Multimodal Markers of Emerging and Early-Stage Psychosis

Gina Brunner

MSci (Hons), MSc (Research)

Submitted in fulfilment of the requirements for the Degree of Doctor of Philosophy

School of Psychology and Neuroscience

College of Medical, Veterinary & Life Sciences

University of Glasgow

May 2024

Abstract

Psychotic disorders such as schizophrenia are a family of severe psychiatric conditions which have been associated with substantial disease burden for patients, caregivers, and healthcare systems. Psychotic disorders are typically preceded by a prodromal phase, where psychotic symptoms are present but below the diagnostic threshold. The clinical at-risk state for psychosis can detect this state, but not all individuals who meet criteria for the at-risk state will ultimately develop psychosis. Being able to accurately predict clinical trajectories could help clinicians assign the most appropriate treatments to patients at the earliest signs of illness, thus reducing the risk of future distress and disability of patients. However, it is not yet known exactly which alterations characterise psychosis risk.

Identifying markers of emerging and early-stage psychosis is therefore an important step in the prediction of clinical outcomes. This work aims at identifying markers of psychosis from multiple data modalities, from behavioural to neuroanatomical and functional neurological features. It shows an association between cognitive function and global functioning, and implicates an important role for the hippocampus and the brain networks it is embedded in as markers of early-stage psychosis. Furthermore, another candidate marker thought to explain alterations to the ventricular system, the choroid plexus, is rejected.

Altogether, the results indicate that functional outcomes in individuals at clinical high-risk for psychosis are predicted by cognition, but are also relatively stable over time. Here, cognitive deficits are associated with psychosis risk, whereas individuals with other psychiatric problems who do not meet clinical high-risk for psychosis criteria do not show the same impairments. In the neuroanatomical domain, hippocampal volumes are decreased in early psychosis, but not in individuals with other psychiatric problems, thus indicating specificity to psychosis. While changes to the hippocampal surface are more regionally confined in clinical high-risk states for psychosis, the majority of the surface shows contraction in first-episode psychosis. The choroid plexus, however, is not associated with either psychosis risk, or early-stage psychosis and chronic schizophrenia. Again highlighting a key role for the hippocampus, functional neuroimaging shows that connectivity between the frontal cortex and hippocampus is lower in early-stage psychosis,

while the overall role of the hippocampus in the network differs between illness stages. No such effects are seen for the clinical control group.

While the identified cognitive, neuroanatomical and functional neuroimaging markers appear to be specific to psychosis in the studied sample, they do not predict clinical outcomes particularly in clinical high-risk markers for psychosis. This suggests that the contributions of each data modality are unique, meaning that the results from this thesis could be used to plan future studies in which multimodal prediction models using these markers may be explored.

Table of Contents

Contents

List of Tables

List of Figures

Acknowledgements

First of all, I'd like to say thank you to all the participants who shared their experiences and made this research possible. I'm grateful for all the time and effort they put into participating, and I hope they will find some of our reports interesting.

I'd like to thank my supervisors and their research groups for their support, valuable expertise, and useful advice throughout my PhD. In particular, I'd like to thank Dr Alessio Fracasso for all the discussions on neuroimaging and analysis methods, and for all the support when my PhD was impacted by an unexpected eye condition. I'd like to thank Dr Peter Uhlhaas for his invaluable clinical expertise and all the input into research design and interpretation. I'd like to thank all members of their research groups for their useful feedback to my ideas.

For neuroimaging training, I'd like to thank Frances Crabbe, Tineke Grent-t'Jong, and Gavin Paterson. For training in machine learning methods and programming advice, I'd like to thank Dr Rodrick Murray-Smith for advice on machine learning and programming. Many thanks also to the University of Glasgow for supporting my PhD project with the Lord-Kelvin-Adam-Smith PhD scholarship.

I would like to thank all the coauthors on the included publications for their work on data collection, study design, and input into the final articles.

All this would not have been possible without my ophthalmologist, who repaired my retina so that I could continue with my PhD even after my retinal detachment. I'd also like to thank friends and family for their interest and interesting discussions, hearing your thoughts from a very different perspective has always been very helpful. Thank you especially to TJ for always being there to support me (and for all the help proofreading!).

Lastly, I'd like to thank my cats for their creative writing contributions, such as: 111.;;;;;;feeee2eeeee22222####]]]]]]4gh55wsaaa,.z52222.

Author's Declaration

I declare that, except where explicit reference is made to the contribution of others, this dissertation is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

Gina Brunner

March 2024

This thesis contains published works, and works submitted for publication. Contributions from all authors are described in Author Contributions, following this section. The published works included in this thesis are as follows:

Chapter 1: Haining*, K., Brunner*, G., Gajwani, R., Gross, J., Gumley, A. I., Lawrie, S. M., Schwannauer, M., Schultze-Lutter, F. & Uhlhaas, P. J. (2021). The relationship between cognitive deficits and impaired short-term functional outcome in clinical high-risk for psychosis participants: a machine learning and modelling approach. *Schizophrenia Research*, *231*, 24-31.

Chapter 2: Brunner, G., Gajwani, R., Gross, J., Gumley, A. I., Krishnadas, R., Lawrie, S. M., Schwannauer, M., Schultze-Lutter, F., Fracasso, A▪. & Uhlhaas▪, P. J. (2022). Hippocampal structural alterations in early-stage psychosis: Specificity and relationship to clinical outcomes. *NeuroImage: Clinical*, *35*, 103087.

* Equal contributions (first author)

▪ Equal contributions (last author)

The following works contained in this thesis have been submitted for publication and are under review at the time of thesis submission:

Chapter 3: Brunner, G., Gajwani, R., Gross, J., Gumley, A. I., Timmerman, R.H., Taylor, R., Krishnadas, R., Lawrie, S. M., Schwannauer, M., Schultze-Lutter, F., Uhlhaas▪, P. J., Fracasso, A▪. & (in review). Choroid plexus morphology in schizophrenia and early-stage psychosis: A cross-sectional study. *Schizophrenia Research, TBC*.

Chapter 4: Brunner, G., Gajwani, R., Gross, J., Gumley, A. I., Krishnadas, R., Lawrie, S. M., Schwannauer, M., Schultze-Lutter, F., & Uhlhaas, P.J.▪, Fracasso, A.▪ (in review). Altered connectivity of the hippocampus in cortico-subcortical networks in early psychosis. *Biological Psychiatry CNNI, TBC*.

▪ Equal contributions (last author)

The contents of published and submitted works are presented unaltered, and represent my own work as first author, with contributions from the articles' coauthors as stated above.

The Introduction (Chapter 0) and Discussion (Chapter 5) chapters were conceptualised and written by G.B., and edited in accordance with feedback from A.F.

Author Contributions

As this thesis features chapters published or submitted for publication, the final version includes contributions from all co-authors. In this section, descriptions of each author's contributions are given.

The following authors made contributions to the chapters:

Gina Brunner (G.B.), Kate Haining (K.H.), Alessio Fracasso (A.F.), Ruchika Gajwani (R.G.), Joachim Gross (J.G.), Andrew I. Gumley (A.G.), Rajeev Krishnadas (R.K.), Stephen M. Lawrie (S.L.), Matthias Schwannauer (M.S.), Frauke Schultze-Lutter (F.S.), Rebecca Taylor (R.T.), Rosanne H. Timmerman (RH.T.), Peter Uhlhaas (P.U.).

The following applies to each chapter: G.B. wrote all analysis code, which includes the use of software packages written by others (e.g. numpy for Python), as described in each chapter. P.U., R.G., J.G., A.G., S.L. and M.S. designed the study protocol. P.U. acquired funding for the study. P.U. and A.F. provided supervision. All authors contributed to the final manuscript.

Chapter 1: G.B. and K.H. conducted the literature review, and G.B. identified machine learning methods suitable for the analysis. K.H. contributed to data collection. G.B., K.H., and P.U. planned the analysis. G.B. created all code used to preprocess the data, conduct the machine learning analysis, and generate the corresponding figures. G.B. and K.H. wrote the first the subsequent drafts of the manuscript, and P.U. contributed to the draft editing. More specifically, G.B. and K.H. wrote the introduction and discussion collaboratively, and G.B. wrote the machine learning methods and results, while K.H. wrote data collection methods and results regarding sample characteristics. Note that the results from this analysis are also described in K.H.'s PhD thesis, as G.B. and K.H. are joint first authors with equal contributions made to the work.

Chapter 2: G.B. conducted the literature review. G.B. conceptualised and planned the analysis together with A.F., whereby A.F. contributed the denoising steps of the preprocessing pipeline, and G.B. identified methods for segmentation and analysis. G.B. conducted the analysis, assessed image quality, and generated all figures. G.B. wrote the first and subsequent drafts of the manuscript, while A.F. and P.U. contributed to the editing of the drafts.

Chapter 3: G.B. conducted the literature review and conceptualised the analysis. G.B. instructed R.T. and RH.T. on choroid plexus segmentation. G.B., R.T., and RH.T. created manual segmentations of the choroid plexus. G.B. processed the data and extracted automated segmentations, whereby G.B. and A.F. contributed to the conceptualisation of the modified Gaussian mixture segmentation. G.B. conducted the analysis, inspected image quality, and generated all figures. G.B. wrote the first and subsequent drafts of the manuscript, while A.F. and P.U. contributed to the editing of the drafts.

Chapter 4: G.B. conducted the literature review, and conceptualised the analysis. A.F. and P.U. contributed to the planning of the analysis. G.B. identified data processing and analysis methods, and conducted the data processing and analysis. G.B. inspected image quality and generated all figures. G.B. wrote the first and subsequent drafts of the manuscript, while A.F. and P.U. contributed to the editing of the drafts.

Definitions/Abbreviations

AAL: Automated anatomical labelling

ACC: Anterior cingulate cortex

AUC: Area under the curve

BACS: Brief assessment of cognition in schizophrenia

BOLD: Blood-oxygen level dependent (signal)

CAARMS: Comprehensive assessment of at-risk mental states

CHR-P: Assessed positive for clinical high-risk for psychosis

CHR-N: Assessed negative for clinical high-risk for psychosis

CSF: Cerebrospinal fluid

CP: Choroid plexus

DiCER: Diffuse cluster estimation and regression

DMN: Default mode network

DSM: Diagnostic and Statistical Manual

EEG: Electroencephalography

EP: Early-stage psychosis

FEP: First-episode psychosis

FC: Functional connectivity

fMRI: Functional magnetic resonance imaging

GABA: γ-Aminobutyric acid

GAF: Global assessment of functioning

GFO: Good functional outcome

GLM: General linear model

GNB: Gaussian naïve bayes

HC: Healthy (non-clinical) control

ICA: Independent component analysis

LDA: Linear discriminant analysis

LR: Logistic regression

MEG: Magnetoencephalography

MRI: Magnetic resonance imaging

MRS: Magnetic resonance spectroscopy

NMDA: N-methyl-D-aspartate

PCA: Principal component analysis

PET: Positron emission tomography

PFC: Prefrontal cortex

PFO: Poor functional outcome

RFC: Random forest classifier

ROI: Region of interest

ScZ: Schizophrenia

SPI-A: Schizophrenia proneness instrument for adults

SVM: Support vector machine

TBV: Total brain volume

vlPFC: Ventrolateral prefrontal cortex

VV: Ventricular volume

Chapter 0: Introduction

Introduction to Psychosis and Schizophrenia

Psychotic disorders such as schizophrenia (ScZ) are a group of severe psychiatric conditions and a major cause of disability worldwide (Solmi, Seitidis, et al., 2023). ScZ has shown increased global prevalence over the past few decades (Solmi, Seitidis, et al., 2023), and is associated with numerous medical comorbidities as well as significantly increased all-cause mortality (Ali, Santomauro, Ferrari, & Charlson, 2022; Lu et al., 2022) and suicide (X. Huang, Fox, Ribeiro, & Franklin, 2018). Furthermore, patients with ScZ commonly experience decreased quality of life, especially in the social domain (Desalegn, Girma, & Abdeta, 2020), and cognitive disability (Schaefer, Giangrande, Weinberger, & Dickinson, 2013). Accordingly, psychotic disorders are associated with major disease burden and substantial costs to healthcare systems (Crespo-Facorro et al., 2021).

