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Research Paper

Evidence of discontinuity between psychosis-risk and non-clinical samples in the neuroanatomical correlates of social function

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ABSTRACT

Objective: Social dysfunction is a major feature of clinical-high-risk states for psychosis (CHR-P). Prior research has identified a neuroanatomical pattern associated with impaired social function outcome in CHR-P. The aim of the current study was to test whether social dysfunction in CHR-P is neurobiologically distinct or in a continuum with the lower end of the normal distribution of individual differences in social functioning.

Methods: We used a machine learning classifier to test for the presence of a previously validated brain structural pattern associated with impaired social outcome in CHR-P (CHR-outcome-neurosignature) in the neuroimaging profiles of individuals from two non-clinical samples (total n = 1763) and examined its association with social function, psychopathology and cognition.

Results: Although the CHR-outcome-neurosignature could be detected in a subset of the non-clinical samples, it was not associated was adverse social outcomes or higher psychopathology levels. However, participants whose neuroanatomical profiles were highly aligned with the CHR-outcome-neurosignature manifested subtle disadvantage in fluid ($P_{FDR} = 0.004$) and crystallized intelligence ($P_{FDR} = 0.01$), cognitive flexibility ($P_{FDR} = 0.02$), inhibitory control ($P_{FDR} = 0.01$), working memory ($P_{FDR} = 0.0005$), and processing speed ($P_{FDR} = 0.04$).

Conclusions: We provide evidence of divergence in brain structural underpinnings of social dysfunction derived from a psychosis-risk enriched population when applied to non-clinical samples. This approach appears promising in identifying brain mechanisms bound to psychosis through comparisons of patient populations to non-clinical samples with the same neuroanatomical profiles.

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1. Introduction

Schizophrenia is a severe mental illness that presents with positive, negative and cognitive symptoms (American Psychiatric Association, 2013) associated with significant societal (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018) and health-care costs (Germain et al., 2019). The disease burden of schizophrenia is largely attributable to impairments in social role and relationships (Hall et al., 2019; Hodgekins et al., 2015; Velthorst et al., 2017; Vyas et al., 2007; Wiersma et al., 2000). Similar abnormalities are also present in people who experience attenuated or brief psychotic features and are at clinical high risk (CHR) for psychosis, as well as other psychiatric conditions (Addington et al., 2008; Fusar-Poli et al., 2012; Fusar-Poli et al., 2013; Lin et al., 2015; Salokangas et al., 2014). Research aiming to mitigate social dysfunction in CHR-individuals is currently focused on obtaining a better understanding of the underlying mechanisms.

CHR-individuals show decrements of small-to-medium effect size in general intellectual ability, processing speed, memory, executive function, and social cognition (Bora et al., 2014; De Herdt et al., 2013; Kambeitz-Ilankovic et al., 2019; Lee et al., 2015; van Donkersgoed et al., 2015; Zheng et al., 2018). These abnormalities have been linked to social dysfunction (Bolt et al., 2019; Fusar-Poli et al., 2010; Halverson et al., 2019) thus indicating shared neurobiological mechanisms by cognitive and social outcomes in psychosis. This notion is further supported by findings from the multisite study on “Personalised Prognostic Tools for Early Psychosis Management” (PRONIA) (https://www.pronia.eu/) (Koutsouleris et al., 2018). In the PRONIA study, CHR-P individuals were classified as having good or impaired social function, with respect to their interpersonal relationships and occupational and educational attainment. Application of machine learning analyses to their structural magnetic resonance imaging (sMRI) data identified a neuroanatomical pattern (thereafter referred to as the CHR-outcome-neurosignature) which was associated with impaired social outcome; CHR-P individuals with social impairment also experienced persistent symptoms and cognitive dysfunction.

It is currently unknown whether social dysfunction in CHR-P individuals is neurobiologically distinct or in a continuum with the lower end of the normal distribution of individual differences in social functioning. If the continuum hypothesis is correct, then neurosignatures of social dysfunction derived from CHR-P individuals would also predict suboptimal social function in non-clinical samples. To test this hypothesis, the CHR-outcome-neurosignature derived from the PRONIA study, was used to build a binary classifier which was applied to sMRI data of participants from the Human Connectome Project (HCP) (Van Essen et al., 2013) and the Cambridge Centre for Ageing and Neuroscience project (Cam-CAN) (Shafto et al., 2014). Both these studies acquired high-quality neuroimaging data and detailed information on psychopathology and social function; using both datasets enabled testing for the robustness of potential results to variations in sample composition, neuroimaging acquisition parameters and in the assessment of social function. We predicted that if the neuroanatomical correlates of social dysfunction in CHR-P individuals were on a continuum with the general population, then HCP and Cam-CAN participants whose neuroanatomical profiles were aligned with the PRONIA CHR-outcome-neurosignature would also present with social difficulties. Additionally, as social and cognitive dysfunction in CHR-P may be linked, we availed of the detailed cognitive function data in the HCP dataset, to test whether participants whose neuroanatomical profiles were highly aligned with the PRONIA CHR-outcome-neurosignature would manifest neurocognitive problems.

