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EXAMINING THE VARIABILITY OF NEUROCOGNITIVE FUNCTIONING
IN INDIVIDUALS AT CLINICAL HIGH RISK FOR PSYCHOSIS: A META-ANALYSIS

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ABSTRACT:

This study aims to meta-analytically characterize the presence and magnitude of within-group variability across neurocognitive functioning in young people at Clinical High-Risk for psychosis (CHR-P) and comparison groups. Multistep, PRISMA/MOOSE-compliant systematic review (PROSPERO-CRD42020192826) of the Web of Science database, Cochrane Central Register of Reviews and Ovid/PsycINFO and trial registries up to July 1, 2020. The risk of bias was assessed using a modified version of the NOS for cohort and cross-sectional studies. Original studies reporting neurocognitive functioning in individuals at CHR-P compared to healthy controls (HC) or first-episode psychosis (FEP) patients were included. The primary outcome was the random-effect meta-analytic variability ratios (VR). Secondary outcomes included the coefficient of variation ratios (CVR). 78 studies were included, relating to 5162 CHR-P individuals, 2865 HC and 486 FEP. The CHR-P group demonstrated higher variability compared to HC (in descending order of magnitude) in visual memory (VR: 1.41, 95%CI 1.02-1.94), executive functioning (VR: 1.31, 95%CI 1.18-1.45), verbal learning (VR: 1.29, 95%CI 1.15-1.45), premorbid IQ (VR: 1.27, 95%CI 1.09-1.49), processing speed (VR: 1.26, 95%CI 1.07-1.48), visual learning (VR: 1.20, 95%CI 1.07-1.34), and reasoning and problem solving (VR: 1.17, 95%CI 1.03-1.34). In the CVR analyses the variability in CHR-P population remains in the previous neurocognitive domains and emerged in attention/vigilance, working memory, social cognition, and visuospatial ability. The CHR-P group transitioning to psychosis showed greater VR in executive functioning compared to those not developing psychosis and compared to FEP groups. Clinical high risk for psychosis subjects show increased variability in neurocognitive performance compared to HC. The main limitation of this study us the validity of the VR and CVR as an index of variability which has received debate. This finding should be explored by further individual-participant data research and support precision medicine approaches.
INTRODUCTION

Compromised neurocognition is well-established as a core feature of psychotic disorders and is reliably though heterogeneously present in all phases of the illness (1-6), including premorbid stages (7) and clinical high risk states for psychosis (CHR-P) (8). CHR-P individuals have 20% likelihood of developing psychosis at 2-years which is not affected by the age at presentation or psychometric instruments used (9-11). CHR-P individuals as a group tend to demonstrate a neurocognitive deficit severity that is intermediary to healthy controls (HC) and those with a first episode of psychosis (FEP) (8, 12), and some neurocognitive deficits are reliably associated with the longitudinal transition to psychosis (8). Moreover, neurocognitive impairments associated with psychotic disorders and their risk states are among the most significant and consistent predictors of functional outcomes in both cross-sectional and longitudinal studies (13-16).

At the same time, it is equally well known that premorbid-developmental stages and diagnostic-clinical and functional outcomes among psychosis-spectrum groups at all stages are notably heterogeneous (17). The challenge of variability, and its impact on treatment responsiveness and prediction of longitudinal trajectories, is common across psychiatry research, and it has only recently been re-engaged as a focus of quantitative study. Inter-individual neurocognitive variability within psychosis-spectrum groups have been characterized by data-driven cluster analyses and commonly reveal three to four subgroups among adults with established illness (18, 19). In general, subgroups of individuals with schizophrenia-spectrum and bipolar disorders are most distinguished by differential levels of neurocognitive functioning (i.e., a near-normal, “spared” or intact cognition group, a globally or severely impaired group, and one or two subgroups with graded deficits across neurocognitive domains and often referred to as “selectively”
impaired or “intermediate” subtypes falling in between the extremes of near-normal and severely impaired (20-23). Substantial heterogeneity has been previously demonstrated for the CHR-P paradigm. A meta-analysis from our group showed high variability in the level of likelihood of transitioning to psychosis across CHR-P individuals, with those presenting with a Brief and Limited Intermittent Psychotic Episode having substantially higher risk than other subgroups (24-28). There is further evidence showing that most of CHR-P clinical heterogeneity is accounted for by the recruitment and sampling phase selecting individuals undergoing a CHR-P assessment (29-31). The challenge of clinical heterogeneity in CHR-P groups has become a mainstream focus of clinical research promoting the development of precision medicine approaches and the initiation of large-scale international research programmes to deconstruct it (32-34).

