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 with 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; Hodgeskin 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., 2016; 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 psycho-pathology 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 function. We predicted that if the neuroanatomical correlates of social dysfunction in CHR-P individuals were on a continuum with the general function. We predicted that if the neuroanatomical correlates of social dysfunction in CHR-P individuals were on a continuum with the general function. We predicted that if the neuroanatomical correlates of social dysfunction in CHR-P individuals were on a continuum with the general function. We predicted that if the neuroanatomical correlates of social dysfunction in CHR-P individuals were on a continuum with the general function.
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
The decision score was expressed in standard deviations. Thus, the P-value was explicitly corrected for multiple testing.

Continuous variables are shown as number [percentage, %]; categorical variables are shown as number [percentage, %]; variable definitions in Supplementary Table 1 and 2.

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Social function of CRON-pos and CRON-neg individuals in the Cambridge Centre for Ageing and Neuroscience (Cam-CAN) sample.

| Measure                      | HCP      |
|------------------------------|----------|
| CRON-Pos N = 590             | CRON-Neg N = 502 |
| Living with partner*         | 271 [46.01%] | 211 [42.12%] |
| Education (years)**          | 14.80 [1.82] | 15.05 [1.78] |
| Socioeconomic status – Income* | Low (>49,999/year) | 231 [39.35%] | 197 [39.56%] |
| Middle (50,000-99,999/year)  | 260 [44.29%] | 227 [45.58%] |
| High (>100,000/year)         | 96 [16.35%] | 74 [14.68%] |
| Socioeconomic status-Employment | 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*        | 48.34 [8.93] | 47.64 [9.08] |
| Perceived hostility*         | 49.10 [8.67] | 48.30 [8.53] |
| Perceived rejection*         | 48.53 [8.72] | 48.48 [8.83] |
| Perceived stress*            | 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.

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-pos and CRON-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 between CRON-pos and CRON-neg individuals in either sample (Supplementary Table 5).

4.2. CRON and social function

Within each non-clinical sample, comparison of CRON-pos and CRON-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-pos and CRON-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,
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.

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...
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 (Rapaport 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

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.
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-Iankovic: 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 Salkangas: 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.

References

Achenbach, T.M., 2009. The Achenbach System of Empirically Based Assessment (ASEBA): Development, Findings, Theory And Applications. University of Vermont Research Center for Children, Youth and Families, Burlington, VT.

Addington, J., Penn, D., Woods, S.W., Addington, D., Perkins, D.O., 2008. Social functioning in individuals at clinical high risk for psychosis. Schizophr. Res. 99 (1–3), 119–124.

American Psychiatric Association, 2013. Diagnostic And Statistical Manual of Mental Disorders. Washington, D.C.

Bassett, D.S., Bullmore, E., Verchinski, B.A., Mattay, V.S., Weinberger, D.R., Meyer-Lindenberg, A., 2008. Hierarchical organization of human cortical networks in health and schizophrenia. Neuron, 28 (37), 9229–9248.

Basten, U., Hilger, K., Fiebig, C.J., 2015. Where smart brains are different: a quantitative meta-analysis of functional and structural brain imaging studies on intelligence. Intelligence 51, 10–27.

Bernard, J.A., Seidler, R.D., 2013. Relationships between regional cerebellar volume and sensorimotor and cognitive function in young and older adults. Cerebellum 12 (5), 721–737.

Bolt, L.K., Ammingger, G.P., Farhall, J., McGorry, P.D., Nelson, B., Markulev, C., et al., 2019. Neurocognition as a predictor of transition to psychotic disorder and functional outcomes in ultra-high risk participants: findings from the NEURAPRO randomized clinical trial. Schizophr. Res. 206, 67–74.

Bora, A., Wood, S.J., Liddle, P.F., Dazzan, P., Fusar-Poli, P., 2014. Cognitive deficits in youth with familial and clinical high risk to psychosis: a systematic review and meta-analysis. Acta Psychiatr. Scand. 130 (1), 1–15.

