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NEUROCOGNITIVE FUNCTIONING IN INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS: SYSTEMATIC REVIEW AND META-ANALYSIS

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KEY POINTS

Question

What is the updated evidence-based consistency and magnitude of neurocognitive functioning in CHR-P individuals compared to healthy controls?

Findings

In this meta-analysis, the neurocognitive functioning of CHR-P individuals was compared to healthy controls and stratified across their longitudinal risk of developing psychosis. Converging evidence confirms substantial deficits on several neurocognitive tasks, some of which were associated with the longitudinal risk of psychosis onset. These findings were controlled for biases and several moderating factors.

Meaning

This meta-analysis provides state-of-the-art updated knowledge on neurocognitive deficits that differentiate CHR-P and controls or that relate to their longitudinal risk of developing psychosis. These findings may inform future detection strategies, the development of individualised prognostication algorithms and the refinement of effective preventive approaches.

Keywords: psychosis, schizophrenia, clinical high risk, cognition, MATRICS, prediction, prevention

ABSTRACT

Importance

Neurocognitive functioning is a potential biomarker to advance detection, prognosis and preventive care of individuals at Clinical High Risk for Psychosis (CHR-P). The current consistency and magnitude of neurocognitive functioning in CHR-P individuals are undetermined.

Objective

To provide an updated evidence synthesis of the consistency and magnitude of neurocognitive functioning in CHR-P individuals.

Data Sources

Web of Science database, Cochrane Central Register of Reviews, Ovid/PsycINFO and trial registries, up to 1 July 2020.

Study Selection

Multistep, PRISMA/MOOSE-compliant (PROSPERO protocol: CRD42020192826) literature search, performed by independent researchers to identify original studies reporting on neurocognitive functioning in CHR-P individuals.

Data Extraction and Synthesis

Independent researchers extracted the data, clustering the neurocognitive tasks according to 7 MATRICS and 8 CHR-P domains. Random-effect model meta-analyses, assessment of publication biases and study quality, and meta-regressions were conducted.

Main outcomes

The primary effect size measure was the Hedges' g of neurocognitive functioning in CHR-P individuals (i) compared to healthy controls (HC) or (ii) first-episode psychosis (FEP) or (iii) stratified for the longitudinal transition to psychosis.

Results

A total of 78 independent studies were included, consisting of 5162 CHR-P individuals (mean age 20.16, 49% females), 2865 HC (mean age 21.07, 52% females) and 486 FEP (mean age 23.03, SD=2.01, range 19.1-26.4, 55% females) individuals. Compared to HC, CHR-P individuals showed medium to large deficits on the Stroop Test: Word (ES=-1.17; 95%CI -1.86 to -0.48), HVLT-R (ES=-0.86; 95%CI -1.43 to -0.28), DST (ES=-0.74; 95%CI -1.19 to -0.29), BACS SC (ES=-0.67; 95%CI -0.95 to -0.39), UPSIT (ES=-0.55; 95%CI -0.97 to -0.12), Hinting (ES=-0.53; 95%CI -0.77 to -0.28), RAVLT (ES= -0.50; 95%CI -0.78 to -0.21), CVLT (ES=-0.50; 95%CI -0.64 to -0.36) and NART (ES=-0.52; 95%CI -1.01 to -0.03) tasks. CHR-P were less impaired than FEP individuals. Longitudinal transition to psychosis from a CHR-P state was associated with medium to large deficits in the CVLT task (ES=-0.58; 95%CI -1.12 to -0.05). Meta-regressions found significant effects for age and education on processing speed.

Conclusions and Relevance

Meta-analytical evidence supports neurocognitive dysfunction as a potential detection and prognostic biomarker in CHR-P individuals. These findings may advance clinical research and inform preventive approaches.

INTRODUCTION

Indicated prevention (for details see[1]) in young people at Clinical High Risk for Psychosis (CHR-P)[2] is a promising avenue for enhancing clinical outcomes[3-5]. Neurocognitive dysfunction may represent a useful biomarker to identify CHR-P individuals and refine their risk of developing psychosis (30% at 4-years), which is fiftyfold higher than the general population[6]. Furthermore, neurocognitive functioning is a core successful delivery of the recommended preventive cognitive behavioural therapy[7]. Establishing reproducible, robust neurocognitive biomarkers serves a critical need to advance individualised clinical research knowledge[89] and tailored interventions, which are currently lacking[10].

Following our earlier meta-analysis[11], a number of other evidence syntheses have characterized neurocognitive functioning in CHR-P individuals[12-17]; since the last one, many more studies have been released at a rapid pace, making periodic reviews essential. The main aim of the present study is to provide a meta-analytical examination of the consistency and magnitude of neurocognitive functioning in CHR-P individuals.

METHODS

This review (study protocol registered on PROSPERO-CRD42020192826) was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, eTable 1)[18], MOOSE (eTable 2)[19], and EQUATOR guidelines[20].

Search strategy and selection criteria

A systematic, multistep literature search (search terms appended in eMethods 1) was implemented by two independent researchers (AC & GSP), consistent with our previous study[12]. Web of Science database (Clarivate Analytics), incorporating the Web of Science

Core Collection, BIOSIS Citation Index, KCI-Korean Journal Database, MEDLINE, Russian Science Citation Index, and SciELO Citation Index, as well as Cochrane Central Register of Reviews, PubMed and Ovid/PsycINFO databases were searched until 1 July 2020. Articles identified were screened as abstracts, and after the exclusion of those not relevant, the full texts were assessed for eligibility. The references of previously published meta-analyses and systematic reviews and of the articles included were then manually searched.