In the Diagnostic and Statistical Manual, 5th edition (DSM-5), the following psychotic disorders are defined: schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, brief psychotic disorder, and it further includes psychosis secondary to drug misuse or another medical condition (American Psychiatric Association & Association, 2013; Bhati, 2013; Tandon et al., 2013). For a diagnosis of ScZ, an individual must experience at least two of the following symptoms: hallucinations, delusions, speech disturbances, grossly disorganised behaviour and negative symptoms; and these symptoms must be present for at least one month. In schizoaffective disorder, psychotic symptoms are further associated with mood disturbances such as depressed mood. Brief psychotic disorder requires symptoms to resolve within one month, and schizophreniform disorder requires the condition to last more than one month but less than six. Delusional disorder is defined by the presence of unusual beliefs which are resistant to change in the face of contradicting evidence for at least one month (American Psychiatric Association & Association, 2013).

Common across psychotic disorders is a disruption in the patients' understanding and relationship with themselves and reality (Bhati, 2013; Tandon et al., 2013). Although the concept of psychosis has undergone several historical shifts (Bürgy, 2008), contemporary frameworks and historical

frameworks generally share this common core. In contemporary research, clinical symptoms are further divided into positive, negative, and cognitive or disorganised symptoms (Kay, Fiszbein, & Opler, 1987). Here, positive symptoms refer to experiences which are absent in individuals without psychosis, such as hallucinations and delusions. Negative symptoms represent a reduction or absence of a function which is normally present, examples of this include flatted affect or reduced speech. Finally, cognitive and disorganised symptoms reflect a decline in cognitive function relative to a pre-morbid baseline.

Illness stages are often divided into premorbid, prodromal, early-stage illness, and chronic psychosis. Each stage is characterised by a set of risk and disease markers, which theories of schizophrenia draw from to explain the development and progression of psychotic disorders.

Major Theories of Schizophrenia and Psychosis

ScZ-like clinical cases have been documented since ancient times, but the development of concepts of ScZ and psychosis are relatively recent (Jablensky, 2010). Two particularly influential historical perspectives are those of Kraepelin and Bleuler (Bleuler, 1931; Kraepelin, 1919), whose views still influence contemporary theory (Bürgy, 2008; Jablensky, 2010). Historically, ScZ has been conceptualised as both a developmental and a degenerative disorder. Kraepelin introduced the concept of dementia praecox (Adityanjee, Aderibigbe, Theodoridis, & Vieweg, 1999; Kraepelin, 1919), whereby ScZ was described as an early-onset form of dementia. Here, familial risk was noted, which was thought to reflect a hereditary component. Further, ScZ was thought of as a degenerative, incurable illness involving lesions to the cortex and other brain regions. Although patients often experienced periods of remission, the degenerative process would eventually resume, and it would do so much sooner than in other conditions classed as dementias, where old age is typically a main risk factor (Adityanjee et al., 1999).

Bleuler on the other hand argued that schizophrenia was not always degenerative, and argued that the concept of ScZ should be broad to encompass a range of clinical presentations. Bleuler instead emphasised the loosening of mental associations and flattened affect over a progressive course

of illness and overt psychotic symptoms such as hallucinations (Bleuler, 1931). He further distinguished between two types of ScZ depending on their clinical presentation and clinical outcomes, indicating that some patients may recover over time whereas others do not. Like Kraepelin, Bleuler argued that pathological processes in the brain were the underlying cause behind psychotic disorders (Adityanjee et al., 1999).

Modern developments in ScZ research further emphasised the importance of brain changes in ScZ and other psychotic disorders. Several prominent theories of psychosis further highlight the role of specific neurotransmitter systems in disease development and progression. Here, elements of many theories can broadly be classed as neurodegenerative or neurodevelopmental. In the former case, it is assumed that degeneration occurs over time, whereas in the latter case brain changes are assumed to emerge early in development and remain relatively stable. Many frameworks incorporate both of these elements, but differently so for different brain structures and stages of illness.

The Dopamine Hypothesis

Following the discovery that dopaminergic antagonists reduced psychotic symptoms (Seeman & Lee, 1975), the development of the dopamine hypothesis began. In its simplest form, the dopamine hypothesis assumes that excessive dopaminergic neurotransmission underlies the positive symptoms of psychosis (Benes, 2009; Howes & Kapur, 2009; Seeman & Lee, 1975). In line with this idea, it has been observed that baseline occupancy of dopamine D2 receptors is increased in ScZ (Abi-Dargham et al., 2000), which likely reflects increased baseline activity at these receptor sites. Similarly, dopamine agonists such as amphetamines can be used to induce psychosis-like symptoms in non-clinical human participants as well as animal models (Bell, 1965).

The dopamine system is involved in motor control, reinforcement learning, cognition, and the processing of salience – multiple of these processes have shown alterations in ScZ patients (Björklund & Dunnett, 2007; Winton-Brown, Fusar-Poli, Ungless, & Howes, 2014). Dopamine receptors are typically separated into two classes, with D1 and D5 receptors in one class (D1-like), and D2-D4 in the other (D2-like). D1-like receptors are primarily postsynaptic, and are found in the striatum and subcortex (including the nucleus

accumbens, substantia nigra, caudate and putamen, thalamus, subthalamic nucleus) and hippocampus, whereas D2-like receptors are predominantly presynaptic and can be found in the substantia nigra and ventral tegmental area, hippocampus, amygdala, thalamus and cerebellum, as well as outside of the brain in the kidneys and vascular system (Jackson & Westlind-Danielsson, 1994; Vallone, Picetti, & Borrelli, 2000).

The primary dopamine pathways are the nigrostriatal, mesocortical, mesolimbic, and tuberoinfundibular pathways (Björklund & Dunnett, 2007; Vallone et al., 2000). The dopamine hypothesis of ScZ generally proposes that psychotic symptoms emerge when dopaminergic activity in striatal regions becomes abnormally elevated, and that suppressing striatal dopamine activity with D2 antagonist drugs reduces these symptoms (Howes & Kapur, 2009; Winton-Brown et al., 2014). Excess dopaminergic activity in the striatum is hypothesised to produce aberrant salience, thus giving rise to abnormal percepts and beliefs in the form of hallucinations and delusions (Winton-Brown et al., 2014).

The Glutamate Hypothesis

While dopamine antagonists reliably reduce psychotic symptoms and the efficacy of antipsychotic drugs is related to their ability to antagonise D2 receptors (Kapur & Seeman, 2000), it has been observed that administering these drugs preventatively does not decrease individuals' risk of developing a psychotic disorder (Zhang et al., 2020). It has thus been proposed that although excessive striatal dopamine activity is a clinical feature of acute psychosis, it may be a consequence of the disease process rather than its cause. The glutamate hypothesis proposes that disruptions in the excitatory-inhibitory balance related to glutamatergic receptors may instead drive the disease process and generate striatal hyperdopaminergia (Benes, 2009; Moghaddam & Javitt, 2012). Based on the psychosis-like effects of dissociative drugs such as ketamine or phencyclidine which act on N-methyl-D-aspartate (NMDA) receptors, NMDA receptor hypofunction has been theorised as an aetiological factor behind psychosis (Farber, 2003).

Glutamate is the most prominent excitatory neurotransmitter in the human brain (Platt, 2007). Excess glutamatergic activity can lead to cell death (excitotoxicity), and may occur for a wide range of reasons including traumatic

brain injury, vascular conditions, or neurodegenerative disease (Lau & Tymianski, 2010). Major glutamate receptor classes include NMDA receptors, AMPA receptors, and metabotropic receptors; NMDA receptors in particular may play an important role in maintaining the normal excitatory-inhibitory balance in the brain and have been implicated in conditions of excessive excitation such as seizures or excitotoxicity (Lau & Tymianski, 2010; Platt, 2007). In rodent models, NMDA receptors in the hippocampus, cortex, thalamus and striatum show abnormal activity in response to oxygen deprivation, whereby the hippocampus appears to be particularly susceptible to cell damage induced by the resulting excitotoxicity (Lau & Tymianski, 2010). Besides their involvement in such disease processes, NMDA receptors may play an important role in maintaining normal cognitive function, and their suppression produces cognitive deficits resembling those seen in ScZ (Rowland et al., 2005).

The hippocampus, a brain region which has shown alterations in both ScZ patients and their unaffected relatives (Boos, Aleman, Cahn, Pol, & Kahn, 2007; Ho & Magnotta, 2010), is proposed as a key aetiological site: Here, NMDA receptor hypofunction produces excessive activation of the hippocampus, which in turn causes a decline in its regulatory function over striatal dopamine (Lodge & Grace, 2006; McHugo et al., 2019). This in turn leads to excitotoxic volume loss of the hippocampus itself, and striatal dopamine neurotransmission becomes disinhibited, giving rise to the disruptions in salience also proposed by the dopamine hypothesis of ScZ (Grace, 2012; Lodge & Grace, 2006). Importantly, the glutamate hypothesis implies that pathogenic processes may already be active before the individual patient develops clinically overt psychosis, indicating that risk markers could be used at an earlier stage to predict clinical outcomes and progression.

Alternative Hypotheses

Many hypotheses have been developed to highlight the involvement of different brain systems in psychosis, such as the serotonergic system (Eggers, 2013), cholinergic system (Raedler, Bymaster, Tandon, Copolov, & Dean, 2007), or the γ-Aminobutyric acid (GABA) system (Fujihara, 2023). Other theoretical frameworks emphasise non-biological explanations, such as societal structures (Bhattacahrjee et al., 2011) or social isolation (Jaco, 1954).

While often presented separately, many of these theories are not mutually exclusive, nor competitors to the dopamine and glutamate hypotheses, but rather describe different contributions to psychosis risk and aetiology. For instance, alterations to the overall excitatory-inhibitory balance will likely affect multiple neurotransmitter systems, and each may make its own unique contributions to psychosis symptoms and aetiology. Furthermore, social contributions to psychosis risk likely also affect multiple brain systems (see for example Xiong, Hong, Liu, and Zhang (2023)), so that neuroscientific and sociological hypotheses largely describe different but compatible aspects of psychosis risk and aetiology. While some hypotheses may make different predictions regarding the brain systems which are first to show alterations (e.g. NMDA receptors, in the case of the glutamate hypothesis), the fine details of this are outside the scope of the present work which deals with markers of early-stage and emergent psychosis in adults and adolescent people.

This work will focus primarily on the dopamine and glutamate hypotheses as they are particularly relevant to the present research, and suggest specific, falsifiable hypotheses, such as the role of abnormal hippocampal activity in early-stage psychosis. It should be noted that the aim of this work is not to verify or falsify any particular major hypothesis of schizophrenia, but the dopamine and glutamate hypotheses are discussed to provide theoretical context and rationale for individual hypotheses.

Early-stage Psychosis and Clinical Trajectories

The Clinical At-Risk State

Psychotic disorders are often preceded by a prodromal phase, during which risk markers are present but individuals do not meet the diagnostic criteria for a psychotic disorder yet (Fusar-Poli et al., 2013). While familial risk markers (e.g. first-degree relatives with a psychotic disorder) are sometimes used (Miklowitz, 1994) clinical questionnaires such as the CAARMS or SPI-A (Schultze-Lutter, Addington, Ruhrmann, & Klosterkötter, 2007; Yung, Phillips, Yuen, & McGorry, 2006) establish clinical at-risk status for psychosis (CHR-P) by assessing behavioural symptoms. These behavioural criteria can further be subdivided into high-risk symptoms which are thought to predict the potential

development of a psychotic disorder on a short to medium timescale (Yung et al., 2006), and basic symptoms which reflect more subtle alterations in basic mental processes which may be present long before the onset of psychosis (Schultze-Lutter et al., 2007).