2. Methods

2.1. Samples

2.1.1. Human Connectome Project

The HCP (www.humanconnectome.org) recruited 1113 adults living in the USA. Following exclusion of participants with medical morbidity, we used sociodemographic, clinical, cognitive and sMRI data from 1092 individuals (585 female), aged 22–37 years (details in Supplementary material and Supplementary Fig. 1).

2.1.2. Cambridge Centre for Ageing and Neuroscience Project

The Cam-CAN Project (www.mrc-cbu.cam.ac.uk) recruited 652 adults living in the UK. Following exclusion of participants with medical morbidity and/or poor image quality, we used sociodemographic, clinical and sMRI data from 492 individuals (244 female), aged 18–87 years (details in Supplementary material and Supplementary Fig. 1).

We used de-identified data from publicly available repositories. Ethical approval and informed consent were obtained by the respective coordinating study centres.

2.2. Behavioural assessments

2.2.1. Social functioning

The HCP and Cam-CAN studies included information on educational attainment, occupational and economic status, and intimate partner relationship status. Although the domains assessed were conceptually identical, the specific instruments differed (defined in Supplementary Tables 1 and 2). In the HCP sample only, there was additional information on the quality of social relationships in terms of perceived hostility, rejection, and social support (Supplementary Table 2). We consider this a strength of the study design as it enabled testing the independence of potential results to the instrument used to assess social function.

2.2.2. Personal and parental mental health

The level of current depressive and anxious symptoms of HCP and Cam-CAN participants was respectively assessed with the Achenbach Adult Self- Report (ASR) (Achenbach, 2009) and the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). In the HCP sample, we also considered measures of psychotic-like experiences based on the ASR items for hallucinations, bizarre thought content and behaviour. Additionally, both samples included information on personal and parental lifetime psychiatric diagnoses. Details of all measures are provided in Supplementary Table 3.

2.2.3. Neurocognition

Extensive cognitive data were only available for the HCP participants based on the NIH Toolbox (Weintraub et al., 2013) which includes tests that have also been widely used in schizophrenia research. NIH Toolbox includes tasks of executive function (Dimensional Change Card Sort Test and Flanker Task), working memory (List Sorting) and Processing Speed (Pattern Comparison Processing Speed Test), and yield composite scores for fluid and crystalized intelligence (details in Supplementary Table 4).

2.3. Neuroimaging acquisition and processing

Whole-brain T_1-weighted images of the HCP and Cam-CAN participants were respectively acquired on a 3T Siemens Connectome-Skyra and a 3T Siemens TIM Trio scanner. Raw images were downloaded from the respective repositories and processed using procedures identical to those of the PRONIA study implemented in the open-source CAT12 toolbox (version r1155; http://dbm.neuro.uni-jena.de/cat12/), an extension of SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/). In each participant, areal parcellation was performed by warping the individual space to a template in standard space using the