We recently completed a meta-analysis quantifying group mean differences in levels of performances across neurocognitive domains and tests. This study demonstrated a worse group-level neurocognitive performance in the olfaction, verbal learning, reasoning and problem-solving, visual memory, verbal memory, working memory, visual learning, executive functioning, general intelligence, processing speed, attention or vigilance, premorbid intelligence, visuospatial ability, social cognition, and motor functioning domains for CHR-P individuals compared to HC (8). And a better performance in the general intelligence, verbal learning and executive functioning neurocognitive domains compared to first-episode psychosis (FEP). This meta-analysis also found that those CHR-P individuals developing psychosis had worse neurocognitive functioning in the verbal learning, visual memory, processing speed, attention or vigilance, and general intelligence domains compared to those not developing psychosis.

Overall, these findings extends previous neurocognitive meta-analyses in this area (8, 35). Yet, these studies did not test whether these estimates are meaningfully representing a
largely universal average-effect across this heterogeneous population or whether it is confined to a subgroup of CHR-P individuals. (8, 35, 36).

The current study aims to expand our prior meta-analysis by studying the degree of inter-individual variability within CHR-P groups compared to HC and FEP groups. In other words, we hypothesize that the CHR-P groups may not only differ from HC and FEP in terms of their means but also their variances. Meta-analyses of variability has been used previously to study the immune system (37), brain volumes (38, 39), treatment response (40-43), and clinical features (44) in patients and provides additional evidence of subgroups. Furthermore, we have previously investigated variability in the response to preventive treatments in CHR-P populations (45). More specifically, heterogeneity/homogeneity of a certain estimate can be quantified using the variability ratio (VR) and the coefficient of variation (CVR) (46, 47) in patient groups compared to controls. To our knowledge, these methods have never been applied to examining variability of neurocognitive functioning in the CHR-P population. Given the high clinical variability observed in the CHR-P group we hypothesised a higher neurocognitive variability in CHR-P individuals compared to HC.

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) (48), MOOSE (eTable 2)(49), and EQUATOR guidelines(50). The results of the initial meta-analytic review, in terms of Hedges´g, have been previously described (8). The search terms are detailed in eMethods 1.

Outcome measures and data extraction
A detailed description of the extraction procedure and neurocognitive tests used are explained elsewhere (8) (eTable 3). Neurocognitive tasks were organized in accord with the 7 MATRICS Consensus Cognitive Battery and 8 additional domains or tests within domains as detailed in eTable3. To merge the non-independent neurocognitive tasks, we used a previously described method (8). Primary outcome measures included the VR in the whole CHR-P group, CHR-P developing psychosis or not, controls and FEP. Secondary outcome measures included the CVR calculations in the whole CHR-P group, CHR-P developing psychosis or not, HC and FEP.

**Statistical analyses**

The primary analysis investigated the VR (the logarithm of the ratio of the standard deviations (SDs), named log “variability ratio”) across the different neurocognitive domains in CHR-P individuals compared to HC, between CHR-P developing psychosis and not developing psychosis and between CHR-P and first-episode psychosis (FEP). Given the presence of between-group mean variability in neurocognitive performance, we also conducted secondary mean-scaled CVR analyses (the logarithm of the ratio of the coefficients of variation (CV), termed the log “CV ratio”) to validate the VR analyses (51), again comparing CHR-P individuals vs HC, CHR-P transitioning vs those not transitioning and CHR-P individuals vs FEP. Comparative tests and effect sizes were reported for each neurocognitive task and then across each larger neurocognitive domain. Overall, our analyses yielded an in-depth characterization of neurocognitive variability in this dataset using baseline clinical and longitudinal clinical outcome (i.e., the transition to psychosis).