High-risk criteria are met when an individual experiences a general decline in global function over the past year coupled with either positive symptoms (substantial but below the threshold for a psychotic disorder), brief limited intermittent psychosis (suprathreshold positive symptoms which went into remission within one week), or familial high risk (first-degree relative with a psychotic disorder). In contrast, basic symptom criteria assess subjective changes in cognition, perception, and speech, including for instance visual disturbances, thought blockages, or experiences of derealisation (Schultze-Lutter et al., 2007). Basic symptom criteria can further be subdivided into cognitive disturbances (COGDIS), and cognitive-perceptive basic symptoms (COPER).

Taken together, there are therefore five sets of criteria that can be used to establish CHR-P status: brief limited intermittent psychosis (BLIPS), attenuated psychotic symptoms (APS), familial high risk, cognitive disturbances (COGDIS), and cognitive-perceptive basic symptoms (COPER). Individuals may meet one or more of these criteria, whereby meeting multiple such criteria has been associated with a higher risk of transition to a psychotic disorder compared with individuals who only meet one (Schultze-Lutter, Klosterkötter, & Ruhrmann, 2014).

Overall, CHR-P individuals have substantially elevated risk of developing a psychotic disorder compared to the general population, but the majority of them will go on to be diagnosed with psychiatric disorders other than psychosis (Gonzalo Salazar De Pablo et al., 2022; Fusar-Poli et al., 2013). Identifying markers which are specific to psychosis risk and early-stage illness rather than proneness to mental health problems more generally is therefore of particular interest.

Clinical and Cognitive Markers and Outcomes

Transition to psychosis refers to a CHR-P individual meeting diagnostic criteria for a psychotic disorder such as ScZ for the first time. This is also referred to

as first-episode psychosis, or FEP, while early-stage psychosis (EP) is typically defined as the first 5 years following disease onset. CHR-P status is associated with a significantly increased risk of transition to a psychotic disorder, albeit the exact magnitude of this risk has not remained stable across time (Gonzalo Salazar De Pablo, Radua, Pereira, Bonoldi, Arienti, Besana, Soardo, et al., 2021). While earlier studies reported transition rates upwards of 30%, more recent research has seen a marked decrease in transition rates, with some studies showing rates as low as 10-20%. Most recently, a meta-analysis estimated the transition rate at approximately 25%-35%, 3 years and 10 years after establishing CHR-P status, respectively. This represents a large increase compared to the incidence of psychosis of approximately 1% in the general population (Solmi, Seitidis, et al., 2023), but also highlights that CHR-P criteria alone are not sufficiently specific to predict the onset of a psychotic disorder with certainty.

The majority of CHR-P individuals will develop a psychiatric condition regardless of whether they transition to psychosis or not, with only approximately 20% of CHR-P individuals not having a diagnosed illness in some studies (Addington et al., 2017; Gonzalo Salazar De Pablo et al., 2022). The most common diagnoses other than psychosis in CHR-P cohorts are mood and anxiety disorders, as well as substance misuse and personality disorders (Addington et al., 2017; Gonzalo Salazar De Pablo et al., 2022; Lu et al., 2022; Solmi, Soardo, et al., 2023). While a decrease in symptom severity over time is observed for mood and anxiety disorders in particular, most individuals will continue to present with clinically relevant psychopathology for at least several years (Addington et al., 2017; Gonzalo Salazar De Pablo et al., 2022).

Compared to non-clinical, healthy controls (HC), CHR-P individuals score lower on multiple domains of cognitive function. This includes social cognition, emotion recognition, executive function, attention, verbal learning and memory, as well as motor and processing speed, and may be associated with a decline in global functioning as well as social and role (academic/work) function (Carrión et al., 2011; Carrión et al., 2013; Catalan et al., 2021; Eslami, Jahshan, & Cadenhead, 2011; Glenthøj et al., 2016; Lin et al., 2011; Niendam et al., 2006). CHR-P individuals generally show less substantial impairments than chronic ScZ patients, and the severity of cognitive impairment in CHR-P individuals may further be associated with the risk of transition to psychosis (Catalan et al., 2021). The association between

cognitive disability and functioning in psychosis alongside the relatively low specificity of CHR-P criteria in predicting functional and clinical outcomes thus highlights the need to improve clinical outcome prediction. Chapter 1 of this work will present an analysis of global functioning, cognitive, and clinical behavioural data whereby machine learning is used to predict functional outcomes. This highlights markers of psychosis in the behavioural data modality.

Anatomical Markers of Psychosis

Markers of Psychosis Risk

Besides behavioural alterations, psychosis is associated with numerous anatomical alterations in the brain at all stages of illness. Individuals with familial high risk show decreased grey matter volumes and larger ventricles compared to controls with no family history of psychosis (Boos et al., 2007; Ho & Magnotta, 2010). In a meta-analysis, grey matter volume differences were found to be largest in the hippocampus (Boos et al., 2007).

CHR-P status has been associated with decreased grey matter volume in cortical regions including the anterior cingulate cortex, prefrontal cortex, temporal cortex, fusiform gyrus, and insula (Fusar-Poli et al., 2013; Jalbrzikowski et al., 2021; Zikidi et al., 2020). White matter integrity may be reduced in CHR-P (Di Biase et al., 2021), particularly in the superior and inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus (Waszczuk et al., 2021). This indicates impaired long-range anatomical connectivity in CHR-P.

Multiple studies have reported decreased hippocampal volumes in CHR-P (Fabienne Harrisberger, Buechler, et al., 2016; F Harrisberger, Smieskova, et al., 2016; J. Lieberman et al., 2018; Provenzano et al., 2020; Vissink et al., 2022; Wood et al., 2010), although some have not replicated this finding (Walter et al., 2016). There is some evidence that shrinkage may be more pronounced in the hippocampal subregion CA1 (J. Lieberman et al., 2018). Subcortical regions such as the thalamus may also be affected (Fabienne Harrisberger, Buechler, et al., 2016).

There is inconsistent evidence regarding enlargement of the ventricles in CHR-P, with some meta-analytic evidence suggesting it (Vissink et al., 2022) but

other research indicating ventricular volumes to be no different from controls in the CHR-P group as a whole (Berger et al., 2007). However, the transition to psychosis may be associated with enlarged ventricles in CHR-P (Chung et al., 2017; Chung et al., 2015), indicating a potential involvement of the ventricular system in early disease processes. The choroid plexus is a small layer of epithelial cells within the ventricular system which is involved in maintaining the blood-cerebrospinal fluid (CSF) barrier as well as the production of CSF and various immune factors and neurotransmitters (Strazielle & Ghersi-Egea, 2000). Some have suggested that it could contribute to potential abnormalities of the ventricular system in the CHR-P (Deepthi Bannai et al., 2024), but because the choroid plexus is part of the ventricular system and scales with it, problems with collinearity may arise without appropriate statistical corrections.

Markers of Early-Stage Psychosis

Individuals experiencing FEP or EP show more substantial anatomical changes than individuals with elevated psychosis risk (Fusar-Poli, Smieskova, Serafini, Politi, & Borgwardt, 2014), although there is considerable overlap regarding affected brain regions. FEP individuals show reduced overall brain volumes and increased ventricular volumes (Ellison-Wright, Glahn, Laird, Thelen, & Bullmore, 2008; Matéos et al., 2023; Vieira et al., 2021). More specifically, volumes of the temporal (inferior and mid), fusiform, lingual and orbital gyri as well as the insula have been found to be smaller in FEP, whereas right superior temporal gyrus volume may be increased (Vieira et al., 2021). In addition to the cortex, volumetric contraction has been observed in subcortical structures including the amygdala and thalamus (Fan et al., 2019).

The hippocampus has consistently shown decreased volumes in FEP (Fan et al., 2019; J. Lieberman et al., 2018; Nakahara, Matsumoto, & van Erp, 2018; Vieira et al., 2021), whereby the largest contraction may be located in subregion CA1, although CA4 is also implicated (Nakahara et al., 2018).

Anatomical connectivity may be disrupted in FEP, with a meta-analysis implicating the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus, which have shown decreased integrity in CHR-P also (Waszczuk et al., 2021; L. Yao et al., 2013). The meta-analysis further identified decreased white matter integrity in the interhemispheric fibres and cingulum bundle (L.

Yao et al., 2013), indicating that long-range and interhemispheric anatomical connectivity could be disrupted in FEP to a greater extent than in CHR-P.

There is some longitudinal evidence that grey and white matter integrity loss occurs after the onset of FEP (Asami et al., 2012) in non-affective psychosis and particularly in frontal cortical regions (Ohtani et al., 2018). Hippocampal volumes on the other hand may be stable over time in FEP (McHugo et al., 2020; Wood et al., 2001), although hippocampal size at FEP onset may be related to the duration of the first psychotic episode and could be prognostic of the further clinical course (Hýža, Kuhn, Češková, Ustohal, & Kašpárek, 2016). This suggests that volume loss of the hippocampus may occur at the time of FEP onset but not afterwards. Since FEP and CHR-P were not directly compared in this regard, this raises the question whether volume loss starts at the FEP stage, or could already occur in CHR-P individuals. Direct comparisons across illness stages will be required to assess this.

Markers of Chronic Psychosis

Finally, chronic ScZ is associated with widespread volume loss across the brain compared to HC, as well as increased ventricular volumes (Ellison-Wright et al., 2008; Glahn et al., 2008; Vita, De Peri, Deste, & Sacchetti, 2012). Multiple subcortical regions show volumetric decreases in ScZ, including the thalamus, nucleus accumbens, and amygdala (Adriano, Spoletini, Caltagirone, & Spalletta, 2010; Van Erp et al., 2014; Van Erp, Hibar, Rasmussen, Glahn, Pearlson, Andreassen, Agartz, et al., 2016). The globus pallidus and caudate on the other hand was increased in volume (Van Erp, Hibar, Rasmussen, Glahn, Pearlson, Andreassen, Agartz, et al., 2016; van Haren et al., 2016). While some volumetric decline occurs as part of normal aging, subcortical volumes declined over time in ScZ more so than in HC (van Haren et al., 2016). Volumetric decline is also seen in cortical grey matter and total brain volumes, and coincides with further ventricular enlargement (Haijma et al., 2013; Vita et al., 2012).

Abnormalities in the choroid plexus may contribute to ventricular enlargement, with some studies suggesting that choroid plexus volumes too are increased in ScZ (Paulo Lizano, Lutz, Ling, Lee, Eum, Bishop, Kelly, et al., 2019). Recent advances in choroid plexus segmentation however call into question the reliability of past reports, as the identification of choroid plexus boundaries can

differ substantially across segmentation methods (Deepthi Bannai et al., 2024; Tadayon et al., 2020). This indicates that further investigation is needed to determine the extent to which the choroid plexus is altered in psychotic disorders, and how this may differ across illness stages.

Specificity of Anatomical Markers

While CHR-P, FEP, and ScZ are reliably associated with multiple neuroanatomical alterations, this is true also of psychiatric conditions other than psychosis. For instance, hippocampus volumes are decreased in major depressive disorder (MDD)(Cole, Costafreda, McGuffin, & Fu, 2011; Videbech & Ravnkilde, 2004), post-traumatic stress disorder (PTSD) (Kribakaran, Danese, Bromis, Kempton, & Gee, 2020), or alcohol misuse (Wilson, Bair, Thomas, & Iacono, 2017). Similarly, ventricular and choroid plexus enlargement have both been demonstrated in MDD (Noha Althubaity, Schubert, Martins, Yousaf, Nettis, Mondelli, Pariante, et al., 2022; Kempton et al., 2011), which may suggest that these markers are not specific for either one disorder, but could instead be markers of overall psychopathology.

However, distinguishing markers of psychosis from those of other disorders or general pathology is of particular importance when researching emerging psychosis. CHR-P individuals who will later develop psychosis will likely require different treatment compared to individuals who will develop MDD or an anxiety disorder; for early intervention to occur, clinicians will need to know which specific condition an individual is currently developing, as opposed to knowing about the presence of general psychopathology. The latter in particular is already evident through CHR-P status – thus, establishing specificity of markers will make an important contribution to the study of emerging psychosis.