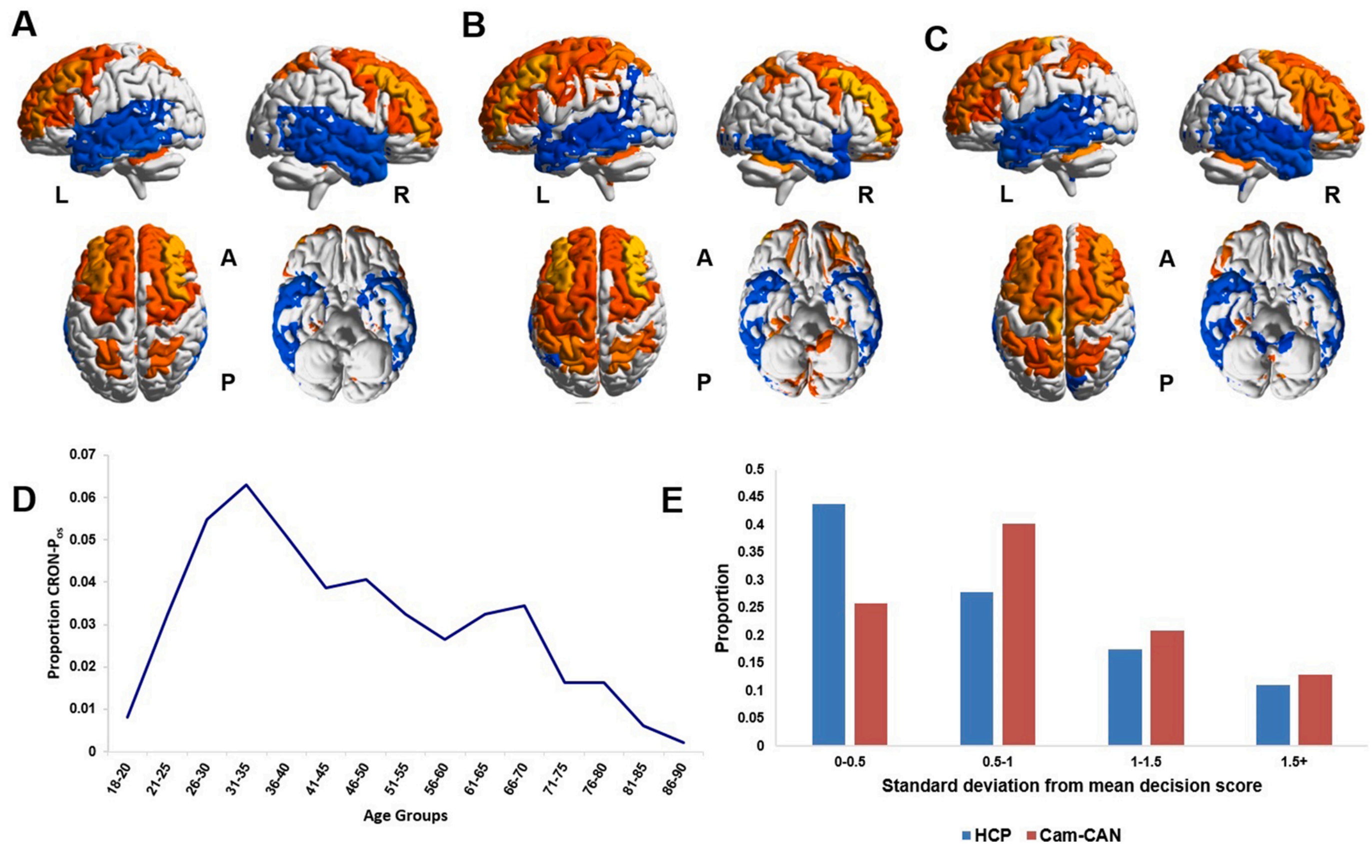

Fig. 1. Spatial definition and prevalence of the clinical-high-risk-outcome-neurosignature (CRON) in the HCP and Cam-CAN samples.
Spatial definition of the clinical-high-risk-outcome-neurosignature (CRON) in (A) the Human Connectome Project (HCP); (B) the Cambridge Centre for Ageing and Neuroscience (Cam-CAN), under 40 years of age; (C) Cambridge Centre for Ageing and Neuroscience, over 40 years of age; (D) proportion of clinical-high-risk-outcome-neurosignature positive (CRON-Pos) individuals in the entire Cam-CAN sample; the corresponding data for the HCP in Supplementary Fig. 3; (E) proportion of CRON-Pos individuals at varying standard deviations from the mean decision score in the HCP and Cam-CAN samples.

SPM nonlinear registration algorithm. Details of the acquisition sequences, preprocessing and quality assessment procedures are provided in the Supplementary material.

2.4. CHR-outcome-neurosignature in the PRONIA study

A linear support vector machine with 10-fold cross-validation, implemented in the open-source software NeuroMiner (www.pronia.eu/neurominer/), was applied to sMRI data of CHR-P individuals (aged 15–40 years) from the PRONIA study and identified a brain structural pattern (Supplementary Fig. 2) associated with impaired social function as measured by the Global Functioning: Social scale at baseline (accuracy 58.1%) and at 12-month follow-up (accuracy 76.2%). This CHR-outcome-neurosignature (CRON) predicted more persistent symptoms but otherwise showed relative specificity for the prediction of social function as its association with cognitive problems was only limited to worse working memory task performance (Supplementary material and Supplementary Fig. 3). Full details have been published (Koutsouleris et al., 2018) and are summarized in the Supplementary material.

2.5. Detection of the CRON in the HCP and Cam-CAN samples

To test whether the CRON (identified in the PRONIA CHR-P individuals) could be detected in the sMRI brain scans of a subset of the non-clinical samples, the gray matter volume maps of HCP and of Cam-CAN participants were submitted to separate binary classifiers implemented in Neurominer. Each HCP and Cam-CAN participant was classified as either CRON-positive ($CRON_{Pos}$) or CRON-Negative ($CRON_{Neg}$) based on the presence or absence of the CRON in their neuroanatomical data. Further, each $CRON_{Pos}$ or $CRON_{Neg}$ participant was assigned a decision score which quantified the degree to which their sMRI data respectively converged or diverged from the CRON. Higher positive decision scores in the $CRON_{Pos}$ individuals indicated greater alignment with the CRON while increasingly negative decision scores in the $CRON_{Neg}$ participants indicated greater divergence from the CRON.

In all further analyses, the Cam-CAN sample was divided into two sub-sets comprising individuals aged 18–40 years or older than 40 years; the younger Cam-CAN sub-set matched the age-range of the HCP sample and the CHR-P sample in the PRONIA study.