The VR has gained recent attention as an indicator of inter-individual variability for various clinical factors, such as treatment effect (45, 46) and its logarithm (needed to approach normality) was calculated according to the formula below:
\[ \ln VR = \log \left( \frac{SD_{Tx}}{SD_{Ct}} \right) + \frac{1}{2 \cdot (n_{Tx} - 1)} - \frac{1}{2 \cdot (n_{Ct} - 1)} \]

\[ SE_{\ln VR} = \sqrt{\frac{1}{2 \cdot (n_{Tx} - 1)} + \frac{1}{2 \cdot (n_{Ct} - 1)}} \]

\( n_{Tx} \) and \( SD_{Tx} \) are the sample size and standard deviation in the CHR-P (and transition) group, whilst \( n_{Ct} \) and \( SD_{Ct} \) are the sample size and standard deviation in the comparative groups (e.g. HC, FEP or CHR-P not developing psychosis).

If different subgroups of CHR-P individuals with different neurocognitive profiles do not exist, the variability in this group should be similar to that observed comparative groups (e.g HC). Therefore, a VR of 1 demonstrates equal variability in neurocognitive tasks between those at CHR-P and HC (or other comparative groups). A VR greater than 1 suggests greater variability in the neurocognitive tasks of those in the CHR-P group (or other comparative groups), whereas a VR less than 1 indicates less variability in the CHR-P group (or other comparative groups). The log-VR was back-transformed into the linear scale (VR) to aid the interpretation of the results. For all calculations, we set an _a priori_ significance threshold of \( p < 0.05 \). Lastly, we conducted a standard random-effects meta-analysis with restricted maximum likelihood estimation of the heterogeneity to pool the different studies' logCV (Coefficient of Variation for Log-transformed Data). We exponentiated the logVR in the forest plot to back-transform from the log scale for the benefit of interpretability.

Metaregressions evaluated the impact of several factors: age, sex, years of education, ethnicity, global functioning (measured by Global Assessment Functioning scale), attenuated positive and negative psychotic symptoms (measured by the SIPS, Structured Interview for Psychosis-Risk Syndromes), NOS (Newcastle Ottawa Scale) quality scale
(11, 31), baseline antipsychotic exposure and type of CHR-P instrument used). Meta-regressions were conducted when at least 7 studies were available.

All analyses were conducted within R 1.4.1106 (52), the VR and CVR analyses were performed using the metafor package (53).

RESULTS

Characteristics of the dataset

A total of 262 eligible studies were screened; 78 of them were included (Figure 1 and eTable 5) comprising 5162 CHR-P individuals (mean age 20.16 years, SD=3.25, range 12-29.01, 49% females), 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). 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).

VR and CVR variability of neurocognitive functioning: CHR-P vs HC

The pooled VR neurocognitive domains are shown in table 2. The CHR-P group presented greater variability than HC across most neurocognitive domains, including (in decreasing order of magnitude) in visual memory (VR: 1.41, 95%CI 1.02, 1.94), executive functioning (VR: 1.31, 95%CI 1.18, 1.45), verbal learning (VR: 1.29, 95%CI 1.15, 1.45), premorbid IQ (VR: 1.27, 95% 1.09, 1.49), processing speed (VR: 1.26, 95% 1.07, 1.48), visual learning (VR: 1.20, 95%CI 1.07, 1.34), and reasoning and problem
solving (VR: 1.17, 95%CI 1.03, 1.34). In the CVR analyses, these results remained similar with greater variability for the CHR-P group in visual memory (CVR: 2.27, 95%CI 1.00, 5.13), verbal learning (CVR: 1.45, 95%CI 1.29, 1.62), processing speed (CVR: 1.42, 95%CI 1.21, 1.67), premorbid IQ (CVR: 1.33, 95%CI 1.11, 1.58), visual learning (CVR: 1.30, 95%CI 1.14, 1.48), social cognition (CVR: 1.19, 95%CI 1.03, 1.37), attention/vigilance (CVR: 1.17, 95%CI 1.08, 1.26), reasoning and problem solving (CVR: 1.17, 95%CI 1.03, 1.34), visuospatial ability (CVR: 1.17, 95%CI 1.08, 1.27), executive functioning (CVR: 1.15, 95%CI 1.01, 1.31), and working memory (CVR: 1.14, 95%CI 1.07, 1.21) (Table 1).