Summary of Anatomical Markers

Psychotic disorders are associated with a loss of grey matter volume and white matter integrity at multiple stages of illness. The hippocampus may be one of the earliest structures to show volumetric decrease, with alterations potentially visible from the CHR-P state and becoming more substantial with the emergence of FEP. Although there is evidence to suggest that hippocampal

shape may be affected particularly in some subregions such as CA1, it is not yet clear if this is the case for both CHR-P and FEP, and how anatomical alterations in the hippocampus and subcortex differ when comparing directly across illness stages.

Furthermore, the ventricular system consistently shows enlargement in diagnosed psychosis. The choroid plexus may play a role in this, but due to methodological limitations in choroid plexus segmentation, the extent to which choroid plexus alterations are present across illness stages in psychosis is not yet clear (see Chapter 3 for a more detailed discussion).

Based on these findings, the hippocampus and several subcortical structures were selected for anatomical analysis (Chapter 2) as well as the choroid plexus and ventricular system (Chapter 3) to identify markers of psychosis from the neuroanatomical data modality. Here, a clinical control group of individuals experiencing various psychiatric problems who did not meet CHR criteria (CHR-N) were further analysed to assess the specificity of markers to psychosis and psychosis risk.

Accounts of Anatomical Changes in Psychosis

While several anatomical changes such as decreased hippocampal volumes are observed across illness stages in psychosis, their role in the disease process is not yet clear. Furthermore, the majority of studies compare each illness stage with HC rather than draw comparisons across illness stages, which leaves open the questions: if and how neuroanatomical alterations differ between stages of psychotic illness.

Echoing historical debates regarding the degenerative nature (or not) of psychotic disorders, some have argued that anatomical changes, especially grey matter volume loss, are progressive in nature (Keshavan, 1999; J. A. Lieberman, 1999), whereas others argue that developmentally very early onset alterations instead drive the disease process (Gilmore, 2010). Yet others argue that volume loss may be confined to periods of active illness – that is, pathological processes during acute psychotic episodes, which subside as the episode comes to an end (Wyatt, 1991). It should be noted that these views are not mutually exclusive, as they could be applied to different brain structures or stages of a process within the same framework (Keshavan, 1999;

J. A. Lieberman, 1999). However, when applied to a specific brain region, they have different implications for comparisons across illness stages. For instance, an early developmental lesion would not be expected to change between the premorbid and FEP stages, whereas a neurodegenerative view would suggest that volume loss should be more substantial the longer the individual has been ill. Comparing neuroanatomy across stages of psychotic illness can therefore give insights into pathological processes.

This, however, still leaves the question how these anatomical changes come to be. Prominent theoretical frameworks, including the glutamate hypothesis, predict that changes in brain structure are, at least to an extent, the result of abnormal brain function in psychosis (Lau & Tymianski, 2010; Moghaddam & Javitt, 2012). Here, it is proposed that NMDA receptor hypofunction leads to aberrant baseline excitation of the hippocampus. This in turn diminishes its regulatory function on striatal dopamine transmission, thus causing disinhibition (Grace, 2012; Lodge & Grace, 2006). A link to neuroanatomical changes has been established in animal models, where the aforementioned excessive excitation causes excitotoxic damage to the hippocampus, resulting in volume loss (Grace, 2012; J. Lieberman et al., 2018). While this is by no means the only instance where abnormal brain activity may lead to anatomical and behavioural deficits in models of ScZ, the hippocampus has consistently emerged as an anatomical region of interest (ROI) in human research, and animal research provides a potential link between alterations from the anatomical and functional imaging modalities. This implies that functional imaging should reveal further alterations in early and emerging psychosis, and may offer a more complete picture compared to anatomical analysis alone.

Brain Networks in Psychosis

Anatomical alterations in psychosis may be caused at least in part by changes in brain function. Non-invasive neuroimaging methods, such as functional MRI (fMRI), or magneto/electroencephalography (M/EEG), can be used to detect changes in brain function in human subjects, while more invasive methods such as single cell recordings can be used in animal models of psychosis. Across illness stages, several functional alterations can be seen in psychosis, although open questions remain regarding the role of particular structures

such as the hippocampus, the specificity to psychosis, and potential differences between illness stages.

More specifically, the glutamate hypothesis suggests that the excitatory-inhibitory balance becomes disrupted in ScZ due to NMDA receptor hypofunction (Benes, 2009). In the case of the hippocampus, this causes it to become excessively excited at baseline, and lose its regulatory function over subcortical dopamine neurotransmission, thus resulting in excessive dopaminergic activity in the striatum (Grace, 2012). Recent work has emphasised the role of cortico-striato-thalamic brain networks in such processes (Sabaroedin, Tiego, & Fornito, 2023). Here, it is proposed that due to different disease processes, chronic ScZ is characterised by global decreases in connectivity across the entire network, while functional connectivity alterations at earlier stages of illness (FEP, CHR-P) may be more varied.

This is not the only network where disease-relevant processes likely occur, as changes have also been identified in sensorimotor networks (Kaufmann et al., 2015) or fronto-parietal control network (Tu, Lee, Chen, Li, & Su, 2013). An overview over alterations in functional connectivity will now be given for the different illness stages, whereby the hippocampus and cortico-striato-thalamic networks are particularly of interest (Sabaroedin et al., 2023). This is not because other networks do not matter in emerging psychosis, but because this network provides a bridge between our anatomical findings and potentially associated changes in brain function.

Measuring Brain Networks

The extent to which a given set (or pair) of brain regions is connected or networked can be measured in multiple ways. In fMRI studies, functional connectivity (FC) is commonly used. This is typically given as the correlation between two time-courses of blood-oxygen level dependent (BOLD) signals taken from two brain regions. Functional connectivity can be recorded during resting state, that is, when individuals do not do anything in particular in the scanner, or it can be recorded while participants perform a task.

Using general linear modelling (GLM) approaches, it is possible to examine changes in activity in a given region or regions depending on task conditions.

Connected networks of brain regions can either be defined a priori, or found with data-driven methods such as independent component analysis (ICA). fMRI can be used to image the entire brain with good spatial resolution, but the BOLD signal is an indirect measure of brain activity and relatively sluggish temporally (Boly, Gosseries, Massimini, & Rosanova, 2016). For a more extensive characterisation of the BOLD signal and its meaning, see e.g. Logothetis and Wandell (2004).

With electrophysiological methods such as electroencephalography (EEG) or magnetoencephalography (MEG), temporal resolution is very high, but spatial resolution is relatively poor. Regions further away from the scalp such as the subcortex cannot be measured well using EEG/MEG, thus these methods also have limited spatial coverage (Boly et al., 2016).

In both types of functional neuroimaging methods, brain networks can be assessed using correlational methods, data-driven methods (e.g. ICA), or graph theory. Graph theory is a branch of mathematics which deals with the formal analysis of networks, also known as graphs. It is therefore of particular interest to the analysis of brain networks (Fornito, Zalesky, & Bullmore, 2016), and key aspects will now be described. In graph theory, networks have two basic components: nodes and edges. Nodes represent individual objects, such as brain regions, and edges reflect the connections between them, which could be given e.g. by FC. Networks can either be binary or weighted. The edges are either present or absent between any pair of nodes in the former, and in the latter, non-zero edges can have a range of values to indicate, for example, the strength of the connection. Using this information, graph theory provides tools to describe both the properties of the overall network, as well as the nodes within it. Measures of centrality or node importance can indicate what role a given node plays in the network – for instance, how many total connections it has (degree centrality), or the extent to which it acts as a bridge between different clusters in the network (betweenness centrality). The overall connectedness of the network can also be described, for example by giving the average number of steps required to get from each node to every other node in the network (Fornito et al., 2016).

Brain activity and networks can therefore be described by investigating changes in activity in response to some condition, by measuring the correlation between a pair of brain regions, or by using graph theory to

describe the network as a whole. A brief summary of findings using such methods in different illness stages of psychosis will now be given.

Markers of Psychosis Risk

CHR-P status is associated with BOLD signal decreases in the inferior, superior and medial frontal gyri and the anterior cingulate (Fusar-Poli, 2012), as well as increased recruitment of the frontal cortex and thalamus, and decreased recruitment of the striatum alongside reduced cognitive task performance (Fusar-Poli et al., 2007), although several alterations in activation are seen in the absence of overt behavioural differences (Andreou & Borgwardt, 2020). The hippocampus has shown increased regional cerebral blood flow at baseline, which is suggestive of hyperactivity at rest (Allen et al., 2016). The involved regions are ordinarily recruited during a broad range of tasks, including cognitive control, sensory gating, reinforcement learning, or memory formation. Multiple of these regions are also part of the salience network (Peters, Dunlop, & Downar, 2016), and could potentially make early contributions to aberrant salience.

In studies using EEG, mismatch negativity and the P300 component are decreased compared to healthy controls (Hamilton, Boos, & Mathalon, 2020). Mismatch negativity here refers to a negative EEG signal which occurs in response to infrequent auditory stimuli, while the P300 is measured when an infrequent, irrelevant stimulus occurs during a task. Both components thus indicate response to unexpected stimuli, and are tied to the salience and attention networks (de la Salle et al., 2021). This is further corroborated by fMRI investigations, whereby the salience network as a whole was found to have lower functional connectivity (FC) at rest in CHR-P compared to HC (Del Fabro et al., 2021).

In network analyses, reduced centrality was seen in the anterior cingulate cortex (ACC)(Lord et al., 2012). While theoretical frameworks such as the glutamate hypothesis imply that the centrality of the hippocampus may also be altered, this has not been investigated yet in CHR-P to my knowledge.

Markers of Early-Stage Psychosis

In FEP patients, hypoactivation is observed in multiple brain regions during cognitive tasks. More specifically, a meta-analysis suggests lowered BOLD signal during tasks in the striatum, insula, and precuneus. Several included studies identified reduced activation in the (pre)frontal cortex and anterior cingulate cortex (Soldevila-Matías et al., 2022). The salience network, default mode network (DMN), and central executive networks have lower overall connectivity in individuals with FEP compared to HC (O'Neill, Mechelli, & Bhattacharyya, 2019). Connectivity between the inferior frontal cortex and hippocampus may be decreased (Benetti et al., 2009).

Non-task related, spontaneous BOLD signal fluctuations are increased in FEP compared to HC in the striatum and middle frontal gyrus, but decreased in the inferior frontal and precentral gyrus (Cattarinussi, Grimaldi, & Sambataro, 2023). This, coupled with previous findings of decreased task-related activity, could indicate increased baseline activation. This has also been found for the hippocampus, where baseline BOLD signal is increased in FEP, but decreased during cognitive tasks, coinciding with lower performance compared to HC (McHugo et al., 2019).

At the level of the network, decreased network connectivity among nodes from the DMN, sensorimotor network, and cingulate has been observed in FEP (Rikandi et al., 2022); some network analyses however found network properties to be preserved and stable in FEP patients (Ganella et al., 2018).

Markers of Chronic Psychosis

ScZ patients show widespread changes in functional connectivity. Thalamic connectivity with sensory areas was found to be elevated in ScZ compared to HC, while connectivity with frontal regions was reduced in a meta-analysis (Giraldo-Chica & Woodward, 2017). The hippocampus and frontal gyrus may show reduced task-induced activation (Ledoux et al., 2013), although the hippocampus has also shown increased functional connectivity during memory tasks (Kraguljac, Srivastava, & Lahti, 2013), indicating that the direction of effects may be task dependent.

Alterations in functional connectivity did not show specific associations with cognitive function, but rather generalised cognitive disability was found to

coincide with widespread changes in brain function (Sheffield & Barch, 2016). Hypoconnectivity was found to recover to an extent with antipsychotic admission, particularly between the midbrain and ACC (Hadley et al., 2014).

At the level of brain networks, a meta-analysis did not find evidence for hyperconnectivity in any brain networks identified through ICA in ScZ, but instead observed hypoconnectivity in the DMN, sensory, core, and self-referential networks (S. Li, Hu, et al., 2019). Widespread hypoconnectivity has also been noted in networks involving the frontal cortex, subcortex, as well as hippocampus (Sabaroedin et al., 2023).