Inclusion criteria were: a) original articles published in a peer-reviewed journal; b) studies including CHR-P individuals (defined according to validated CHR-P psychometric interviews, eMethods 2); c) studies focusing on neurocognitive tasks (see below and eMethods 2); d) studies including a control group, preferably HC or stratifying the neurocognitive functioning according to longitudinal transition to psychosis; e) studies written in English. Exclusion criteria were: a) reviews, clinical cases, abstracts, conference proceedings, or study protocols, b) studies using non-established CHR-P psychometric interviews (eMethods 2), c) studies not reporting meta-analysable data, d) studies that reported only composite neurocognitive data (to avoid potentially spurious or pseudo specific results[13]), e) studies lacking an HC group and/or data stratification on the transition to psychosis, f) studies overlapping on the same sample and neurocognitive task. Corresponding authors were contacted by email to retrieve additional information. To further minimise data missingness, we used WebPlotDigitizer[22] to extract data that were only available in figures[23]. When there were two or more overlapping studies, the largest one was chosen.

Outcome Measures and Data Extraction

Three researchers (CA, SD, VS) independently extracted data from all identified studies (eMethods 4). The databases were then cross-checked, and discrepancies were resolved through consensus under the supervision of a senior researcher (PFP).

Consistent with our earlier meta-analysis[12], neurocognitive tasks were clustered into 7 MATRICS domains[21,24]: (1) processing speed, (2) attention/vigilance, (3) working memory, (4) verbal learning, (5) visual learning, (6) reasoning and problem-solving, and (7) social cognition (eMethods 3). To ensure the comprehensiveness of our review, we also considered additional CHR-P tasks that had been included in studies of this population and that are not included in the more limited MATRICS framework (eMethods3). These tasks were categorised by senior experts (AG, WS) into the following 8 domains: (8) general intelligence, (9) premorbid Intelligence Quotient (IQ), (10) visuospatial ability, (11) verbal memory, (12) visual memory, (13) executive functioning, (14) motor functioning, and (15) olfaction.

Statistical analyses

The primary meta-analytical effect size measure was Hedges' g, with negative values reflecting worse functioning in CHR-P individuals compared to controls (or FEP, see below) or in CHR-P transitioning versus those not transitioning to psychosis.

For the main meta-analysis, each specific neurocognitive task (see full details in eMethods 3) was analysed separately when at least three independent studies were available. We conducted two primary comparisons of neurocognitive functioning: i) cross-sectional meta-analysis of CHR-P versus HC individuals and ii) longitudinal meta-analysis of CHR-P transitioning to psychosis versus those not transitioning.

Three supplementary meta-analyses included: iii) comparing neurocognitive functioning in CHR-P individuals to FEP individuals (when these contrasts were reported in the articles retrieved), iv) estimating the pooled CHR-P vs HC and CHR-P vs FEP effect sizes across each of the 15 neurocognitive domains and (v) in relation to transition to psychosis (eMethods 5).

We used a random-effects model[25] as heterogeneity was expected to be high. Heterogeneity was assessed using the Q statistic and I^2 index[26]. Publication biases were evaluated by visually inspecting funnel plots and performing Egger's test[27]. When publication biases were detected, "trim and fill "[28] sensitivity analyses[29] were employed. Study quality was assessed using a modified version of the Newcastle–Ottawa scale, previously validated in CHR-P meta-analyses[30,31] (eTable 3). When at least 7 studies were available, meta-regressions evaluated the impact of several factors (eMethods 5). Analyses were carried out with the Comprehensive Meta-Analysis Version 3 (Biostat, Englewood, NJ, USA)[32] and STATA version 16[33]. For a comprehensive glossary of terms, see eMethods 7.

RESULTS

Characteristics of the database

A total of 262 eligible studies were screened; 78 of them were included (Figure 1 and eTable 4) comprising 5162 CHR-P individuals (mean age 20.16 years, SD=3.25, range 12-29.01, 49% females) and 2865 HC (mean age 21.07 years, SD=3.56, range 12.58-29.23, 52% females) and 486 FEP individuals (mean age 23.03, SD=2.01, range 19.1-26.4, 55% females). The average education years were 11.86 (SD=1.64) for CHR-P, 13.02 (SD=1.69) for HC and 11.57 (SD=1.57) for FEP individuals. Within the CHR-P

group, 71.81% fulfilled attenuated psychotic symptoms (APS) criteria, 7.24% brief limited intermittent psychotic symptoms (BLIPS) criteria, 13.57% genetic risk and deterioration syndrome (GRD) and 7.39% basic symptoms (BS). At baseline, 19.9% of CHR-P individuals had been treated with antipsychotic medication (at any dosage).

Neurocognitive functioning in CHR-P individuals compared to HC

Within the 7 MATRICS domains (Figure 2), CHR-P individuals performed worse than HC in the following tasks (in descending order of magnitude): Stroop Test: Word (Stroop W) (ES=-1.17; 95%CI -1.86 to -0.48), Hopkins Verbal Learning Test-Revised (HVLT-R) (ES=-0.86; 96%CI -1.43 to -0.28), Digit Symbol Coding Test (DST) (ES=-0.74; 95%CI -1.19 to -0.29), Brief Assessment of Cognition Symbol Coding (BACS SC) (ES=-0.67; 95%CI -0.95 to -0.39), Hinting Task (ES=-0.53; 95%CI -0.77 to -0.28), Rey Auditory Verbal Learning Test (RAVLT) (ES=-0.50; 95%CI -0.78 to -0.21), California Verbal Learning Test (CVLT) (ES=-0.50; 95%CI -0.64 to -0.36), Wechsler Memory Scale Immediate Visual Memory (WMS VM) (ES=-0.49; 95%CI -0.73 to -0.25), Brief Visuospatial Memory Test-Revised (BVMT-R) (ES=-0.47; 95%CI -0.66 to -0.28), Letter Number Span (LNS) (ES=-0.46; 95%CI -0.57 to -0.34), Wechsler Memory Scale-III Spatial Span Subtest (WMS-III: SS) (ES=-0.43; 95%CI -0.60 to -0.27), Neuropsychological Assessment Battery Mazes (NAB Mazes) (ES=-0.46; 95%CI -0.74 to -0.19), Animal Fluency (ES=-0.39; 95%CI -0.54 to -0.24), Continuous Performance Test-Identical Pairs version (CPT–IP) (ES:0.39; 95%CI -0.49 to -0.29), Letter Number Sequencing Test (LNST) (ES=-0.39; 95%CI -0.57 to -0.22), Trail Making Test – Part A (TMT-A) (ES=-0.34; 95%CI -0.59 to -0.09) and Letter Fluency (ES=-0.31; 95%CI -0.59,-0.04) (Figure 2, eTable 5) task. There were no differences in the Stroop Test: Colour (Stroop C), Arithmetic, Rey–Osterrieth Complex Figure Immediate Recall (ROCF),