3. Statistical analyses

Unless otherwise specified, the threshold of statistical significance was adjusted for multiple testing using the Benjamini-Hochberg false-discovery rate (FDR) within each assessment domain; P_{FDR} values >0.05 were considered non-significant and are not reported.

Two types of analyses were undertaken: (i) within each non-clinical sample, $CRON_{Pos}$ and $CRON_{Neg}$ participants were compared using Student's *t*-test or chi square tests in terms of demographics, educational attainment, social role and relationships, personal and parental diagnoses; (ii) functional data analysis was used to assess the association between CRON alignment and continuous variables pertaining to the quality of social relationships, psychopathology and cognitive test performance thus accommodating ambiguities about class assignment (Ramsay and Silverman, 2005). CRON alignment. This alignment is captured by the decision score which quantify the distance from the classifier decision boundary. Higher positive decision scores indicate

Table 1
Social function of CRON-$_{\text{Pos}}$ and CRON-$_{\text{Neg}}$ individuals in the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) sample.

	Cam-CAN <40 years		Cam-CAN >40 years	
	CRON-P_{os} N = 99	CRON-N_{eg} N = 65	CRON-P_{os} N = 125	CRON-N_{eg} N = 203
Living with partner[a,b]	48 [48.48%]	32 [50.00%]	81 [64.80%]	135 [66.50%]
Educational attainment[c,d]				
Higher degree	74 [74.75%]	51 [79.69%]	75 [60.00%]	123 [60.89%]
A-levels	17 [17.17%]	6 [9.38%]	24 [19.20%]	40 [19.80%]
GCSE/O-level	7 [7.07%]	7 [10.94%]	18 [14.40%]	30 [14.85%]
No qualifications	1 [1.01%]	0 [0%]	8 [6.40%]	9 [4.46%]
Socioeconomic status – Occupation[e,f]				
I - Professional	20 [20.83%]	22 [37.29%]	17 [13.71%]	39 [19.31%]
II – Intermediate	40 [41.67%]	20 [33.90%]	58 [46.77%]	87 [43.07%]
IIIN – Skilled non-manual	12 [12.50%]	4 [6.78%]	20 [16.13%]	23 [11.39%]
IIIM – Skilled manual	18 [18.75%]	10 [16.95%]	16 [12.90%]	42 [20.79%]
IV – Partly skilled	5 [5.21%]	3 [5.08%]	13 [10.48%]	7 [3.47%]
V – Unskilled	1 [1.04%]	0 [0%]	0 [0%]	4 [1.98%]
Socioeconomic status - Weekly hours employed[g,h]	37.54 [10.76]	40.30 [15.14]	38.00 [13.48]	37.36 [13.87]

Continuous variables are shown as mean [standard deviation]; categorical variables are shown as number [percentage, %]; variable definitions in Supplementary Tables 1 and 2.
[a] Cam-CAN <40 years: $\chi^2 = 0.04$, P = 0.85.
[b] Cam-CAN>40 years: $\chi^2 = 0.10$, P = 0.75.
[c] Cam-CAN <40 years: $\chi^2 = 3.12$, P = 0.37.
[d] Cam-CAN>40 years: $\chi^2 = 0.60$, P = 0.90.
[e] Cam-CAN <40 years: $\chi^2 = 6.06$, P = 0.30.
[f] Cam-CAN>40 years: $\chi^2 = 14.26$, P = 0.01.
[g] Cam-CAN <40 years: T = -1.32, P = 0.19.
[h] Cam-CAN>40 years: T = 0.40, P = 0.69.

greater alignment with the CRON and negative decision scores indicate lower alignment with the CRON. The functional analysis is a statistical method that treats a metric curve as a function of decision scores (Bassett et al., 2008; Doucet et al., 2017). For each of the variables (defined in Supplementary Tables 2–4), we computed the average curve (x-axis = decision score, y-axis = variable value) for CRON-$_{\text{Pos}}$ and CRON-$_{\text{Neg}}$ participants separately. The decision score was expressed in standard deviations (SD) from the mean in increments of 0.25 SD, from 0 to 2 SD, ensuring that each SD-bin had a minimum of 30 individuals. We then calculated the area between the curves of the two classes (i.e., CRON-$_{\text{Pos}}$ and CRON-$_{\text{Neg}}$) by summing the class differences in the y-values of the two groups at each value of x (corresponding to the SD units of the decision scores). Class differences were tested for significance using non-parametric permutation testing, whereby the class identity of each individual was randomly reassigned without replacement to create pairs of pseudo-groups; the average curves of the pseudo-groups were determined, and the area between them was estimated. This process was repeated 10,000 times creating a set of 10,000 random curve difference values that served as the null distribution. The P-value of the true class difference was defined as the number of times the random curve values were greater than the true curve value, divided by the number of iterations. Thus, the P-value was explicitly corrected for multiple testing.

Table 2
Social function of CRON-$_{\text{Pos}}$ and CRON-$_{\text{Neg}}$ individuals in the Human Connectome Project (HCP) sample.