Graph-theoretic analyses have not been consistent, with the most recent meta-analysis not identifying any reliable alterations in ScZ patients (Gao et al., 2023), while an older review suggested that local network alterations may be present in ScZ, particularly with regard to network clustering which was reduced (Van Den Heuvel & Fornito, 2014). In the older review, evidence is noted in particular for reduced long-range connectivity in ScZ (Van Den Heuvel & Fornito, 2014). There is currently no consensus regarding graph analysis methods in neuroimaging, which likely contributed to the heterogeneity in observed findings (Gao et al., 2023).

Summary of Functional Markers

Common across multiple illness stages are findings of increased baseline activation coupled with decreased recruitment during cognitive tasks in multiple brain regions. Here, the hippocampus consistently emerges, as well as potentially the striatum. Altered activation in the frontal cortex and multiple subcortical sites is replicated several times across illness stages, implying that activity at these sites could reveal markers of psychosis risk.

While chronic psychosis may be characterised by widespread reductions in connectivity, alterations could be more varied in earlier stages of illness. While hypoconnectivity is observed in both CHR-P and FEP, the question remains whether the magnitude of this is comparable across these stages, or whether alterations are more substantial with later stages of illness.

Graph-theoretic analyses in particular are strongly affected by methodological choices, which likely resulted in inconsistent meta-analytic results in ScZ. The extent to which network alterations are present in CHR-P and FEP also remains

unclear. The number of investigations which conduct such analyses in CHR-P remain very limited; and those in FEP do no show consistent results, which may again be linked to the lack of methodological consensus in graph-theoretic analysis of brain networks. Furthermore, although the theoretical frameworks suggest a pivotal role for the hippocampus in particular brain networks (see e.g. Sabaroedin et al. (2023)), to my knowledge, it has not yet been the focus of investigation in either CHR-P or FEP. This is why Chapter 4 of this thesis presents an analysis of the role of the hippocampus in cortical-subcortical brain networks, while paying particular attention to methodological issues and drawing from the latest developments in fMRI preprocessing and denoising.

Research Aims

Alterations in early-stage and emergent psychosis are not confined to any one data modality, but can be identified behaviourally, neuroanatomically, and in functional neuroimaging. The existing literature suggests that neither approach on their own can provide a complete picture of psychosis, but that multimodal research is needed to elucidate markers of psychosis from all these perspectives. To contribute to the existing body of knowledge, this thesis therefore aims to identify markers of early-stage and emerging psychosis and clinical outcomes using these three modalities.

Chapter 1 draws from the behavioural modality: Here, we investigate the association between cognition and functional outcomes in CHR-P individuals, using a machine learning approach to determine the extent to which cognitive markers could be used for individualised predictions.

Chapters 2 and 3 use magnetic resonance imaging (MRI) data to identify neuroanatomical markers of CHR-P and early-stage psychosis. As previously discussed, there is evidence that both the subcortex, including the hippocampus, and the ventricular system are altered in psychosis, but the extent to which such alterations differ between CHR-P and FEP individuals remains unclear. As alterations have been identified in other clinical conditions also, we incorporated a clinical control group to assess the specificity of alterations to psychosis in our sample. Furthermore, the literature on the choroid plexus within the ventricular system in particular could be enhanced

by addressing certain methodological issues relating to statistical controls as well as choroid plexus segmentation. These chapters therefore aim to identify neuroanatomical markers in the subcortex and ventricular systems in a rigorous way, and assess their specificity to psychosis.

Chapter 4 involves the analysis of functional MRI data (fMRI), which can provide insights into brain function. Because theoretical models drawing from the glutamate hypothesis in particular suggest that changes in brain function may give rise to anatomical deficits in cortical-subcortical networks involving the hippocampus, we focus on this network. We compare changes across illness stages, and assess the specificity to psychosis using the CHR-N clinical control group. Furthermore, we draw from recent advances in fMRI preprocessing to minimise the risk of false positive findings due to e.g. motion artifacts. The relationship between identified effects and anatomy is further assessed, as well as the relationship with clinical features.

The thesis as a whole therefore has the following aims: Firstly, to identify markers specific to psychosis at different stages of illness. This is addressed by comparing patients with psychotic disorders to both a clinical and a non-clinical control group. Secondly, to identify markers specific to psychosis risk, and assess whether such markers resemble markers of disease. We investigate this by comparing individuals at clinical high-risk of psychosis to a clinical and a non-clinical control group, and by comparing clinical high-risk individuals to patients with early-stage and chronic psychosis. Finally, this thesis aims to determine if the identified markers are associated with each other, or if they are independent. That is, do these potential markers capture similar aspects of psychosis, or is the information conveyed by each marker unique?

Chapter 1: The relationship between cognitive deficits and impaired short-term functional outcome in clinical high-risk for psychosis participants: A machine learning and modelling approach.

Kate Haining, MSc*, Gina Brunner, MSc*, Ruchika Gajwani, Ph.D. , Joachim Gross, Ph.D., Andrew I. Gumley, Ph.D., Stephen M. Lawrie M.D., Matthias Schwannauer, Ph.D., Frauke Schultze-Lutter, Ph.D., & Peter J. Uhlhaas, Ph.D.

* these authors contributed equally

Abstract

Poor functional outcomes are common in individuals at clinical high-risk for psychosis (CHR-P), but the contribution of cognitive deficits remains unclear. We examined the potential utility of cognitive variables in predictive models of functioning at baseline and follow-up with machine learning methods. Additional models fitted on baseline functioning variables were used as a benchmark to evaluate model performance.

Data were available for 146 CHR-P individuals of whom 118 completed a 6- and/or 12-month follow-up; as well as 47 participants not fulfilling CHR criteria (CHR-Ns) but displaying affective and substance use disorders; and 55 healthy controls (HCs). Predictors of baseline global assessment of functioning (GAF) scores were selected by L1-regularised least angle regression and then used to train various classifiers, evaluated with 10-fold cross-validation, to predict functional outcome in CHR-P individuals.

In CHR-P participants, cognitive deficits together with clinical and functioning variables explained 41% of the variance in baseline GAF scores while cognitive variables alone explained 12%. These variables allowed classification of functional outcome with an average balanced accuracy (BAC) of 63% in both mixed- and cross-site models. However, higher accuracies (68%-70%) were achieved using classifiers fitted only on baseline functioning variables.

Our findings suggest that cognitive deficits, alongside clinical and functioning variables, displayed robust relationships with impaired functioning in CHR-P participants at baseline and follow-up. Moreover, these variables allow for prediction of functional outcome. However, models based on baseline functioning variables showed a similar performance, highlighting the need to develop more accurate algorithms for predicting functional outcome in CHR-P participants.

Introduction

Psychotic disorders, such as schizophrenia, continue to pose a significant challenge for the field given that many patients experience poor outcomes and the absence of significant advances in treatments over the last decades (Millan et al., 2016; Owen et al., 2016). Schizophrenia may be preceded by a clinical high-risk for psychosis (CHR-P) state lasting approximately 5-6 years (Schultze-Lutter et al., 2015) and clinical criteria have been developed to detect individuals prior to the onset of full-blown psychosis (Fusar-Poli et al., 2013). CHR-P criteria include attenuated psychotic symptoms, brief frank psychosis and functional decline with genetic risk (Yung et al., 2005) as well as self-experienced perceptual and cognitive anomalies known as basic symptoms (Schultze-Lutter, 2009; Schultze-Lutter et al., 2012). Approximately 20% of individuals meeting CHR-P criteria will transition to psychosis within a 2-year period (Fusar-Poli et al., 2016). Moreover, around 40-50% of nonconverters continue to experience impairments in social and role functioning (Carrión et al., 2013; Koutsouleris et al., 2018). Therefore, understanding the underlying factors as well as predictors of poor functioning in CHR-P individuals is an important objective for early detection and intervention.

Negative symptoms, disorganised symptoms, impairments in social and role functioning and poor premorbid psychosocial adjustment have been found to predict poor baseline functioning and/or poor functional outcome at follow-up (Carrión et al., 2013; Glenthøj et al., 2016; Koutsouleris et al., 2018; Salokangas et al., 2014). Although positive symptom severity is predictive of transition to psychosis, effects on functioning remain inconsistent (Carrión et al., 2016; Meyer et al., 2014).

While there is emerging evidence for a relationship between cognitive deficits and impaired functioning in CHR-P individuals, the contribution of specific cognitive deficits varies across studies. Cognitive deficits, predominantly in verbal memory, are an established mediator of functional outcomes in chronic schizophrenia (Green, 1996; Schmidt et al., 2011). Interestingly, in studies of early psychosis, reasoning, problem solving and motor skills more frequently predict short-term (< 2 years) functional outcome while language/verbal skills and global/general cognition more often predict longer-term (> 2 years) functional outcome (Allott et al., 2011). In CHR-P individuals specifically, impairments in verbal memory, emotion recognition and processing speed have been linked with impairments in social and/or role functioning at baseline and follow-up (Carrión et al., 2011, 2013; Glenthøj et al., 2016; Lin et al., 2011; Modinos et al., 2019; Niendam et al., 2006). Moreover, deficits in verbal learning and fluency, motor speed and executive function have also been associated with poor functioning in CHR-P individuals (Carrión et al., 2013; Eslami et al., 2011; Lin et al., 2011; Niendam et al., 2006).

In the current study, we sought to clarify the contribution of cognitive deficits towards impaired functioning in CHR-participants. To identify predictors of functioning, we employed a machine learning approach in which we first identified variables associated with baseline functioning using LASSO-LARS regression and then predicted functional outcome at follow-up with classifiers evaluated using 10-fold cross-validation and permutation testing. While machine learning studies have previously shown potential for identifying predictors of transition to psychosis as well as functional outcomes based on clinical, functional and neuroimaging data (Kambeitz-Ilankovic et al., 2016; Koutsouleris et al., 2009, 2012, 2018), a considerable proportion have also failed to provide convincing evidence (Fusar-Poli et al., 2019; Mechelli et al., 2017; Ramyead et al., 2016). Furthermore, previous studies predicting functional outcome using cognitive measures have applied more traditional logistic regressions without cross-validation or regularisation techniques, potentially carrying a risk of overfitting (Carrión et al., 2013; Eslami et al., 2011; Lin et al., 2011; Meyer et al., 2014; Modinos et al., 2019). Even in machine learning studies leveraging these techniques, few have attempted to compare their multi-step machine learning pipelines to simpler predictive models in order to justify this added complexity (DeMasi et al., 2017).

To address these gaps, we firstly examined the contribution of clinical, functioning and cognitive variables to impaired functioning at baseline in CHR-P participants. We also included a sample of participants who did not fulfil CHR-P criteria but were characterised by mood, anxiety and substance use (i.e. alcohol and drug) disorders (CHR-Ns), as well as healthy controls (HCs). We then applied a machine learning approach to those variables associated with impaired functioning at baseline in order to predict short-term functional outcome. We additionally created simpler predictive models of functional outcome using only baseline functioning variables to determine whether our more complex machine learning pipeline provided a significant increase in predictive performance. Given the contribution of cognitive impairment to impaired functioning in established schizophrenia (Green, 1996; Schmidt et al., 2011), we hypothesised that the inclusion of cognitive variables in machine learning models would enhance the prediction of functional outcome in CHR-P participants, outperforming simpler models.

Methods

Participants

The data were collected as part of the Youth Mental Health Risk and Resilience (YouR) study (Uhlhaas et al., 2017), an ongoing longitudinal study funded by the Medical Research Council (MRC), which aims to identify neurobiological and psychological mechanisms and predictors of psychosis risk. CHR-P participants were recruited through an online-screening approach (www.your-study.org.uk; McDonald et al., 2019) and via referrals from NHS patient services and student counselling services. CHR-N participants (N = 47) were also recruited using the former approach while HCs (N = 55) were obtained from an existing volunteer database. CHR-N participants were recruited to allow for a more meaningful comparison with the CHR-P group (Millman et al., 2019). By including participants with affective and substance use disorders (CHR-N group), we aimed to separately assess the impact of psychiatric comorbidity given that such comorbidity is also characteristic of the CHR-P state. Recruitment and assessment visits/ratings were carried out by trained research assistants and MSc/PhD level researchers.