Degraded Facial Affect Recognition (DFAR), Self-Ordered Pointing Test (SOPT) and Reading the Mind in the Eyes Test (RMET) (Figure 2, eTable 5).

Within the 8 CHR-P domains (Figure 3, eTable 5), CHR-P individuals performed worse than HC (in descending order of magnitude) in the following tasks: Wechsler Memory Scale Visual Reproduction Delayed Recall (WMS VR) (ES=-0.75; 95%CI -1.36 to -0.14, uncorrected publication bias), University of Pennsylvania Smell Identification Test (UPSIT) (ES=-0.55; 95%CI -0.97 to -0.12), National Adult Reading Test (NART) (ES=-0.52; 95%CI -1.01 to -0.03), RAVLT Delayed Recall (RAVLT DR) (ES=-0.45; 95%CI -0.67 to -0.22), and Trail Making Test – Part B (TMT-B) (ES=-0.49; 95%CI -0.72 to -0.27), Wisconsin Card Sorting Test (WCST) categories (ES=-0.36; 95%CI -0.66 to -0.07), ROCF Delayed Recall (ROCF DR) (ES=-0.34; 95%CI -0.65 to -0.03), MehrfachWortschaftz-Intelligenz Test-Part B (MWT-B) (ES=-0.33; 95%CI -0.62 to -0.03), Wechsler Adult Intelligence Scale / Wechsler Intelligence Scale for Children Block Design (WAIS/WISC BD) (ES=-0.32; 95%CI -0.44 to -0.2), IQ (ES=-0.31; 95%CI -0.45 to -0.17), WCST perseverative responses (ES=-0.25; 95%CI -0.45 to -0.05), Tapping (ES=-0.24; 95%CI -0.45 to -0.04), WCST perseverative errors (ES=-0.15; 95%CI -0.29 to -0.01, corrected after publication bias). There were no differences in the Stroop Test: Interference, IQ verbal, IQ performance, and WSCT number of correct responses (Figure 3, eTable 5).

Neurocognitive functioning in CHR-P individuals associated with transition to psychosis

Within the subset of longitudinal studies analysing transition to psychosis (*k*=22), CHR-P individuals transitioning to psychosis (Figure 4, eTable 6) presented worse neurocognitive functioning than those not transitioning (in descending order of

magnitude): CVLT (ES=-0.58; 95%CI -1.12 to -0.05), ROCF DR (ES=-0.44; 95%CI -0.74 to -0.14), WCST perseverative errors (ES=-0.42; 95%CI -0.77 to -0.07, corrected after publication bias), DST (ES=-0.39; 95%CI -0.63 to -0.14, uncorrected publication bias), CPT-IP (ES=-0.29; 95%CI -0.51 to -0.08), TMT-A (ES=-0.29; 95%CI -0.48 to -0.09) and IQ (ES=-0.26; 95%CI -0.4 to -0.11). There were no differences in the Animal Fluency, LNST, NART, Tapping and UPSIT tests (Figure 4, eTable 6).

Supplementary meta-analyses

Compared to FEP (Figure 5, eTable 7), CHR-P individuals presented better IQ (ES=0.63; 95%CI 0.35 to 0.91), HVLT-R (ES=0.58; 95%CI 0.22 to 0.95), CVLT (ES=0.40; 95%CI 0.20 to 0.60), WCST perseverative errors (ES=0.37; 95%CI 0.16 to 0.57), WCST categories (ES=0.25; 95%CI 0.01 to 0.50), but were similarly impaired in the Stroop Test: Interference, TMT-A, NART (publication bias detected), and TMT-B tests.

When all neurocognitive tasks were pooled across the 15 broader neurocognitive domains, CHR-P individuals performed more poorly than HC across all domains (in decreasing order of magnitude): olfaction (ES=-0.55; 95%CI -0.97 to -0.12), verbal learning (ES=-0.51; 95%CI -0.63 to -0.39), reasoning and problem-solving (ES=-0.46; 95%CI -0.74 to -0.19), visual memory (ES=-0.45; 95%CI -0.77 to -0.13), verbal memory (ES=-0.45: 95%CI -0.67 to -0.22), working memory (ES=-0.44; 95%CI -0.57 to -0.31), visual learning (ES=-0.43; 95%CI -0.57 to -0.29), executive functioning (ES=-0.42; 95%CI -0.60 to -0.24), general intelligence (ES=-0.39; 95%CI -0.57 to -0.22), processing speed (ES=-0.39; 95%CI -0.56 to -0.21), attention/vigilance (ES: -0.39; 95%CI -0.49 to -0.29), premorbid intelligence (ES=-0.38; 95%CI -0.63 to -0.13), visuospatial ability (ES=-0.32; 95%CI -0.44 to -0.2), social cognition (ES: -0.29; 95%CI -0.50 to -0.07), and