Measure	HCP	
	CRON-P_{os} N = 590	CRON-N_{eg} N = 502
Living with partner[a]	271 [46.01%]	211 [42.12%]
Education (years)[b]	14.80 [1.82]	15.05 [1.78]
Socioeconomic status – Income[c]		
Low (>49,999/year)	231 [39.35%]	197 [39.56%]
Middle (50,000-99,9999/year)	260 [44.29%]	227 [45.58%]
High (<100,000/year)	96 [16.35%]	74 [14.68%]
Socioeconomic status-Employment[d]		
Not working	91 [15.07%]	72 [14.20%]
Part time	112 [18.54%]	81 [15.98%]
Full time	401 [66.39%]	354 [69.82%]
Instrumental support[e]	48.34 [8.93]	47.64 [9.08]
Perceived hostility[f]	49.10 [8.67]	48.30 [8.53]
Perceived rejection[g]	48.53 [8.72]	48.48 [8.83]
Perceived stress[h]	48.35 [9.00]	48.32 [9.36]

Continuous variables are shown as mean [standard deviation]; categorical variables are shown as number [percentage, %]; variable definitions in Supplementary Tables 1 and 2.
[a] $\chi^2 = 1.66$, P = 0.20.
[b] T = -2.27, P = 0.02.
[c] $\chi^2 = 0.49$, P = 0.78.
[d] $\chi^2 = 1.48$, P = 0.48.
[e] T = 1.36, P = 0.17.
[f] T = 1.48, P = 0.14.
[g] T = -0.07, P = 0.94.
[h] T = -0.22, P = 0.83.

4. Results

4.1. The CRON in the HCP and Cam-CAN samples

The spatial distribution of the CRON in the HCP and Cam-CAN samples is shown in Fig. 1A, B and C. As in the PRONIA study (Supplementary Fig. 2), the neurosignature comprised lower gray matter volume in cingulate, orbitofrontal, insular, temporal, parietal, and occipital brain regions, and higher cerebellar and prefrontal volumes. The proportion of CRON-$_{\text{Pos}}$ and CRON-$_{\text{Neg}}$ individuals is shown in Fig. 1C for the Cam-CAN sample and Supplementary Fig. 4 for the HCP sample. The distribution of decision scores in the Cam-CAN and HCP samples is shown in Fig. 1E. Even at uncorrected P-values, there was no association between decision scores and whole-brain gray matter volume in the young (r = 0.02, P = 0.82) and older Cam-CAN sub-sets (Pearson's r = 0.06, P = 0.28) and in the HCP sample (Pearson's r = −0.03, P = 0.27). There were no significant differences in age and sex distribution between CRON-$_{\text{Pos}}$ and CRON-$_{\text{Neg}}$ individuals in either sample (Supplementary Table 5).

4.2. CRON and social function

Within each non-clinical sample, comparison of CRON-$_{\text{Pos}}$ and CRON-$_{\text{Neg}}$ individuals did not yield significant differences in any of measure of functioning pertaining to intimate partner relationships, educational attainment and socioeconomic status (Tables 1 and 2). The same applied to measures pertaining to the quality of social relationships, although these data were only available in the HCP sample (Table 2).

4.3. CRON and psychopathology

Within each non-clinical sample, comparison of CRON-$_{\text{Pos}}$ and CRON-$_{\text{Neg}}$ individuals did not yield significant differences in personal history of psychiatric disorders or in parental history of psychiatric and neurodegenerative disorders (Supplementary Tables 6 and 7), even when parental history for specific disorders (schizophrenia, depression,