Data were available for 146 CHR-P individuals that were recruited across two sites: Glasgow (n = 109; 74.7%) and Edinburgh (n = 37; 25.3%). One hundred and eighteen participants (80.8%) completed a follow-up session at 6 and/or 12 months. Attrition rates were similar across sites (Glasgow: 20.2%; Edinburgh: 16.2%).

Baseline Assessments

The positive scale of the Comprehensive Assessment of At-Risk Mental States (CAARMS; Yung et al., 2005) and the Cognitive Disturbances (COGDIS) and Cognitive-Perceptive Basic Symptoms (COPER) items of the Schizophrenia Proneness Instrument, Adult version (SPI-A; Schultze-Lutter et al., 2007) were administered to all participant groups. Participants were recruited into the CHR-P group if they met SPI-A COGDIS/COPER criteria or one of the following CAARMS criteria: Attenuated Psychosis Symptoms (APS), Genetic Risk and Deterioration Syndrome (GRD) or Brief Limited Intermittent Psychotic Symptoms (BLIPS).

All participants were also assessed with the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), Global Assessment of Functioning (GAF) scale from the DSM-IV-TR, Global Functioning: Social (GF: Social) and Role (GF: Role) scales (Cornblatt et al., 2007), Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982) and Adverse Childhood Experiences Scale (ACES; Felitti et al., 1998). Neuropsychological assessments consisted of the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004) and three tasks from the Penn Computerized Neurocognitive Battery (CNB; Moore et al., 2015): the Continuous Performance Test, the N-Back Test and the Emotion Recognition Task which provide measures of accuracy and response time (RT) for attention, working memory and emotion recognition respectively.

Follow-Up Assessments

Follow-up interviews were conducted at 6- and 12-months following the baseline assessments for the CHR-P and CHR-N groups and involved the positive scale of the CAARMS as well as the GAF, GF: Social and GF: Role scales. The HC group did not complete follow-up assessments.

Statistical Analysis

Preprocessing

Data were analysed using Python (3.7) packages Numpy, Pandas and Scikit-learn (SKL). In accordance with Keefe et al. (2008), BACS raw scores were converted into standardized z-scores using the means and standard deviations of gender-specific HCs. This gender correction was applied because gender has been shown to affect BACS performance in a normative sample (Keefe et al., 2008). For consistency, CNB raw scores were calculated in the same way, albeit without correction for gender. CAARMS severity was calculated by multiplying the global score by the frequency score for each of the four domains and summing these products while SPI-A severity was calculated by summing the frequency scores for each basic symptom. Where participants did not experience a symptom, the associated frequency and distress were set to zero while those with missing data for the outcome variable were removed. Participants and variables with < 70% of the measures of interest were removed and missing values were imputed by Bayesian Ridge regression.

Additional columns were generated for GAF scores to define good (GFO) or poor functional outcome (PFO), whereby GAF scores below 65 were coded as PFO. In line with prior studies (Allen et al., 2015; Modinos et al., 2019), this cut-off was selected because the 61-70 range corresponds to the presence of "some difficulty in social, occupational or school functioning but [the person] has some meaningful interpersonal relationships". We additionally calculated how many participants changed GAF category between baseline and follow-up as well as GAF changes over time.

Group Comparisons

Group differences were analysed using non-parametric Kruskal-Wallis H tests or Mann–Whitney U tests and chi-square tests, followed by appropriate post hoc tests if required.

Regression Analysis

To determine which variables were associated with baseline GAF scores in CHR-P and CHR-N groups, we fitted combined and cognitive models, whereby the former included clinical, cognitive and functioning variables. We used L1-regularised least angle regression (LASSO-LARS; Efron et al., 2004), with 10-fold cross-validation, as implemented in the SKL function LassoLarsCV. This method is particularly appropriate for addressing the high dimensionality of our candidate predictor set (Fonti, 2017). We excluded attention accuracy as its distribution was highly skewed with a small number of extreme outliers.

Classification Analysis

We trained classifiers to categorise CHR-P individuals into GFO/PFO based on the last available follow-up data (6 months [n = 26] or 12 months [n = 92]). Classifiers included gaussian naive bayes (GNB), linear discriminant analysis (LDA), support vector machines (SVM), random forest classification (RFC) and logistic regression (LR). With the exception of class weights, which were set to 'balanced' due to the unequal numbers of PFO and GFO individuals, default SKL hyperparameters were used. Using only those CHR-P participants with follow-up information, variables not set to zero by the LASSO-LARS model were used for these models (Supplementary Figure 1). All variables were rescaled between zero and one to avoid class separability problems induced by differences in scaling. Due to class imbalance with PFO being more common than GFO, we used area under the curve (AUC) scores to determine whether classifiers performed significantly above chance.

Mixed-site classifiers were evaluated using 10-fold cross-validation, whereby the full dataset was used, and performance metrics are reported as averaged across k-folds. Specifically, the SKL function permutation_test_score (10000 permutations), which implements Test 1 from Ojala and Garriga (2010), was used to conduct permutation tests to evaluate AUC significance. We report performance metrics for all classifiers to evaluate their consistency, as very large discrepancies could suggest that the best performing classifiers were simply overfitting (Vieira et al., 2020).

To determine whether transfer could be established between the two test sites, cross-site classifiers were additionally evaluated with AUC scores obtained by

training on the Glasgow data and testing on the Edinburgh data. This split was used as approximately two thirds of the data were collected at the Glasgow site. We report mean AUC, precision, recall, F1 scores (the harmonic mean of precision and recall) and mean balanced accuracy (BAC) for all classifiers. Recall for the two classes (PFO, GFO) corresponds to sensitivity and specificity, respectively. Precision, recall and F1 scores were generated using the functions cross_val_predict and classification_report, whereby the former reports the prediction given for each data point when in the test set. All other scores reflect the mean across k-folds.

We also created two models which utilised only baseline functioning variables to obtain a stricter benchmark for classifier accuracy. In the first model, we split baseline GAF scores into good and poor functioning at baseline using the same threshold and used these data as predictors. In the second model, we trained the classifiers on social and role functioning as well as GAF scores to determine whether these additional variables could significantly improve classification accuracy compared to those based on baseline GAF scores alone.

Results

Demographic Information

In the CHR-P group, 106 (72.6%) and 70 (59.3%) individuals had poor functioning at baseline and follow-up respectively (Table 1). CHR-P individuals were significantly impaired relative to CHR-N and HC participants, displaying greater symptom severity and distress, increased ACES scores, more comorbid anxiety and mood disorders, lower functioning and poorer attention and processing speed. In addition, CHR-P participants were younger and reported fewer years of education. In the CHR-P group, baseline GAF scores were significantly affected by drug abuse/dependence ($p = .022$), anxiety disorders ($p = .031$) and mood disorders ($p < .001$). Age, gender, education and medication use exerted no such effects. Significant differences across study sites for the CHR-P group are displayed in Supplementary Table 1.

Table 1-1. Demographic, clinical, functioning and cognitive characteristics of the entire sample (N = 248)

Variable	CHR-P (N = 146)	CHR-N (N = 47)	HC (N = 55)	*p*-value	Post hoc tests
Age (years), mean (SD)	21.47 (4.22)	22.94 (4.80)	22.31 (3.39)	.025	CHR-P v HC, CHR-N
Gender, female n (%)	104 (71.2)	30 (63.8)	37 (67.3)	.606	-
Education (years), mean (SD)	15.12 (3.09)	16.45 (3.44)	16.38 (2.84)	.006	CHR-P v HC, CHR-N
CAARMS severity, median (range)	28 (0-74)	6 (0-24)	0 (0-12)	< .001	CHR-P v HC v CHR-N
CAARMS mean distress, median (range)	30 (0-86)	3 (0-55)	0 (0-25)	< .001	CHR-P v HC v CHR-N
SPI-A severity, median (range)	7 (0-74)	0 (0-7)	0 (0-2)	< .001	CHR-P v HC, CHR-N
SPI-A mean distress, median (range)	3 (0-28)	0 (0-6)	0 (0-1)	< .001	CHR-P v HC v CHR-N
CHR-P criteria subgroup, n (%)					
CAARMS	45 (30.8)	-	-	-	-
SPI-A	37 (25.3)	-	-	-	-
CAARMS/SPI-A	64 (43.8)	-	-	-	-
ACES total, median (range)	2 (0-8)	1 (0-4)	0 (0-4)	< .001	CHR-P v HC v CHR-N
Comorbidity, n (%)					
Anxiety disorder	104 (71.2)	22 (46.8)	0 (0)	< .001	CHR-P v HC v CHR-N
Mood disorder	97 (66.4)	14 (29.8)	0 (0)	< .001	CHR-P v HC v CHR-N
Alcohol abuse/dependence	46 (31.5)	11 (23.4)	2 (3.6)	< .001	HC v CHR-P, CHR-N
Drug abuse/dependence	24 (16.4)	3 (6.4)	0 (0)	.002	CHR-P v HC
Eating disorder	11 (7.5)	1 (2.1)	0 (0)	.054	-
Medication, n (%)					
Antipsychotic	4 (2.7)	0 (0)	0 (0)	.242	-
Mood stabiliser	4 (2.7)	0 (0)	0 (0)	.242	-
Antidepressant	53 (36.3)	13 (27.7)	0 (0)	< .001	HC v CHR-P, CHR-N
Anti-anxiety	10 (6.8)	1 (2.1)	0 (0)	.076	-
GAF, median (range)	58 (21-95)	70 (43-94)	88 (67-97)	< .001	CHR-P v HC v CHR-N

Poor baseline functioning, n (%)	106 (72.6)	-	-		-
PFO, n (%)	70 (59.3)	-	-		-
Social functioning, median (range)	8 (3-10)	8 (6-9)	9 (8-10)	< .001	CHR-P v HC v CHR-N
Role functioning, median (range)	8 (3-9)	8 (5-9)	9 (5-9)	< .001	CHR-P v HC v CHR-N
PAS average, median (range)	1.22 (0-3.43)	0.86 (0-3.86)	0.43 (0-1.64)	< .001	CHR-P v HC v CHR-N
BACS, mean (SD)					
Verbal memory	-0.22 (1.20)	0.09 (1.05)	0 (1.01)	.295	-
Motor speed	-0.72 (1.21)	-0.39 (1.01)	0 (1.01)	< .001	CHR-P v HC
Attention & processing speed	-0.48 (1.14)	0.08 (1.19)	0 (1.01)	.001	CHR-P v HC, CHR-N
Verbal fluency	-0.09 (1.24)	-0.23 (1.05)	0 (1.01)	.760	-
Executive function	0 (1.34)	0.05 (1.25)	0 (1.01)	.855	-
Working memory	-0.08 (1.41)	0.24 (1.13)	0 (1.01)	.443	-
Composite score	-0.59 (1.71)	-0.07 (1.36)	0 (1.01)	.022	CHR-P v HC
CNB, mean (SD)					
Emotion recognition accuracy	-0.17 (1.13)	-0.10 (0.91)	0 (1.01)	.565	-
Emotion recognition RT	0.59 (1.58)	0.18 (1.33)	0 (1.01)	.037	CHR-P v HC
Attention accuracy	-0.71 (2.60)	0.10 (1.13)	0 (1.01)	.039	CHR-P v HC
Attention RT	-0.11 (0.86)	-0.26 (0.96)	0 (1.01)	.326	-
Working memory accuracy	-0.41 (1.68)	-0.17 (1.23)	0 (1.01)	.286	-
Working memory RT	-0.05 (0.82)	-0.10 (0.98)	0 (1.01)	.691	-

Note. CHR-P, clinical high-risk for psychosis; CHR-N, clinical high-risk-negative; HC, healthy control; CAARMS, Comprehensive Assessment of At-Risk Mental States; SPI-A, Schizophrenia Proneness Instrument, Adult version; ACES, Adverse Childhood Experience Scale; GAF, Global Assessment of Functioning; PFO, poor functional outcome; PAS, Premorbid Adjustment Scale; BACS, Brief Assessment of Cognition in Schizophrenia; CNB, Penn Computerized Neurocognitive Battery; RT, response time

Baseline Regression Analysis

We fitted combined models where clinical, cognitive and functioning variables were entered as candidate predictors, and a cognitive model which only included cognitive variables.

