestures) and apply social rules to a complicated situation; and emotion processing deficits in expression and recognition of facial and prosodic affect.⁷⁷ Overall, we showed these impairments are already evident during the phases preceding the psychotic episode, although we were unable to test their association with psychosis transition. Because HR individuals are experiencing important developmental shifts in interpersonal relationships that are common during this developmental period,⁷ the investigation of social cognition in HR individuals may represent a unique entry point for the exploration of factors that contribute to poor psychosocial functioning⁷⁸ observed during the prodromal period^{79,80} and for the identification of specific social cognitive deficits that increase risk for subsequent conversion to psychosis.⁸¹ Because processing socially relevant information also relies on traditional neurocognitive abilities (ie, attention or memory), future research is needed to clarify the relationship between these two domains during the prepsychotic phases.⁶

We further addressed the role played by a number of potential moderators influencing cognitive performance in HR subjects. Publication year had no effect on cognitive performance. Similarly, we found no evidence that exposure to antipsychotic medication influenced cognitive functioning in HR subjects. However, only a few HR subjects were prescribed antipsychotics, and because of the cross-sectional nature of our analysis, we were not able to establish whether medications may change the natural course of the development of cognitive deficits. Age of participants had a small albeit significant effect on the cognitive performance of HR subjects. The finding of age-related cognitive performance has long been known in established psychosis and in healthy subjects⁸² and should be carefully addressed in future cognitive studies of HR subjects. Further, it is not clear if this could be referred to as an age effect per se or could support the perspective of a more direct impact of the disease on cognition, in which cognition could be less affected in the early, rather than late, prodromal phase. Another sociodemographic variable with a trend-level significance was sex, with females performing better than males. This result is consistent with previous studies that reported more pronounced cognitive dysfunction in male participants with schizophrenia.^{75,83} Again, in the per-

spective of a direct impact of the disease on cognition, this difference could be due to the well-established knowledge of later onset in females. A follow-up study of HR subjects and genetic high-risk groups suggests that family history may be an important component in yielding a more sensitive prediction model. Different neuropsychological profiles between the two groups, with significantly more deficits in the subjects with a family history of psychosis, were shown.⁴⁷ Finally, we tested whether HR inclusion criteria modulated cognitive performance. At present, there are no evidence-based standardized means of assessing and defining the HR state, nor of defining the transition to psychosis.^{10,28,84} The field of psychopathological assessment instruments is currently dominated by two main approaches: UHR and BS. The first approach focuses on the attenuated positive symptoms, while the latter is based on a detailed phenomenological way of describing subjective disturbances before onset of psychosis.¹⁰ We found that cognitive impairment was less marked in studies using the BS approach, intermediate in studies adopting the UHR approach, and more pronounced in studies combining the two approaches. However, these differences were statistically nonsignificant, presumably in light of the limited number of studies included in this subanalysis. We speculate that the inclusion of a further “cognitive” group²⁸ in the UHR criteria may eventually increase the sensitivity of early detection methods to the subtle cognitive disturbances evident during the prodromal phases and better identified in the BS approach.¹⁰

Limitations of the present study are well acknowledged. Although we have uncovered an association between neurocognitive deficits and transition to psychosis, the studies included were mainly cross-sectional. To exactly determine the pattern of neurocognitive deterioration, longitudinal studies⁶¹ are required to compare neurocognitive functioning of the same HR sample before and after a psychotic episode. Also, the trajectory of HR subjects with “stable” vs “declining” neurocognitive functioning should be of interest. This will potentially enhance understanding of how HR neurocognition and outcome are related and may help predict who is likely to benefit from particular interventions. Finally, because of limited data available in the current literature, it was not possible to distinguish the cognitive profile of affective vs schizophrenic psychoses.¹⁰

In conclusion, this meta-analysis indicates that, despite comprising studies that varied in the method of subject ascertainment and the criteria used to define the HR, there are consistent impairments in cognitive functioning in HR subjects as compared with matched controls. Significant deficits are observed in the general intelligence, attention, executive function, verbal fluency, working memory, verbal and visual memory, and social cognition, while no differences were observed in processing speed considered as a whole domain. Age and sex modulated cognitive functioning in the HR subjects. Impairment in verbal fluency and memory functioning were associated with the onset of psychotic symptoms and may be useful in predicting psychosis and targeting early interventions.

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Correspondence: Paolo Fusar-Poli, MD, PhD, Department of Psychosis Studies, Institute of Psychiatry, De Crespigny Park PO63, SE58AF London, England (p.fusar@libero.it).

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