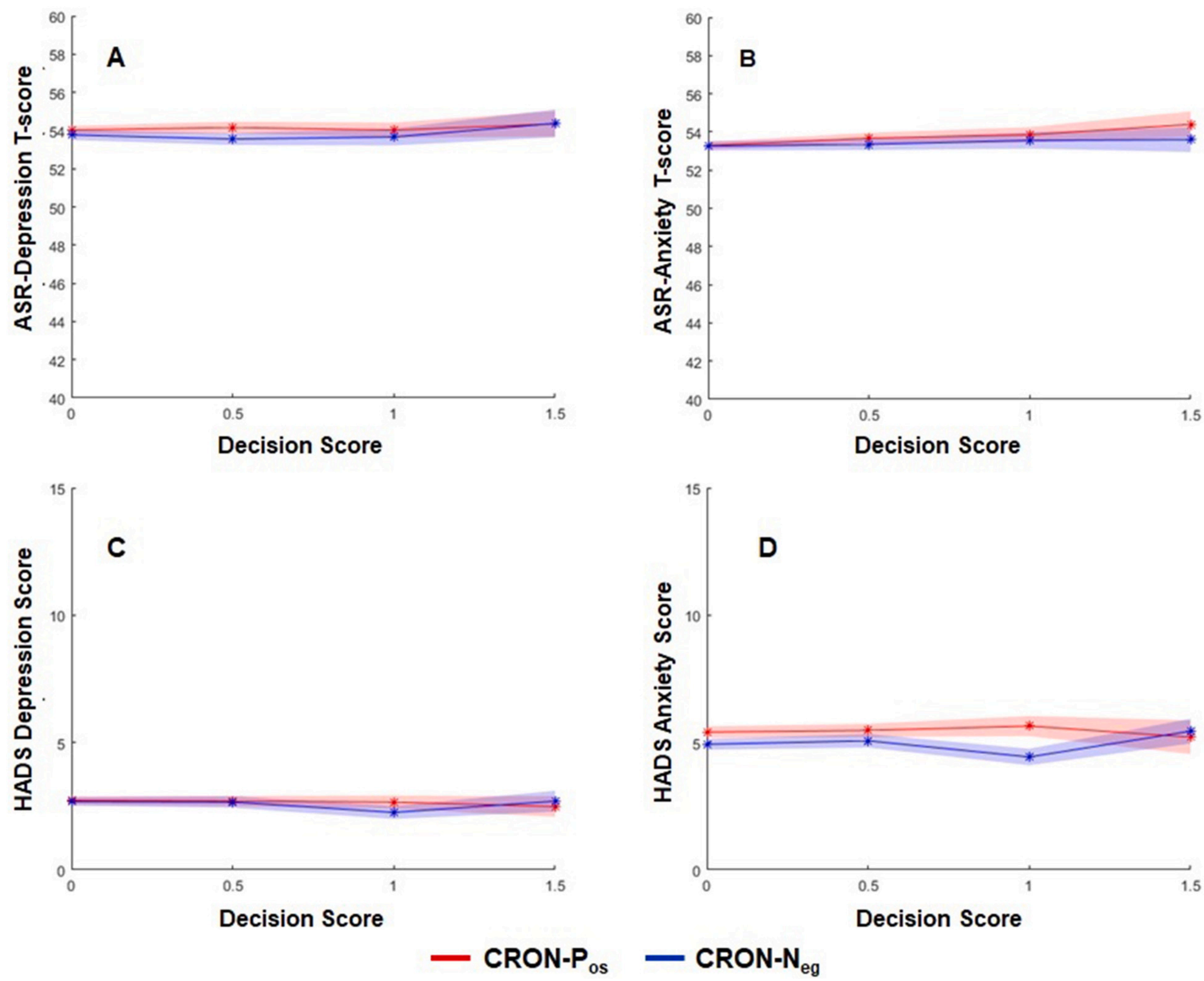

Fig. 2. Depression and anxiety ratings in CRON-$_{Pos}$ and CRON-$_{Neg}$ individuals in the HCP and Cam-CAN samples.
A and B: Achenbach Adult Self- Report (ASR) scores for depressive and anxiety problems the Human Connectome Project (HCP); C and D: Hospital Anxiety and Depression Scale (HADS) scores for depression and anxiety in the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) sample; in each sample the decision score is modeled using the absolute values of the standard deviation units from the mean decision score. CRON = clinical-high-risk-outcome-neurosignature.

bipolar disorder, anxiety disorders and substance use) was examined separately (Supplementary Table 7).The same applied to current depressive and anxiety symptoms (Supplementary Tables 6 and 7). Additionally, no association was found between decision scores and levels of depression and anxiety (Fig. 2) or psychotic like experiences (Supplementary Fig. 5).

4.4. *CRON and neurocognition*

Detailed information on cognitive function was available only for the HCP sample (Supplementary Table 8). Functional analyses followed by permutation testing showed that performance in tasks of fluid (P_{FDR} = 0.004) and crystallized intelligence (P_{FDR} = 0.01) (Fig. 3A and B), processing speed (P_{FDR} = 0.04) (Fig. 3C), cognitive flexibility (P_{FDR} = 0.02) (Fig. 3D), inhibitory control (P_{FDR} = 0.01) (Fig. 3E) and working memory (P_{FDR} = 0.0005) (Fig. 3F) decreased as a function of alignment with the CRON. In CRON-$_{Pos}$ individuals, test underperformance increased with greater alignment with CRON and in CRON-$_{Neg}$ individuals test performance increased as alignment with CRON decreased.

5. Discussion

The primary aim of this study was to test whether a neuroanatomical pattern associated with poor social outcome in CHR-P states in the PRONIA study (CHR-outcome-neurosignature; CRON) retained this association in non-clinical samples. The current findings indicate a lack of continuity in the neuroanatomical correlates of social dysfunction between CHR-P and non-clinical samples. Specifically, although the CRON could detected in a subset of both the HCP- and Cam-CAN samples, its presence was not associated with dysfunction on any measure of social functioning.

The domains of social functioning assessed across study samples were conceptually identical. The overlap between the Global Functioning: Social Functioning scale, used to test the predictive value of the CRON in the PRONIA study, is greatest with the social assessment undertaken in the HCP sample which covered social support, friendship, and perceptions of social interactions. Although there is a theoretical possibility that the CRON is sensitive only for predicting social outcomes measured by the scale used in PRONIA, we consider this unlikely given the overlap in the domains of social functioning assessed.