motor functioning (ES=-0.24; 95%CI -0.45 to -0.04) (eFigure 1; eTable 8). CHR-P performed better than FEP in general intelligence (ES=0.63; 95%CI 0.35 to 0.91), verbal learning (ES=0.46; 95%CI 0.29 to 0.61), and executive functioning (ES=0.33; 95%CI 0,11 to 0.56) (eFigure 3; eTable 10). Longitudinal transition to psychosis was associated with neurocognitive deficits in the verbal learning (ES=-0.58; 95%CI -1.12 to -0.05), visual memory (ES=-0.44; 95%CI -0.74 to -0.14), processing speed (ES=-0.39; 95%CI -0.59 to -0.19), attention/vigilance (ES=-0.29; 95%CI -0.51 to -0.08), and general intelligence (ES=-0.26; 95%CI -0.4 to -0.11) domains (eFigure 2; eTable 9).

Heterogeneity, publication bias and meta-regression

Heterogeneity across studies was moderate to high (eTable 5-eTable 7). The quality rating of the studies ranged from 4 to 8 (average=5.8; median=6, eTable 3). Publication bias are reported in eTable5-eTable 7, eFigure 4-eFigure 20). Meta-regressions for the CHR-P vs HC analysis revealed that greater age (ß=-0.06, p=0.022) and fewer years of education (ß=0.17, p=0.003) were associated with greater processing speed impairments (although several meta-regressions were not feasible: eResults 1 and eTables 11-13).

DISCUSSION

This meta-analysis identified medium to large neurocognitive deficits in CHR-P individuals compared to HC and FEP. Some of these deficits were associated with the longitudinal transition to psychosis.

To our best knowledge, this is the largest meta-analysis characterizing neurocognitive functioning in CHR-P to date. Compared to previous meta-analyses (encompassing from 6 to 49 studies with up to 2506 CHR-P individuals; 32 studies published from 2015-

2020)[12,13,16,17,34-38], we included many more studies (n=78) and participants (5162 CHR-P, 2865 HC and 486 FEP individuals). Our larger sample size confers greater statistical power, which is essential for accurate estimates of biomarkers, in particular for relatively infrequent events such as transition to psychosis[9,10]. Compared to older meta-analyses, this study employed the most comprehensive CHR-P neurocognitive classification scheme by extending the standard 7 MATRICS domains with additional domains frequently employed for CHR-P individual. A further merit is adoption of a complementary analytic approach focusing both on specific neurocognitive tasks and on broader neurocognitive domains.

The first main finding is of a widespread impairment of neurocognitive functioning in CHR-P individuals compared to HC, encompassing all neurocognitive domains, albeit to varying degrees. Overall, these updated findings align with and elaborate previous CHR-P meta-analyses[11-14,16,17,34,35,38]. Given the replication crisis in psychiatry, rapid pace of CHR-P publications and unstable findings (e.g. earlier meta-analytic efficacy of CHR-P preventive interventions[39] has recently been disconfirmed[40]), comprehensive and confirmatory evidence is essential to consolidate reliable clinical knowledge. At the same time, domain-level differences were noted in reasoning and problem-solving, working memory[13] and processing speed[12]. These discrepancies are likely due to the inclusion of more studies (e.g., Tapping: 4 compared to 3[13]; reasoning and problem solving: 8 compared to 4[13]), more rigorous meta-analytical methods to compute pooled estimates (not acknowledged in[34,35]), new tasks[34,35] (e.g. task DFAR had not been analysed before) and different task categorization methods (e.g. task Facial Affect Labeling Test was included in social cognition in[13] but not here and WCST perseverative errors/responses were included in executive functioning[13] in but not here). As noted above, we observed

high variability within different neurocognitive domains. For example, within the processing speed domain, performance on the Stroop W but not the Stroop C was impaired in CHR-P vs HC.

Our second main finding includes having analysed and identified specific, task-level neurocognitive dysfunctions in CHR-P individuals compared to HC or FEP. This is essential to allow accurate reproducibility and implementation of neurocognitive biomarkers in clinical research. Neurocognitive tasks that are more likely to distinguish CHR-P from HC individuals (i.e. have moderate to large effect sizes) include the Stroop W[41], HVLT-R[42], DST[43], BACS SC[44], Hinting Task[45], RVALT[46], UPSIT[47] and NART[48] (see eDiscussion 1). These tasks were all impaired in previous meta-analyses[12-14,17] except the Stroop W[13,14], although some of them (HVLT-R, BACS SC, Hinting, UPSIT, and NART[12,13]) were not analysed. The administration time of these tests ranges from 2-10 (Stroop W[41], HVLT-R[42], DST[43], BACS SC[44], NART[48]) to 20-40 minutes (RVALT[46], Hinting Task, UPSIT[47]), and some of them can be administered via digital devices, facilitating their usability. More to this point, some of these dysfunctions have demonstrated neurobiological correlates in CHR-P individuals[49,50]. This converging evidence suggests that these neurocognitive tasks are good candidates to help distinguish CHR-P individuals from their typically developing peers. In supplementary analyses, we also found that some of these tasks (e.g. HVLT-R, CVLT) can help to distinguish CHR-P from FEP individuals, which is another essential clinical step in the management of young people accessing preventive services[51]. Several other neurocognitive tasks can also differentiate CHR-P from HC but at a lower magnitude (i.e. small to medium effect sizes). Notably, biomarkers with an individual small effect could still hold some value within multivariate approaches, but at the cost of complexity and logistic challenges. Overall,

neurocognitive biomarkers consolidated by this meta-analysis could be further validated by future studies for improving the identification of CHR-P individuals, a key rate-limiting step toward large-scale preventive efforts[52].