Catalan, A., De Pablo, G.S., Aymerich, C., Damiani, S., Sordi, V., Radua, J., et al., 2021. Neurocognitive functioning in individuals at clinical high risk for psychosis: a systematic review and meta-analysis. JAMA Psychiatry 78 (8), 859–867.

De Herdt, A., Wampers, M., Vancampfort, D., De Hert, M., Vanhees, L., Demunter, H., et al., 2013. Neurocognition in clinical high risk young adults who did or did not convert to a first schizophrenic psychosis: a meta-analysis. Schizophr. Res. 149 (1–3), 48–55.

Doucet, G.E., Bassett, D.S., Yao, N., Glahn, D.C., Frangou, S., 2017. The role of intrinsic brain functional connectivity in vulnerability and resilience to bipolar disorder. Am. J. Psychiatry 174 (12), 1214–1222.

Fusar-Poli, P., Byrne, M., Valmaggia, L., Day, F., Tahabrah, P., Johns, L., et al., 2010. Social dysfunctions predicts two years clinical outcome in people at ultra-high risk for psychosis. J. Psychiatr. Res. 44 (5), 294–301.

Fusar-Poli, P., Ronoldi, I., Yong, A.R., Borgwardt, S., Kempston, M.J., Valmaggia, L., et al., 2012. Predicting psychotic meta-analysis of transition outcomes in individuals at high clinical risk. Arch. Gen. Psychiatry 69 (3), 220–229.

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rossler, A., Zunft-Latter, F., 2015. The psychosis high-risk state: a comprehensive state-of-the-art review. JAMA Psychiatry 70 (1), 107–120.

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392 (10159), 1789–1858.

Germain, N., Kymes, S., Lióf, E., Jakubowska, A., François, C., Weatherall, J., 2019. A systematic literature review identifying associations between outcomes and quality of life (QoL) or healthcare resource utilization (HCRU) in schizophrenia. J. Med. Econ. 22 (5), 403–413.

Hall, M.H., Holton, K.M., Ongiah, D., Montrose, D., Keshav, M.S., 2019. Longitudinal trajectory of early functional recovery in patients with first episode psychosis. Schizophr. Res. 209, 234–244.

Halverson, T.F., Orleans-Pobee, M., Merritt, C., Sheeran, P., Fett, A.K., Penn, D.L., 2019. Pathways to functional outcomes in schizophrenia spectrum disorders: meta-analysis of social cognitive and neurocognitive predictors. Neurosci. Biobehav. Rev. 105, 212–219.

Hilger, K., Winter, N.R., Leenings, R., Sassenengan, J., Hahn, T., Basten, U., Fiebibig, C.J., 2020. Predicting intelligence from brain gray matter volume. Brain Struct. Funct. 225 (7), 2111–2129.

Hodgekins, J., Birchwood, M., Christopher, R., Marshall, M., Coker, S., Everard, L., et al., 2015. Investigating trajectories of social recovery in individuals with first-episode psychosis: a latent class growth analysis. J. Psychiatry 207 (6), 536–543.

Ito, M., 2008. Control of mental activities by internal models in the cerebellum. Nat. Rev. Neurosci. 9 (4), 304–313.

Kahn, R.S., Keefe, R.S., 2013. Schizophrenia is a cognitive illness: time for a change in focus. JAMA Psychiatry 70 (10), 1107–1112.

Kambeitz-Iankovic, L., Haas, S.S., Meisenzahl, E., Dwyer, D.B., Weiske, J., Peters, H., Möller, H.J., 2019. Neurocognitive and neuroanatomical maturation in the clinical high-risk states for psychosis: a pattern recognition study. NeurolmageClin. 21, 101624.