In the PRONIA study, the CRON also predicted more severe negative symptoms and impaired recovery from perceptual abnormalities in CHR-individuals (Koutsouleris et al., 2018). However, no association

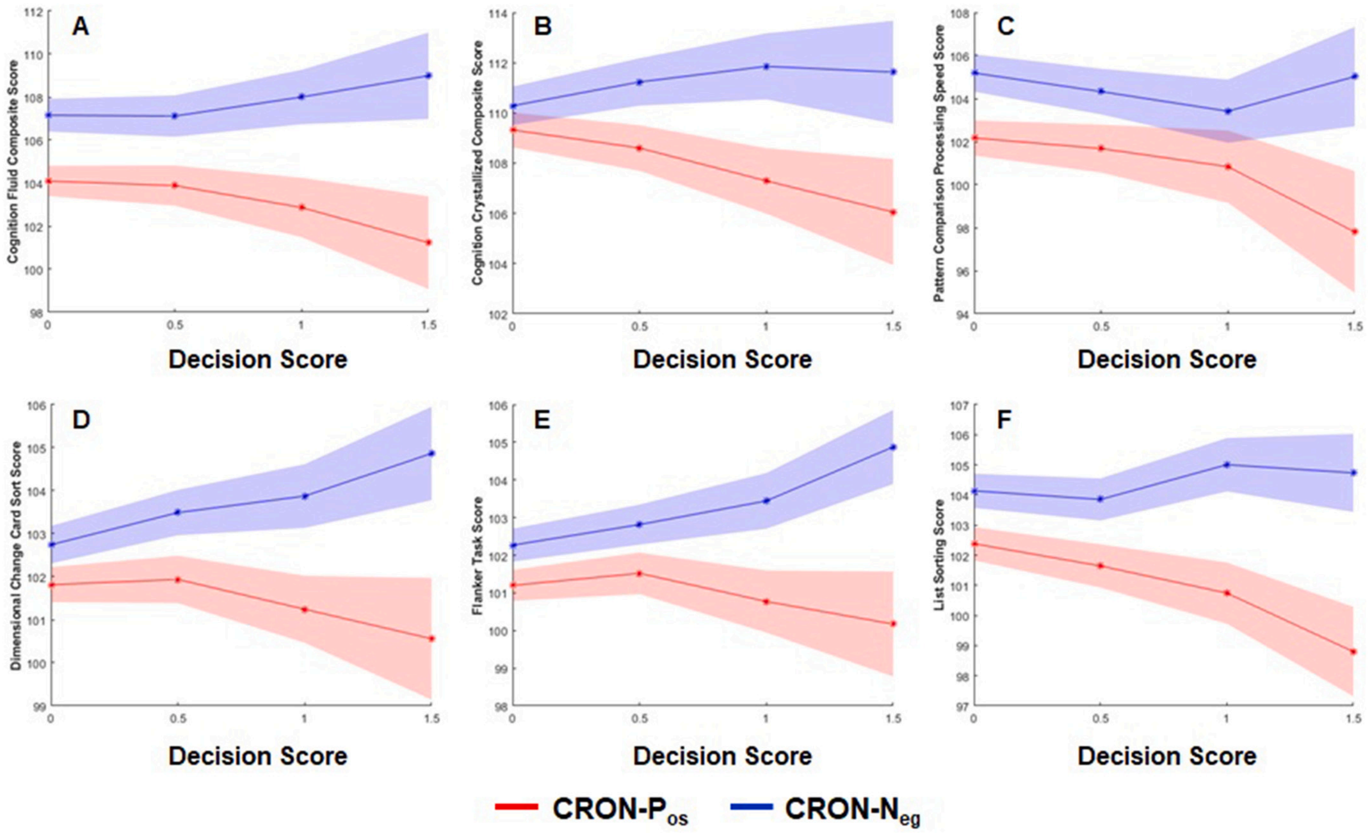

Fig. 3. Neurocognitive function in CRON-$_{Pos}$ and CRON-$_{Neg}$ individuals.
(A) Cognition Fluid Composite; (B) Cognition Crystallized Composite; (C) Pattern Comparison Processing Speed; (D) Dimensional Change Card Sort; (E) Flanker Task; (F) List Sorting. All tests were part of the NIH Toolbox assessment of participants in the Human Connectome Project sample. The decision score is modeled using the absolute values of the standard deviation units from the mean decision score.

was found between the CRON and psychopathology, including psychotic-like experiences, in non-clinical samples. It is unlikely that these findings are attributable to misidentification of future psychosis cases in the HCP and Cam-CAN as no more than 15 individuals in both samples combined could ever present with schizophrenia assuming an approximate lifetime prevalence of 8/1000 persons (McGrath et al., 2008).