The individual VR according to different tasks is reported in figures 2-4. The CHR group presented greater variability than HC in Wechsler Memory Scale Immediate (WMS) Visual Memory (VR: 1.85, 95%CI 1.19-2.89); Hinting task (VR: 1.63, 95%CI 1.32-2.02); Trail Making Test-A (TMT-A) (VR: 1.5, 95%CI 1.17-1.92); California Verbal Learning Test (CVLT) (VR: 1.46, 95%CI 1.23-1.73); Trail Making Test-B (TMT-B) (VR: 1.44, 95%CI 1.18-1.76), Brief Visuospatial Memory Test-Revised (BVMT-R) (VR: 1.38, 95%CI 1.17, 1.61), IQ performance (VR: 1.37, 95%CI 1.10-1.69), Wisconsin Card Sort Test (WCST) number of correct responses (VR: 1.37, 95%CI 1.00-1.87); National Adult Reading Test (NART) (VR: 1.34, 95%CI 1.13, 1.59), Rey Auditory Verbal Learning Test (RAVLT) (VR: 1.29, 95%CI 1.03-1.62), WCST perseverative errors (VR: 1.2, 95%CI 1.03-1.41), Neuropsychological Assessment Battery Mazes (NAB Mazes) (VR: 1.17, 95%CI 1.03-1.34); Wechsler Adult Intelligence Scale/ Wechsler Intelligence Scale for Children Block Design (WAIS/WISC BD) (VR: 1.1, 95% CI 1.01-1.19); WMS-III: SS (VR: 1.09, 95%CI 1.01, 1.18).
In CVR analyses, the following tasks showed greater variability in the CHR-P group: Digit Symbol Coding Test (DST) (CVR: 1.14, 95%CI 1.03-1.27), Stroop Color word reading test (CVR: 1.38, 95%CI 1.03-1.85), Stroop Word reading test (CVR: 1.71, 95%CI 1.23-2.37), TMT-A (CVR: 1.31, 95%CI 1.03-1.66), Continuous Performance Test Identical Pairs (CPT-IP) (CVR: 1.19, 95%CI 1.06-1.32), Letter Number Span (LNS) (CVR: 1.18, 95%CI 1.09-1.29), Letter Naming Sequencing Test (LNST) (CVR: 1.15, 95%CI 1.01-1.31), WMS-III: Spatial Span (CVR: 1.19, 95%CI 1.10-1.29), CVLT (CVR: 1.60, 95%CI 1.35-1.91), RAVLT (CVR: 1.41, 95%CI 1.09-1.82), Hopkins Verbal Learning Test-Revised (HVLT-R) (CVR: 1.36, 95%CI 1.14-1.61), BVMT-R (Brief Visuospatial Memory Test–Revised) (CVR: 1.52, 95%CI 1.28-1.80), WMS Visual Memory (CVR: 1.18, 95%CI 1.05-1.32), Neuropsychological Assessment Battery Mazes (CVR: 1.33, 95%CI 1.09-1.62), Hinting (CVR: 1.74, 95%CI 1.39-2.18), IQ performance (CVR: 1.74, 95%CI 1.39-2.18), NART (CVR: 1.40, 95%CI 1.13-1.73), WAIS/WISC BD (CVR: 1.21, 95%CI 1.11-1.31), WMS Visual Reproduction (CVR: 2.55, 95%CI 1.06-6.14), Wisconsin Card Sorting Test (WCST) categories (CVR: 1.28, 95%CI 1.06-1.54), (eTable 6).