The third main finding is that baseline neurocognitive impairments in verbal learning, visual memory, processing speed, attention/vigilance, and general intelligence were associated with the longitudinal risk of psychosis onset. These findings align with earlier meta-analyses[12,13], except for the working memory domain. The latter discrepancy may be due to the inclusion of new individual studies reporting different findings[50] (e.g. higher LNST scores for CHR-P who transitioned to psychosis compared to those who did not develop the disorder). The neurocognitive tasks that are more likely to predict psychosis onset within CHR-P individuals encompass the CVLT (medium to large effect sizes) and, to a lesser extent, the TMT-A, CPT-IP and IQ (small to medium effect sizes). These potentially prognostic biomarkers are ideal candidates to refine existing individualised multivariable prediction models that integrate multimodal domains (e.g. clinical, neuroimaging, electrophysiological and neurocognitive) predictors[53,54]. A further downstream clinical impact of these findings may be to present an opportunity for refining preventive interventions. At the moment, no effective pharmacological or psychological interventions are available to ameliorate neurocognitive deficits in CHR-P individuals[55,40], and recent neurocognitive remediation trials have produced negative findings[56,57].

We tested several potential moderators of neurocognitive functioning. Younger age was associated with increased neurocognitive impairments between CHR-P and HC, while more years of education were related to decreased differences. Age[58] and education

level[24] are consistently related to neurocognitive function. Importantly, we found no evidence that baseline antipsychotic exposure was associated with neurocognitive functioning. This may align with recent findings showing no evidence that current interventions have a robust impact on clinical outcomes in CHR-P samples[40,55,59]. However, several meta-regressions were underpowered or not feasible due to the lack of data.

This meta-analysis presents some limitations. The validity of these findings is limited mostly to help-seeking samples and cannot be transported to the general population[60]. As neurocognitive functioning is a main determinant of developmental transdiagnostic psychopathology across different psychiatric disorders (and a major domain of the RDoC initiative[61]), transdiagnosticity of these neurocognitive dysfunctions needs further comparative studies with other psychiatric samples[62]. Furthermore, the longitudinal (i.e. transition) estimates were based on a significantly smaller dataset than the cross-sectional analyses. Additionally, like any other biomarker in this field, the magnitude of the observed effect sizes was largely modest and would not likely support accurate univariate prediction. Large-scale international CHR-P consortia recently completed (e.g. NAPLS-3[63], PRONIA[64], PSYSCAN[65], HARMONY[66]) are expected to test if sequential assessment frameworks[67,68] integrating multivariable predictors across modalities can deliver improved prediction models for clinical practice (eLimitations).

Conclusions

Meta-analytical evidence supports neurocognitive dysfunction as a potential detection and prognostic biomarker in CHR-P individuals. These findings characterise the

neurocognitive features of psychosis risk states and can advance clinical research and inform multivariable prediction and preventive approaches.

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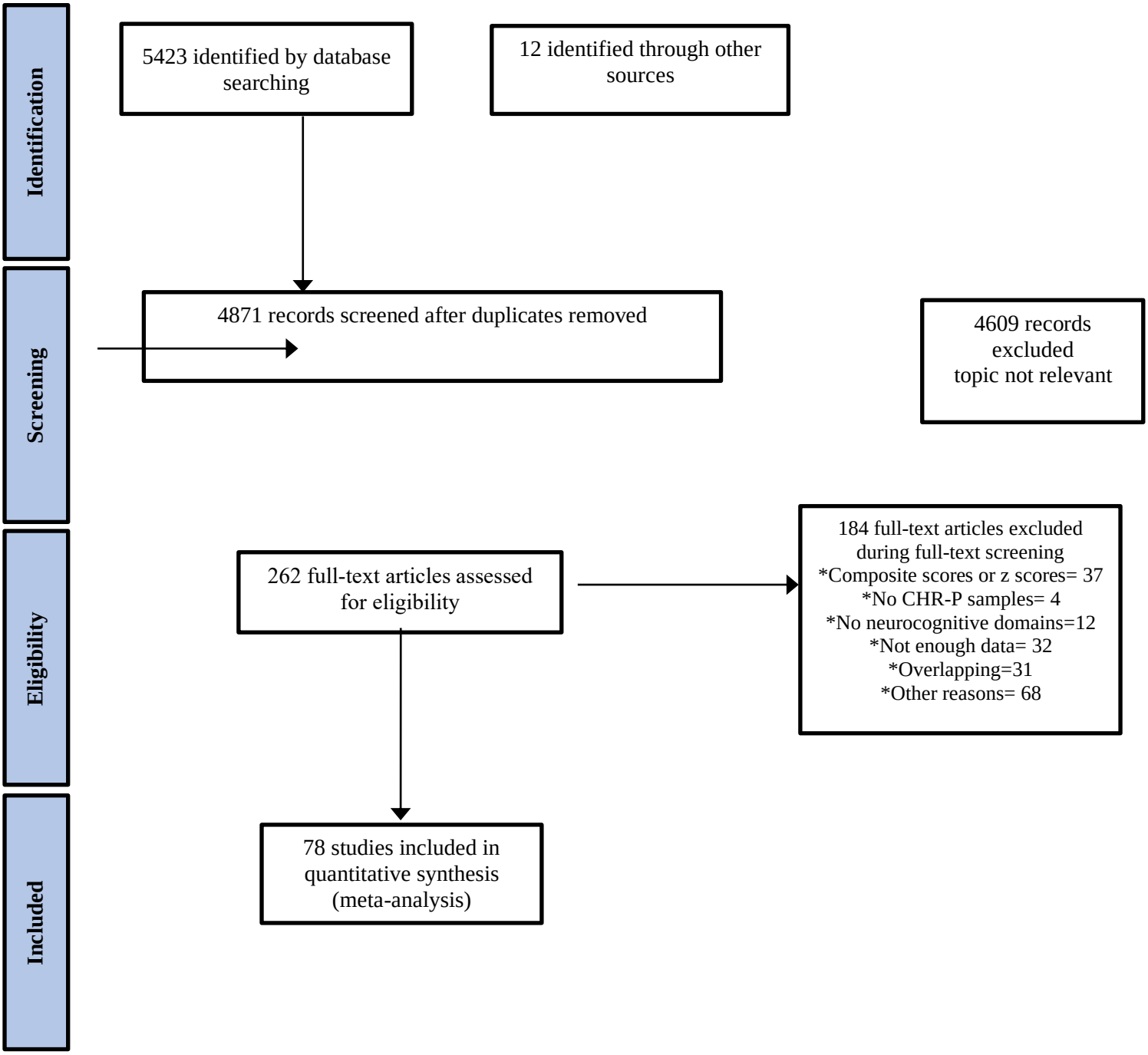
Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart outlining the study selection process