Koutsouleris, N., Kambeitz-Iankovic, L., Ruhrmann, S., Rosen, M., Rief, A., Dwyer, D.B., et al., 2018. Prediction models of functional outcomes for individuals in the clinical high-risk state for psychosis or with recent-onset depression: a multimodal, multisite randomized clinical trial. J. Cogn. Neurosci. 27 (7), 1275–1286.

Lee, T.Y., Hong, S.B., Shin, N.Y., Kwon, J.S., 2015. Social cognitive functioning in prodromal psychosis: a meta-analysis. Schizophr. Res. 151 (1–3), 28–34.

Lin, A., Wood, S.J., Nelson, B., Bevan, A., McGorry, P., Yong, A.R., 2015. Outcomes of non-transitioned cases in a sample at ultra-high risk for psychosis. Am. J. Psychiatry 172 (3), 249–258.

Magrath, J., Saha, S., Chant, D., Welham, J., 2008. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol. Rev. 30, 67–76.

Morcom, A.M., Johnson, W., 2015. Neural reorganization and compensation in aging. J. Cogn. Neurosci. 27 (7), 1275–1285.

Ramsay, J.O., Silverman, B.W., 2005. Functional data analysis. In: Springer Series in Statistics, Second edition.

Rapport, M., van Reekum, R., Mayberg, H., 2000. The role of the cerebellum in cognition and behavior: a selective review. J. Neuropsychiatry Clin. Neurosci. 12 (2), 193–198.

Salokangas, R.K., Heinimaa, M., Fron, L., Öystyniemi, E., Ionen, T., Luotonen, S., et al., 2014. Short-term functional outcome and premorbid adjustment in clinical high-risk patients: results of the EPoS project. Eur. Psychiatry 29 (6), 371–380.
Shafto, M.A., Tyler, L.K., Dixon, M., Taylor, J.R., Rowe, J.B., Cusack, R., et al., 2014. The Cambridge Centre for Ageing and Neuroscience (Cam-CAN) study protocol: a cross-sectional, lifespan, multidisciplinary examination of healthy cognitive ageing. BMC Neurol. 14, 204.

van Donkersgoed, R.J., Wunderink, L., Nieboer, R., Aleman, A., Pijnenborg, G.H., 2015. Social cognition in individuals at ultra-high risk for psychosis: a meta-analysis. PLoS One 10 (10), e0141075.

Van Essen, D.C., Smith, S.M., Barch, D.M., Behrens, T.E., Yacoub, E., Ugurbil, K., WU-Minn HCP Consortium, 2013. The WU-Minn Human Connectome Project: an overview. Neuroimage 80, 62–79.

Velthorst, E., Fett, A.J., Reichenberg, A., Perlman, G., van Os, J., Bromet, E.J., Kotov, R., 2017. The 20-year longitudinal trajectories of social functioning in individuals with psychotic disorders. Am. J. Psychiatry 174 (11), 1075–1085.

Vyas, N.S., Hadjulis, M., Vourdas, A., Byrne, P., Frangou, S., 2007. The Maudsley early onset schizophrenia study. Predictors of psychosocial outcome at 4-year follow-up. Eur. Child Adolesc. Psychiatry 16 (7), 465–470.

Weintraub, S., Dikmen, S.S., Heaton, R.K., Tulsky, D.S., Zelazo, P.D., Bauer, P.J., et al., 2013. Cognition assessment using the NIH Toolbox. Neurology 80 (11 Suppl 3), S54–S64.

Wiersma, D., Wanderling, J., Dragomirecka, E., Ganev, K., Harrison, G., An Der Heiden, W., et al., 2000. Social disability in schizophrenia: its development and prediction over 15 years in incidence cohorts in six European centres. Psychol. Med. 30 (5), 1155–1167.

Zheng, W., Zhang, Q.E., Cai, D.B., Ng, C.H., Ungvari, G.S., Ning, Y.P., et al., 2018. Neurocognitive dysfunction in subjects at clinical high risk for psychosis: a meta-analysis. J. Psychiatr. Res. 103, 38–45.

Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67 (6), 361–370.