Multiple studies have established that CHR-P individuals experience neurocognitive dysfunction of small to moderate effect size in multiple domains (Bora et al., 2014; Catalan et al., 2021). In the non-clinical samples examined here, greater alignment between participants' sMRI-based neuroanatomical profile with the CRON was associated with subtle neurocognitive disadvantage in intelligence, processing speed, and aspects of executive function involving cognitive flexibility, inhibitory control and working memory. Neurocognitive dysfunction has been proposed as the defining feature of schizophrenia (Kahn and Keefe, 2013). This view is only partially supported by the observation that a CHR-P derived neurosignature indexed neurocognitive vulnerability in two non-clinical samples.

Prior literature has consistently reported positive associations between global and regional brain volumetric measures with both general intellectual ability and domain-specific measures of cognition (Basten et al., 2015; Hilger et al., 2020). Particular emphasis has been placed on the role of fronto-cerebellar circuitry in which the cerebellum supports a wide range of prefrontally linked cognitive processes (Rapoport et al., 2000; Ito, 2008). Fronto-cerebellar circuits may also provide compensatory engagement to maintain cognitive efficiency in the presence of dysfunction in other regions (Bernard and Seidler, 2013; Morcom and Johnson, 2015). The cognitive underperformance of individuals whose neuroanatomical profile was aligned with CRON is subtle, which may reflect both the widespread pattern of lower gray matter volume and the enhanced fronto-cerebellar volumes that define the CRON.

The predictive value of CRON for psychopathology and social function appears to be bound to CHR-P states. Accordingly, there are three main implications from our findings. First, they suggest that the predictive continuity of neurosignatures identified in clinical sample cannot be assumed but has to be empirically tested. Second, neurosignatures identified in CHR-P (or other clinical groups) should not be used as biological screening tools for early detection in unselected samples unless their predictive continuity in such samples is empirically confirmed. Third, in non-clinical samples, the CRON may represent a pattern of "miswiring" behaviourally manifesting as subtle cognitive task underperformance with minimal impact on clinical and functional outcomes. Its predictive value for social outcomes in CHR-P states is likely to be predicated on presence of psychotic experiences.

5.1. Limitations

The current study leveraged data from two large and geographically distinct samples with high-quality imaging and behavioural data. We made no attempt at harmonization of the imaging and non-imaging data as we were interested in testing whether the pattern of findings would be consistent despite methodological variation across studies. Both samples were cross-sectional and therefore issues regarding the early exposures, neurodevelopment and long-term outcome of CRON-$_{Pos}$ individuals could not be addressed and should be an important topic of future investigations. We focused on the CHR-outcome-neurosignature provided by PRONIA but our approach could be applied to other neuroanatomical patterns linked to psychosis to establish their base prevalence and correlates in non-clinical populations. The same applies to classifiers using other imaging modalities. Finally, we were not able to test the association of the CHR-outcome-neurosignature to genetic risk for psychosis. The addition of a genetic component and examination of early life exposures in future studies could aid in refining our understanding of the behaviour of this neurosignature in non-clinical samples.

6. Conclusions

A neuroanatomical signature associated with impaired social outcome in CHR-P individuals did not retain this association in non-clinical samples. These results argue for further investigation of the continuities and discontinuities of neurobiological mechanisms underpinning psychopathology, neurocognition and social function in clinical and non-clinical samples.

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CRediT authorship contribution statement

Shalaila S Haas: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original draft, Visualization; Gaelle E Doucet: Conceptualization, Validation, Formal analysis, Investigation, Visualization; Mathilde Antoniades: Methodology, Formal analysis; Amirhossein Modabbernia: Methodology; Cheryl M Corcoran: Resources; René S Kahn: Resources, Joseph Kambeitz: Resources, Data curation; Lana Kambeitz-Ilankovic: Resources, Data curation; Stefan Borgwardt: Resources, Data curation; Paolo Brambilla: Resources, Data curation; Rachel Upthegrove: Resources, Data curation; Stephen J Wood: Resources, Data curation; Raimo KR Salokangas: Resources, Data curation; Jarmo Hietala: Resources, Data curation; Eva Meisenzahl: Resources, Data curation; Nikolaos Koutsouleris: Conceptualization, Methodology, Software, Investigation, Resources, Data curation; Sophia Frangou: Conceptualization, Supervision, Project administration, Writing - Original draft. All coauthors: Writing - Review & editing.

Declaration of competing interest

Drs Koutsouleris and Meisenzahl hold issued patent US20160192889A1 ('Adaptive pattern recognition for psychosis risk modelling'). Dr. Upthegrove reported receiving personal fees from Sunovion Pharmaceuticals, Inc, outside the submitted work. Dr. Hietala reported receiving personal fees from Orion Company, Ltd, Otsuka Pharmaceutical Co, Ltd, and H. Lundbeck A/S, outside the submitted work. No other disclosures were reported.

Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.scog.2022.100252.

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