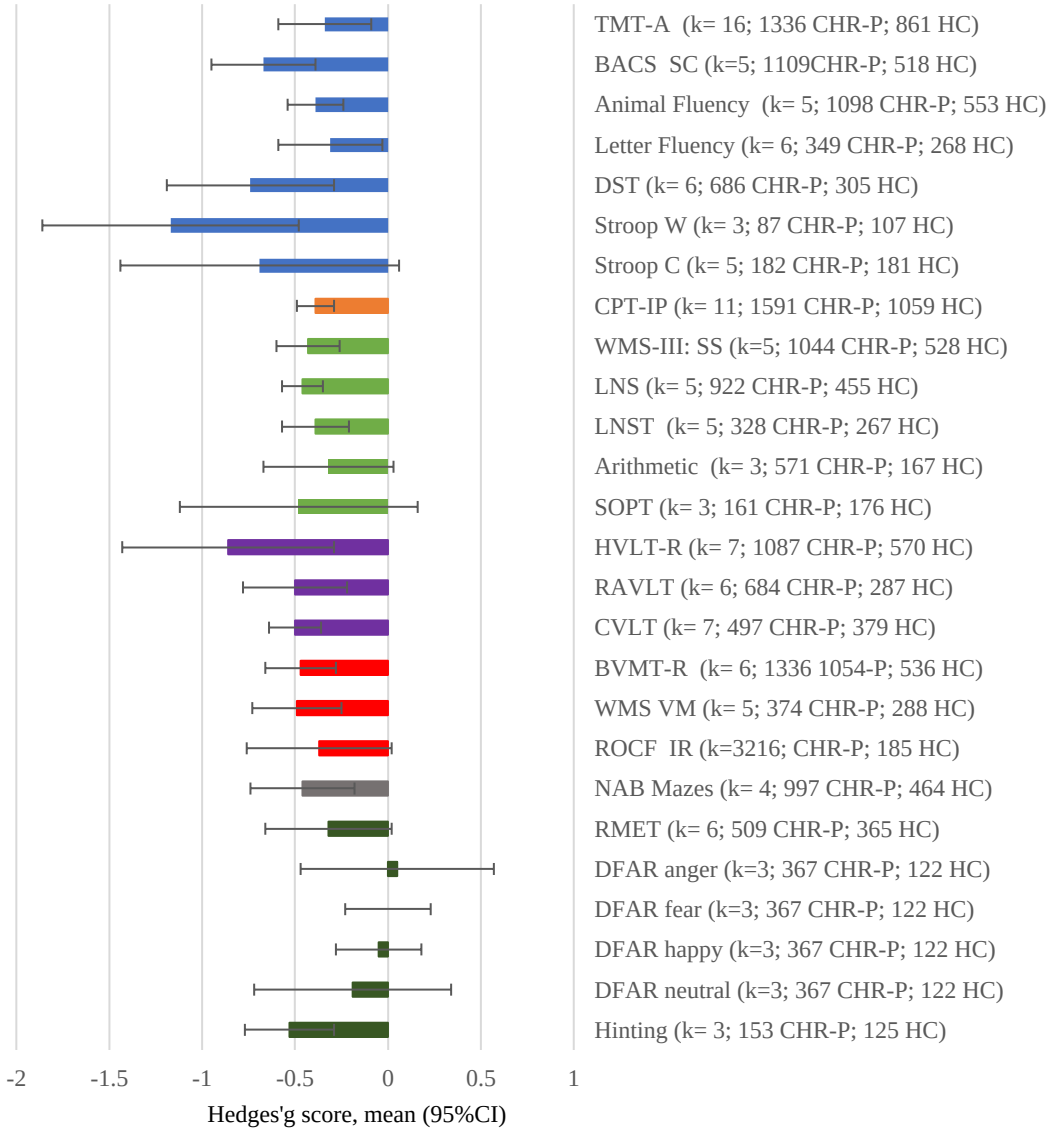


Figure 2. Neurocognitive task-level functioning of CHR-P individual compared with HC across the 7 MATRCIS domains. Hedges' g scores (mean and 95% CI) are given (negative values indicate worse functioning in the CHR-P vs the HC group), along with number of studies included (k) and sample size. TMT-A, Trail Making Test-Part A; BACS SC, Brief Assessment of Cognition Scale Symbol Coding; DST, Digit Symbol Coding Test; Stroop W, Stroop Test: Word ; Stroop C, Stroop Test: Colour; CPT-IP, Continuous Performance Test-Identical Pairs; WMS-III: SS, Wechsler Memory Scale III: Spatial Span; LNS, Letter Number Span; LNST, Letter Number Sequencing Test; SOPT, Self-Ordered Pointing Task; HVLT-R, Hopkins Verbal Learning Test-Revised; RAVLT, Rey Auditory Verbal Learning Test; CVLT, California Verbal Learning Test; BVMT-R, Brief Visuospatial Memory Test Revised; WMS VM Weschler Memory Scale Visual Memory; ROCF, Rey-Osterrieth Complex Figure Test Immediate Recall; NAB Mazes, Neuropsychological Assessment Battery Mazes; RMET, Reading the Mind in the Eyes Test; DFAR, Degraded Facial Affect Recognition.