VR and CVR variability of neurocognitive functioning: CHR-P transitioning to psychosis vs CHR-P non-transitioning

The pooled VR neurocognitive domains (table 1) showed that the CHR-P transitioned group presented greater variability than CHR-P non-transitioned in executive functioning VR: 1.38, 95%CI 1.07, 1.78. In the case of CVR this result remained significant (CVR: 1.38, 95%CI 1.07, 1.78).

The VR between CHR-P developing psychosis and CHR-P not developing psychosis is reported in figure 3. The VR was higher for CHR-P transitioned group in WCST.
perseverative errors (VR: 1.38, 95%CI 1.07-1.78). This result was also significant (CVR: 1.21, 95%CI 1.01-1.46) in CVR analyses; moreover, animal fluency (CVR: 1.19, 95%CI 1.01-1.4) showed also greater variability in CHR-P transitioned.

VR and CVR variability of neurocognitive functioning: CHR-P vs FEP

The pooled VR neurocognitive domains (table 1) demonstrated that the FEP group presented greater variability than CHR-P in executive functioning (VR: 1.28, 95% 1.08, 1.51). CVR analyses presented a greater variability for the FEP group in verbal learning (CVR: 1.23, 95% 1.09, 1.39).

The VR between CHR-P and FEP is reported in figure 4. This VR variability was higher in WCST Perseverative Errors (VR: 1.03, 95% 1.4, 1.14, ) while CVR presented greater variability in CVLT (CVR: 1.24, 95%CI 1.07-1.44), and WCST categories (CVR: 1.81, 95%CI 1.18-2.79).

Study quality, heterogeneity and metaregressions

The quality rating of the studies ranged from 4 to 8 (average=5.8; median=6), see eTable 5. Heterogeneity ranged from small 0% (DST, arithmetic, WMS-III SS, VMS VM, RMET, and tapping tasks) to large 98.68% (DFAR fear task) in CHR-P vs HC comparisons, from 0% (animal fluency, CVLT, TMT-A, and tapping tasks) to 81.74% (NART) task) in CHR-P not transitioning vs CHR-P transitioning, and from 0% (HVLT) to 91.84% (WCST categories task) in CHR-P vs FEP groups.

Regarding metaregressions, in the CHR-P vs HC analyses, higher age (β= -0.06, SE= 0.02, p= 0.007) was associated with reduced variability of processing speed. Any other
metaregression (age, sex, years of education, race, functioning, attenuated psychotic symptoms, NOS) was not significant (see eTable 7-9).

**DISCUSSION**

We have presented the first large-scale meta-analytic comparative investigation of within-group neurocognitive performance variability in a help-seeking CHR-P population, compared to HC and FEP. Our first main finding is that the within-studies variability was greater in several neurocognitive domains (visual memory, executive functioning, verbal learning, premorbid IQ, processing speed, visual learning, and reasoning and problem solving) in the CHR-P state with respect to HC using both the VR and CVR metrics. Besides, the CVR analyses demonstrated also a greater variability in attention/vigilance, working memory, social cognition, and visuospatial ability.

This is the first meta-analysis investigating variability of neurocognitive profiles in the CHR-P population compared with HC. Importantly, the CVR analysis confirmed increased variability in the very same domains. This greater variability in CHR-P was a highly robust finding, as it was confirmed by two variability measurements, thus improving the confidence with which we can infer that the variability is strengthened by meaningful neurocognitive mechanisms as opposed to confounding factors. Recent work (54) identified a two-cluster solution comprising a neurocognitively non-impaired and a neurocognitively impaired subgroup in a combined sample of both CHR-P and HC and found that the impaired subgroup was more prevalent in the CHR-P population, confirming that the neurocognitive profile of CHR-P may vary broadly (54). This study moves beyond the between-study variance reported in our prior paper (such as with the $I^2$ statistic) (8), by showing that CHR-P individuals had higher VR/CVR variability in several neurocognitive domains compared to HC. This indicates that the average
measurement of neurocognitive functioning may not represent a solid estimate in this
group. Overall, these findings call for future research deconstructing the demonstrated
variability of neurocognitive functioning at the individual subject level. Individual
participant data meta-analyses may prove to be particularly useful, as well as precision
medicine approaches that leverage neurocognitive domains (55, 56).