In the combined model for the CHR-P group, cognitive (verbal memory, working memory RT, emotion recognition accuracy, motor speed), functioning (premorbid adjustment, social and role functioning) and clinical (SPI-A and CAARMS severity and distress, ACES total) variables were associated with baseline GAF scores (Figure 1). The combined model explained 41% of the variance in GAF scores in the CHR-P group, whereas the cognitive model explained 12%. The cognitive model contained verbal memory, working memory accuracy and RT, executive function, emotion recognition accuracy and attention RT (Supplementary Figure 2). Unexpectedly, motor speed and executive function were negatively related to GAF scores in the combined and cognitive models, respectively, while attention RT was positively related to GAF scores in the cognitive model.

Table 1-2: Nonzero LASSO-LARS regression coefficients for CHR-P (N = 146) and CHR-N (N = 47) baseline models

Variable	β coefficient		
	CHR-P combined	CHR-P cognitive model	CHR-N
Social	2.97		1.12
PAS average	-2.15		
Role functioning	1.24		2.07
Working memory	-0.96	-1.88	
SPI-A mean	-0.85		-0.63
ACES total	-0.51		
Motor speed	-0.24		
Verbal memory	0.24	1.88	
Emotion	0.11	1.75	
Total CAARMS	-0.10		
SPI-A severity	-0.05		

CAARMS mean	-0.02
Attention RT	1.27
Executive	-0.60
Working memory	0.05

Note. CHR-P, clinical high-risk for psychosis; CHR-N, clinical high-risk-negative; CAARMS, Comprehensive Assessment of At-Risk Mental States; SPI-A, Schizophrenia Proneness Instrument, Adult version; ACES, Adverse Childhood Experience Scale; GAF, Global Assessment of Functioning; PAS, Premorbid Adjustment Scale; RT, response time

Concurring with permutation feature importance scores (Supplementary Table 2), social functioning (β = 2.97) emerged as the strongest predictor in the combined model (Table 2; Supplementary Table 3) whereas verbal memory (β = 1.88) was a particularly strong predictor in the cognitive model (Table 2).

The combined model for the CHR-N group explained 17% of the variance in baseline GAF scores. This model included clinical (SPI-A distress) and functioning (social and role functioning) variables (Supplementary Figure 3) with role functioning (β = 2.07) emerging as the strongest predictor (Table 2, Supplementary Table 2). The cognitive model for the CHR-N group, however, failed to explain any variance in GAF scores.

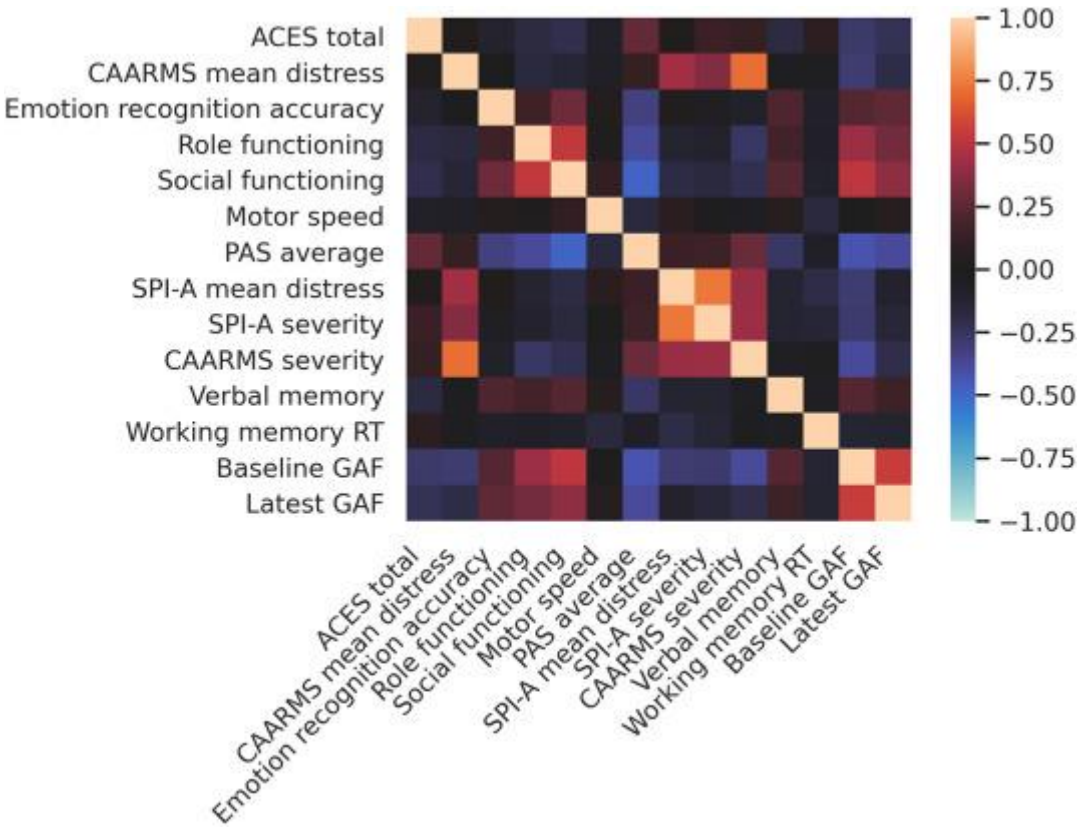


Figure 1-1 Correlation matrix showing the relationship between nonzero predictors and baseline GAF scores for the combined LASSO-LARS regression model for the CHR-P group (N = 146). The latest GAF score is added to this figure for visualisation purposes only and has not been entered in the regression model.

Follow-up Classification Analysis

At follow-up, 59.3% of CHR-P individuals presented with PFO. Mixed-site classifiers were trained to predict PFO versus GFO in CHR-P individuals based on variables associated with baseline GAF (Figure 1). Permutation tests on AUC scores indicated that all mixed-site classifiers performed significantly above chance (Table 3). The classifiers performed consistently, showing a mean BAC of 63% and a mean AUC of 0.72, while LR performed best (mean AUC = 0.74; mean BAC = 0.65). Mean sensitivity and specificity across classifiers was 68% and 56%, respectively, suggesting a bias towards predicting PFO.

Performance among the cross-site models was consistently lower than for the mixed-site models (Table 3), with a mean AUC of 0.64 and a mean BAC of 0.63 across classifiers. Again, sensitivity was consistently higher than specificity.

Table 1-3: Mixed-site and cross-site classifiers in the CHR-P sample (N = 146)

Model	Mean AUC	Precision (PFO/GFO)	Recall (PFO/GFO)	F1 (PFO/GFO)	Mean BAC	*p*-value[a]
Mixed-site classifiers						
GNB	0.70	0.68/0.48	0.54/0.62	0.60/0.55	0.59	.002
LDA	0.73	0.71/0.59	0.73/0.56	0.72/0.57	0.65	.005
SVM	0.72	0.73/0.55	0.64/0.65	0.68/0.60	0.65	.014
LR	0.74	0.72/0.56	0.66/0.62	0.69/0.59	0.65	.003
RFC	0.72	0.64/0.55	0.81/0.33	0.72/0.42	0.61	.013
Average	0.72	0.70/0.55	0.68/0.56	0.68/0.55	0.63	-
Cross-site classifiers						
GNB	0.61	0.71/0.50	0.63/0.58	0.67 /0.54	0.61	-
LDA	0.64	0.68/0.50	0.68/0.50	0.68/0.50	0.59	-
SVM	0.62	0.72/0.54	0.68/0.58	0.70/0.56	0.63	-
LR	0.65	0.72/0.54	0.68/0.58	0.70/0.56	0.63	-
RFC	0.66	0.73/0.67	0.84/0.50	0.78/0.57	0.67	-
Average	0.64	0.71/0.55	0.70/0.55	0.71/0.55	0.63	-

Note. GNB, gaussian naive bayes; LDA, linear discriminant analysis; SVM, support vector machines; RFC, random forest classification; LR, logistic regression; AUC, area under the curve; PFO, poor functional outcome; GFO, good functional outcome; BAC, balanced accuracy.

[a] Permutation tests on AUC, corrected for multiple comparisons (Bonferroni).

Classifiers using baseline functioning variables only (GAF, social and role functioning) performed better than either mixed- or cross-site models on average (mean AUC = 0.76; mean BAC = 0.68). The baseline GAF model, which

used good and poor baseline functioning categories as predictors, yielded an AUC of 0.67 and BAC of 0.70.

Table 1-4: Classifiers using baseline functioning variables in the CHR-P sample (N = 146)

Model	Mean AUC	Precision (PFO/GFO)	Recall (PFO/GFO)	F1 (PFO/GFO)	Mean BAC	*p*-value[a]
GNB	0.80	0.76/0.59	0.67/0.69	0.71 /0.63	0.68	.001
LDA	0.78	0.73/0.64	0.77/0.58	0.75/0.61	0.68	.001
SVM	0.79	0.78/0.59	0.66/0.73	0.71/0.65	0.70	.001
LR	0.79	0.77/0.60	0.67/0.71	0.72/0.65	0.69	.001
RFC	0.70	0.69/0.57	0.71/0.54	0.70/0.55	0.65	.019
Simple GAF[b]	0.67	0.71/0.69	0.84/0.50	0.77/0.58	0.70	-
Average	0.76	0.74/0.61	0.73/0.63	0.73/0.61	0.68	-

Note. GNB, gaussian naive bayes; LDA, linear discriminant analysis; SVM, support vector machines; RFC, random forest classification; LR, logistic regression; AUC, area under the curve; PFO, poor functional outcome; GFO, good functional outcome; GAF, Global Assessment of Functioning; BAC, balanced accuracy.

[a] Permutation tests on AUC, corrected for multiple comparisons (Bonferroni).

[b] Associated values reflect single values rather than means due to the nature of the model.

GAF Score Changes

For the CHR-P group, median absolute change in GAF during follow-up was 10.0, whereas median raw change in GAF (including negative change as is) was 0.5 (Supplementary Figure 4A-B). Eighty-three (70.3%) individuals did not change GAF category between baseline and follow-up, whereby 59 (50.0%) and 24 (20.3%) presented with poor and good functioning at both time points respectively. By contrast, 35 (29.7%) individuals did change GAF category

between baseline and follow-up, whereby 24 (20.3%) changed from poor to good functioning and 11 (9.3%) changed from good to poor functioning. These results were statistically significant ($p < .001$) with the highest proportion of CHR-P participants presenting with poor functioning at both time points. Notably, raw GAF score changes between baseline and 6-month follow-up were not significantly different from changes between baseline and 12-month follow-up in CHR-P individuals ($n = 84$) with both follow-up assessments ($p = .590$; Supplementary Figure 4C-D).

Discussion

We investigated the contribution of cognition towards impaired functioning as well as the potential utility of incorporating cognitive variables into predictive models of functional outcome. Although cognitive deficits explained 41% of the variance in baseline GAF scores when combined with clinical and functioning variables, cognitive variables alone explained only 12%. The combination of cognitive variables with functioning and clinical variables allowed classification of CHR-P individuals into GFO and PFO groups at follow-up with an average BAC of 63% in both mixed- and cross-site models. Furthermore, we were able to predict functional outcomes with acceptable accuracy using simple classifiers incorporating only baseline functioning variables.