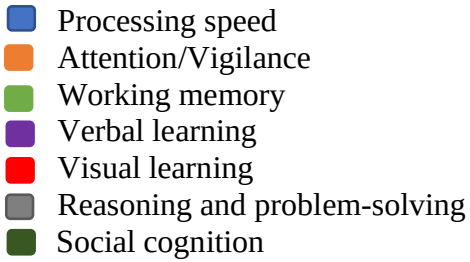


Figure 3. Neurocognitive task-level functioning of CHR-P individual compared with HC across the CHR-P domains.
Hedges' g scores (mean and 95% CI) are given (negative values indicate worse functioning in the CHR-P vs the HC group), along with the number of studies included (k) and sample size. IQ, Wechsler Intelligence Scales full; IQ verbal, Wechsler Intelligence Scales verbal; IQ performance, Wechsler Intelligence Scales performance; NART, National Adult Reading Test; MWT-B, MehrfachWortschaftz-Intelligenz Test-Part B; RAVLT DR, Rey Auditory Verbal Learning Test Delayed Recall; ROCF DR, Rey-Osterrieth Complex Figure Test Delayed Recall; WMS VR, Weschler Memory Scale Visual Reproduction Delayed Recall; TMT-B, Trail Making Test-Part B; WCST categories, Wisconsin Card Sorting Test categories; WCST number of correct responses, Wisconsin Card Sorting Test number of correct responses; WCST perseverative errors, Wisconsin Card Sorting Test perseverative errors; WCST perseverative responses, Wisconsin Card Sorting Test perseverative responses; UPSIT, University of Pennsylvania Smell Identification Test.
*affected by publication bias