To address these questions, we also demonstrated that the specific neurocognitive tasks
affected by high variability (in VR and CVR analyses) involve WMS Visual Memory,
Hinting task, TMT-A, CVLT, BVMT-R, NART, RAVLT, NAB Mazes, WAIS/WISC
BD, WMS-III: SS in CHR-P population. Several predicting psychosis models, which
include neurocognitive domains, in CHR-P has been proposed (57-64). These models are
based on previous literature about this topic in this population. This study could help
select the most valuable tasks for these prediction models highlighting these tasks with
the higher power of finding the subjects more deteriorated prior the onset of the psychosis.

The present data also investigated whether this variability in neurocognitive profiles may
be associated with the heterogeneous clinical outcomes of the CHR-P stage, with only
about one third of them fully remitting from their initial problems (65). We found that the
variability in the neurocognitive performance in CHR-P not developing psychosis was
similar to the CHR-P developing psychosis group (except for the perseverative errors task
showed higher variability in CHR-P developing psychosis compared to CHR-P not
developing psychosis) and the FEP subjects (except for the perseverative errors task
showed higher variability in FEP compared to CHR-P), suggesting that neurocognitive
variability is equally presented across the two stages of the disorders. Our findings are
consistent with a broad literature showing that neurocognitive impairments predate the
onset of psychosis and with findings showing limited neurocognitive changes between
the latter part of the CHR-P period and the onset of the FEP (66, 67). We therefore suggest that a majority of neurocognitive variability may occur before psychosis onset. Similarly, longitudinal studies of children who later develop psychoses show lower levels of overall cognitive abilities (IQs) and lower levels of academic achievement (68, 69).

Interpreting these findings altogether is challenging. The observed increased variability in CHR-P could just be the same variability that exists in healthy people – i.e., there is a constant effect. Accordingly, the CHR-P group would represent those from the general population that would have been at the tail end of the bell curve in the healthy population if they had never developed a disorder. However, CHR-P individuals are symptomatic at presentation and not generally representative of the general population because of important sampling biases discussed in the introduction (29). An alternative hypothesis is that in some CHR-P individuals, the development of a psychotic disorder had a drastic impact on neurocognitive functioning, while it had no/minimal effect in others, this leading to no VR/CVR differences between CHR-P and FEP.

There are several limitations to consider in this study. Firstly, the validity of the VR and CVR as an index of variability has received debate in the context of other clinical factors, such as individual treatment response and subgroup effects (70). Second, we have been unable to find variability into the VR across different subgroups of CHR-P (BLIPS, APS and GRD) because these data were not reliably available in enough studies. This is the first study addressing this topic so future evidence-syntheses approaches in the CHR-P field could consider individual CHR-P subgroups(28). This is more likely obtained in large-scale prospective cohorts such as ProNET(71), PRESCIENT(72) that are now ongoing. This is also the case in the FEP groups, where there are not enough data to explore the differences in the neurocognitive domains according to the specific
designation. Third, whilst the analyses did not show an association with all clinical features, this may be attributable to low statistical power of our metaregressions. And finally, focus of future studies may clarify those potential influential factors that could not be studied in terms of their relationship to domain/task variability. Sources of variability in previous neurocognitive studies include premorbid developmental status, substance exposure, adversity/trauma or poverty during the developmental period. Psychometric features of specific tasks may be also an important contributing factor to these results; presumably, those that have lower reliability would likely yield greater variability. Some of that variable reliability may be associated with examiner effects related to administration and scoring. So, some of the observed heterogeneity may be a function of test features and their administration and scoring. The main aim of precision psychiatry (55, 73) approaches is to embed personalised information into clinical care by generating a comprehensive matrix of information for each patient, based on disease pathophysiology, in order to forecast outcomes or response to interventions at the individual subject level. Our results suggest a disorder-related variability above the level typically observed in the healthy population. This may rule out a constant effect of CHR-P status on neurocognitive performance, e.g., that there is uniform reduction of IQ shifting the overall neurocognitive profile of this patient group. Instead, our findings indicate that different CHR-P individuals are affected by variable neurocognitive deficits. These findings strengthen the implication of precision psychiatry approaches: an increased variability requires personalising preventive interventions in this group. The detection of these specific subgroups according to their neurocognitive profile provides evidence to personalise the interventions; this study may represent the starting point for future interventional research in this area.
Although an increased neurocognitive variability in CHR-P individuals compared to controls was to be expected based on their underlying heterogeneity, this is the first study to have empirically demonstrated it for the neurocognitive domain. Furthermore, before this study it was not clear which specific neurocognitive domain was more or less affected by increased variability. We demonstrated that the variability was greater in several neurocognitive domains (visual memory, executive functioning, verbal learning, premorbid IQ, processing speed, visual learning, and reasoning and problem solving) in the CHR-P state with respect to HC.