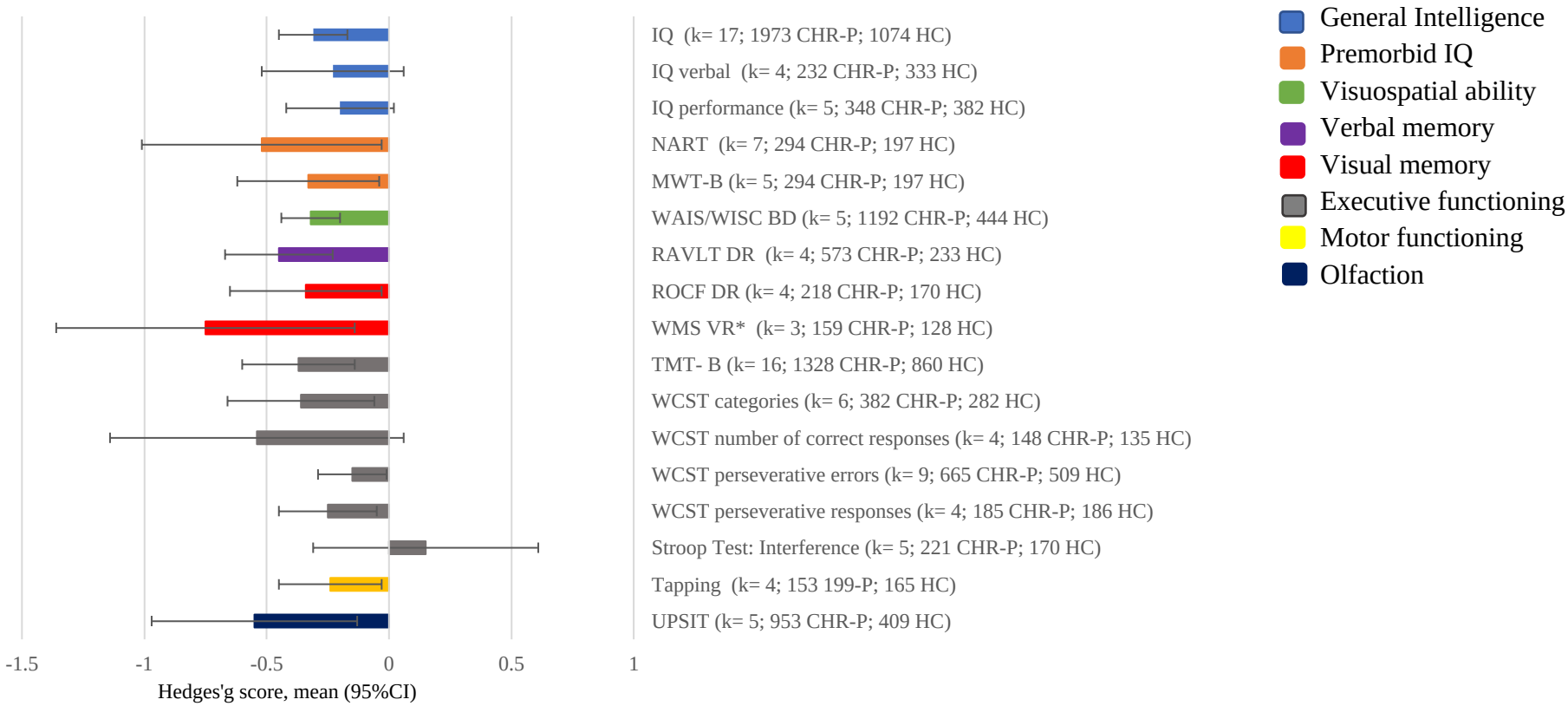


Figure 4. Neurocognitive task-level functioning of CHR-P individuals developing psychosis compared with those not developing it across the MATRICS and CHR-P domains. Hedges' g scores (mean and 95% CI) are given (negative values indicate worse functioning in the CHR-P transitioning vs non-transitioning group), along with the number of studies included (k) and sample size. TMT-A, Trail Making Test-Part A; DST, Digit Symbol Coding Test; CPT, Continuous Performance Test-Identical Pairs; LNST, Letter Number Sequencing Test; CVLT, California Verbal Learning Test; IQ, Wechsler Intelligence Scales full; NART, National Adult Reading Test; ROCF DR, Rey-Osterrieth Complex Figure Test Delayed Recall; WCST perseverative errors, Wisconsin Card Sorting Test perseverative errors; UPSIT, University of Pennsylvania Smell Identification Test. *affected by publication bias

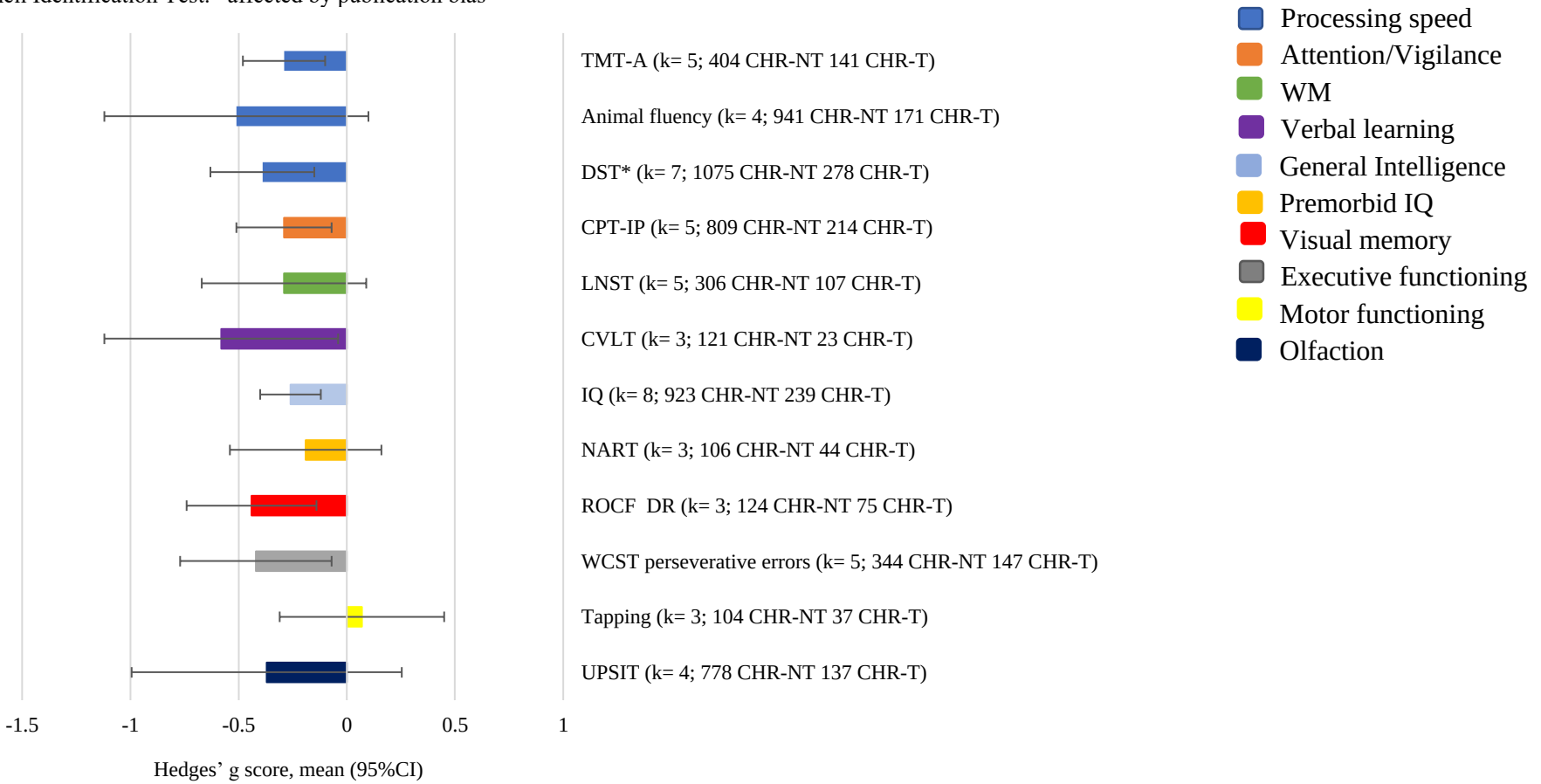


Figure 5. Neurocognitive task-level functioning of CHR-P individuals compared with FEP across MATRICS and CHR-P domains.
Hedges' g scores (mean and 95% CI) across neurocognitive tasks are given (negative values indicate worse functioning in CHR-P compared with the FEP group) along with sample size and the number of studies included (k). TMT-A, Trail Making Test Part A; HVLT-R, Hopkins Verbal Learning Test-Revised; CVLT, California Verbal Learning Test; IQ, Wechsler Intelligence Scales full; NART, National Adult Reading Test; TMT-B, Trail Making Test-Part B; WCST categories, Wisconsin Card Sorting Test categories; WCST perseverative errors, Wisconsin Card Sorting Test perseverative errors; IQ, Wechsler Intelligence Scales full. *affected by publication bias