In conclusions, our findings suggest the existence of significant variability with different neurocognitive profiles of CHR-P groups, suggesting that the average measurement of neurocognitive functioning may not represent a solid estimate in this group. This finding should be explored by further individual-participant data research and support precision medicine 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. Variability ratio (VR) of neurocognitive functioning between CHR-P vs HC.

CHR-P, Clinical high risk for Psychosis; HC Healthy Controls; BACS SC indicates Brief Assessment of Cognition Scale Symbol Coding; DST, digit symbol coding test; Stroop C, Stroop color naming task; StroopW, Stroop color word reading task; TMT-A, Trail Making Test–Part A; CPT-IP, Continuous Performance Test–Identical Pairs; LNS, Letter Number Span; LNST, Letter Number Sequencing Test; SOPT, Self-ordered Pointing Test; WMS-III: SS, Wechsler Memory Scale III: Spatial Span; CVLT, California Verbal Learning Test; RAVLT, Rey Auditory Verbal Learning Test; HVLT-R, Hopkins Verbal Learning Test–Revised; BVMT-R, Brief Visuospatial Memory Test–Revised; WMS VM, Wechsler Memory Scale Immediate Visual Memory; ROCF, Rey-Osterrieth Complex Figure Immediate Recall; NAB Mazes, Neuropsychological Assessment Battery Mazes; DFAR, Degraded Facial Affect Recognition; RMET, Reading the Mind in the Eyes Test

Figure 3. Variability ratio (VR) of neurocognitive functioning between CHR-P vs HC

CHR-P, Clinical high risk for Psychosis; HC Healthy Controls IQ, Wechsler Intelligence Scales full; IQ verbal, Wechsler Intelligence Scales verbal; IQ performance, Wechsler Intelligence Scales performance; NART, National Adult Reading Test; MWT-B, Mehrfach-Wortschatz-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

Figure 4. Variability ratio (VR) of neurocognitive functioning between CHR-P transitioning to psychosis vs CHR-P not transitioning to psychosis

CHR-P, Clinical high risk for Psychosis; DST, Digit Symbol Coding Test; TMT-A, Trail Making Test-Part A; CPT, Continuous Performance Test–Identical Pairs; CVLT, California Verbal Learning Test; IQ, Wechsler Intelligence Scales full; ROCF DR, Rey-Osterrieth Complex Figure Test Delayed Recall; LNST, Letter Number Sequencing Test; UPSIT, University of Pennsylvania Smell Identification Test; WCST perseverative errors, Wisconsin Card Sorting Test perseverative errors; NART, National Adult Reading Test

Figure 5. Variability ratio (VR) of neurocognitive functioning between CHR-P vs FEP

CHR-P, Clinical high risk for Psychosis; FEP, First Episode Psychosis; TMT-A, Trail Making Test Part A; CPT, Continuous Performance Test–Identical Pairs; CVLT, California Verbal Learning Test; IQ, Wechsler Intelligence Scales full; ROCF DR, Rey-Osterrieth Complex Figure Test Delayed Recall; LNS, Letter Number Span; 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

Table 1. VR and CVR in different neurocognitive domains between CHR-P vs HC, CHR-P transitioned vs CHR-P non transitioned, and CHR-P vs FEP; CHR-P Clinical High Risk for Psychosis; HC Healthy Controls; FEP First Episode Psychosis