Predictors of Baseline Functioning

In addition to clinical and functioning variables, cognitive deficits emerged as predictors of baseline functioning, together explaining 41% of the variance in baseline GAF scores in CHR-P participants. Impaired functioning prior to disorder onset is one of the strongest predictors of functional outcome in CHR-P individuals (Salokangas et al., 2014) and in patients with first-episode psychosis or established schizophrenia (Barajas et al., 2013). Indeed, functioning variables comprised the strongest predictors in the current study, illustrating the importance of interventions targeting functional impairments during early psychosis. Cognitive and clinical variables were weaker predictors and evidenced relatively similar importance scores. In line with previous studies, verbal memory (Meyer et al., 2014; Niendam et al., 2006), working memory (Goghari et al., 2014), emotion recognition (Glenthøj et al., 2016), motor speed

(Carrión et al., 2013), ACES total (Kraan et al., 2015), social and role functioning and premorbid adjustment (Salokangas et al., 2014) emerged as predictors of GAF in the combined CHR-P model. The emergence of CAARMS and SPI-A severity and distress scores as predictors, however, contrasts with previous findings (Carrión et al., 2016; Kim et al., 2019; Lin et al., 2011; Meyer et al., 2014; Rekhi et al., 2019).

In the CHR-P group, the relationship observed between impaired cognition and functioning is consistent with studies in established schizophrenia where cognitive deficits have been linked to decreased ability to live independently, poor social skills and inability to maintain employment (Lepage et al., 2014). Cognitive variables alone only explained 12% of the variance in baseline functioning in the CHR-P group, concurring with previous studies in schizophrenia (Fett et al., 2011) and CHR-P cohorts (Carrión et al., 2011). Notably, one of the strongest cognitive predictors was verbal memory, consistent with previous CHR-P studies predicting social functioning (Meyer et al., 2014; Niendam et al., 2006) and schizophrenia studies predicting a variety of functional outcomes (Green, 1996). Although certain cognitive variables (i.e. motor speed, executive function and attention RT) displayed unexpected relationships with baseline functioning in both combined and cognitive CHR-P models, this may partially reflect a speed-accuracy trade off. Moreover, in our CHR-N sample, cognitive variables were unrelated to GAF, suggesting that this relationship may be specific to the CHR-P state. However, this finding may be explained by the absence of significant cognitive deficits in the CHR-N sample and the smaller sample size.

Predictors of Functional Outcome

Mixed-site models combining cognitive variables with clinical and functioning variables were able to predict functional outcome in the CHR-P group. All mixed-site models performed significantly above chance, with a mean AUC of 0.72 and a mean BAC of 63%. Performance was relatively consistent across all algorithms making it unlikely that our best performing classifier (LR; mean AUC = 0.74) was overfitting. These data are in line with previous research utilising clinical, functional and neuroimaging data where functional outcomes have been predicted with AUC scores between 0.70-0.86 and accuracies between 62.5%-82.7% (Kambeitz-Ilankovic et al., 2016; Koutsouleris et al., 2018; Mechelli et

al., 2017). Notably, performance in the current study decreased for the cross-site models (mean AUC = 0.64; mean BAC = 63%), which is a common problem noted for machine learning classifiers in the field (Vieira et al., 2020).

We additionally fitted classifiers on baseline functioning variables. Using baseline data to predict later measures of the same variable often predicts outcomes better than chance and baseline models can provide a more stringent method for evaluating classifier accuracy (DeMasi et al., 2017). Indeed, previous studies identified global and social functioning scores as the most useful variables for predicting social functioning at 1-year follow-up in CHR-P participants (Koutsouleris et al., 2018). In the current study, classifiers fitted only on baseline functioning variables performed better, on average, than both mixed- and cross-site models with a mean AUC and BAC of 0.76 and 68%, respectively. This is possibly explained by the fact that GAF scores appear to be relatively stable across time. Overall, nearly two thirds of our sample showed PFO in agreement with previous studies (Carrión et al., 2013; Koutsouleris et al., 2018) and the majority of individuals (70.3%) remained within the same outcome category.

Limitations

Both the regression and classification analyses could be optimised by increasing the number of participants relative to candidate predictors. Additionally, we only had two test sites, meaning that cross-site classifiers were only trained on a single site, thus limiting their ability to learn patterns across multiple sites. Given that machine learning models have the potential to outperform human judgement, it is highly probable that models predicting functional outcomes in early psychosis can improve in larger datasets (Fusar-Poli et al., 2019). As accuracy tends to exhibit a strong relationship with sample size for machine learning methods in particular (Floares et al., 2017), standardising data acquisition protocols across research centres and thereby facilitating the collection of much larger collaborative datasets is likely to produce significant performance gains in terms of both accuracy and cross-site transfer. Furthermore, due to the small size of CHR-N participants, strong conclusions regarding the contribution of cognitive deficits towards impaired functioning in this group cannot be drawn and, given that only 55% completed follow-up assessments, GAF outcome/change could not be examined in this group.

The current study also highlights the limitations of current functioning measurements in CHR-P populations. The GAF scale, for example, confounds functioning with symptom severity and shows only limited fluctuations over time. However, the GAF scale was chosen over social and role functioning scales in this study as scores obtained from the latter displayed low variability. Accordingly, more sensitive measures are required that trace changes in functioning across several dimensions. Finally, negative symptoms, which have been shown to mediate the relationship between neurocognition and functioning (Glenthøj et al., 2016; Meyer et al., 2014), as well as treatment use over follow-up were not assessed in the current CHR-P sample.

Conclusions

Utilising a machine learning approach, we have shown that cognitive variables alongside clinical and functioning variables predict short-term functional outcome with above-chance performance. With the increasing popularity of complex machine learning models in psychiatry, it is important to consider appropriate benchmark measures to determine whether the potential gains are sufficient to justify their use over simpler alternatives. Our findings suggest, for example, that baseline GAF scores allow a more robust prediction of functional outcomes in CHR-P individuals than complex machine learning approaches. Given the large proportion of CHR-P individuals presenting with PFO, interventions incorporating social skills training, vocational rehabilitation and cognitive remediation are clearly warranted at this stage.

Acknowledgements

This study was supported by project MR/L011689/1 from the Medical Research Council (MRC) and the University of Glasgow's Lord Kelvin/Adam Smith (LKAS) PhD Scholarship. We acknowledge the support of the Scottish Mental Health Research Network (http://www.smhrn.org.uk), now called the NHS Research Scotland Mental Health Network (NRS MHN: http://www.nhsresearchscotland.org.uk/research-areas/mental-health), for providing assistance with participant recruitment, interviews and cognitive assessments. We would like to thank both the participants and patients who took part in the study and the research assistants of the YouR-study for

supporting the recruitment and assessment of CHR-P participants. We also would like to thank Professor Roderick Murray-Smith, School of Computing Science, University of Glasgow, for his feedback regarding machine learning methods.

References

Allen, P., Chaddock, C.A., Egerton, A., Howes, O.D., Barker, G., Bonoldi, I., Fusar-Poli, P., Murray, R., McGuire, P., 2015. Functional Outcome in People at High Risk for Psychosis Predicted by Thalamic Glutamate Levels and Prefronto-Striatal Activation. Schizophr. Bull. 41, 429–439. https://doi.org/10.1093/schbul/sbu115

Allott, K., Liu, P., Proffitt, T.M., Killackey, E., 2011. Cognition at illness onset as a predictor of later functional outcome in early psychosis: Systematic review and methodological critique. Schizophr. Res. 125, 221–235. https://doi.org/10.1016/j.schres.2010.11.001

Barajas, A., Usall, J., Baños, I., Dolz, M., Villalta-Gil, V., Vilaplana, M., Autonell, J., Sánchez, B., Cervilla, J.A., Foix, A., Obiols, J.E., Haro, J.M., Ochoa, S., 2013. Three-factor model of premorbid adjustment in a sample with chronic schizophrenia and first-episode psychosis. Schizophr. Res. 151, 252–258. https://doi.org/10.1016/j.schres.2013.10.027

Cannon-Spoor, H.E., Potkin, S.G., Wyatt, R.J., 1982. Measurement of Premorbid Adjustment in Chronic Schizophrenia. Schizophr. Bull. 8, 470–484. https://doi.org/10.1093/schbul/8.3.470

Carrión, R.E., Demmin, D., Auther, A.M., McLaughlin, D., Olsen, R., Lencz, T., Correll, C.U., Cornblatt, B.A., 2016. Duration of attenuated positive and negative symptoms in individuals at clinical high risk: Associations with risk of conversion to psychosis and functional outcome. J. Psychiatr. Res. 81, 95–101. https://doi.org/10.1016/j.jpsychires.2016.06.021

Carrión, R.E., Goldberg, T.E., McLaughlin, D., Auther, A.M., Correll, C.U., Cornblatt, B.A., 2011. Impact of neurocognition on social and role functioning in individuals at clinical high risk for psychosis. Am. J. Psychiatry 168, 806–813. https://doi.org/10.1176/appi.ajp.2011.10081209

Carrión, R.E., McLaughlin, D., Goldberg, T.E., Auther, A.M., Olsen, R.H., Olvet, D.M., Correll, C.U., Cornblatt, B.A., 2013. Prediction of functional outcome in individuals at clinical high risk for psychosis. JAMA Psychiatry 70, 1133–1142. https://doi.org/10.1001/jamapsychiatry.2013.1909

Cornblatt, B.A., Auther, A.M., Niendam, T., Smith, C.W., Zinberg, J., Bearden, C.E., Cannon, T.D., 2007. Preliminary findings for two new measures of social and

role functioning in the prodromal phase of schizophrenia. Schizophr. Bull. 33, 688–702. https://doi.org/10.1093/schbul/sbm029

DeMasi, O., Kording, K., Recht, B., 2017. Meaningless comparisons lead to false optimism in medical machine learning. PLoS One 12, 1–17. https://doi.org/10.1371/journal.pone.0184604

Efron, B., Hastie, T., Johnstone, I., Tibshirani, R., Ishwaran, H., Knight, K., Loubes, J.M., Massart, P., Madigan, D., Ridgeway, G., Rosset, S., Zhu, J.I., Stine, R.A., Turlach, B.A., Weisberg, S., Johnstone, I., Tibshirani, R., 2004. Least angle regression. Ann. Stat. 32, 407–499. https://doi.org/10.1214/009053604000000067

Eslami, A., Jahshan, C., Cadenhead, K.S., 2011. Disorganized Symptoms and Executive Functioning Predict Impaired Social Functioning in Subjects at Risk for Psychosis. J. Neuropsychiatr. 23, 457–460. https://doi.org/10.1176/appi.neuropsych.23.4.457

Felitti, V.J., Anda, R.F., Nordenberg, D., Williamson, D.F., Spitz, A.M., Edwards, V., Koss, M.P., Marks, J.S., 1998. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med 14, 245–258. https://doi.org/doi: 10.1016/s0749-3797(98)00017-8

Fett, A.K.J., Viechtbauer, W., Dominguez, M. de G., Penn, D.L., van Os, J., Krabbendam, L., 2011. The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis. Neurosci. Biobehav. Rev. 35, 573–588. https://doi.org/10.1016/j.neubiorev.2010.07.001

Floares, A.G., Ferisgan, M., Onita, D., Ciuparu, A., Calin, G.A., Manolache, F.B., 2017. The Smallest Sample Size for the Desired Diagnosis Accuracy. Int. J. Oncol. Cancer Ther. 2, 13–19.

Fonti, V., 2017. Feature Selection using LASSO. VU Amsterdam 1–26. https://doi.org/10.1109/ACCESS.2017.2696365

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rössler, A., Schultze-Lutter, F., Keshavan, M., Wood, S., Ruhrmann, S., Seidman, L.J., Valmaggia, L., Cannon, T., Velthorst, E., De Haan, L., Cornblatt, B., Bonoldi, I., Birchwood, M., McGlashan, T., Carpenter, W., McGorry, P., Klosterkötter, J., McGuire, P., Yung, A., 2013. The psychosis high-risk state: A comprehensive state-of-the-art

review. Arch. Gen. Psychiatry 70, 107–120. https://doi.org/10.1001/jamapsychiatry.2013.269

Fusar-Poli, P., Cappucciati, M., Borgwardt, S., Woods, S.W., Addington, J., Nelson, B., Nieman, D.H., Stahl, D.R., Rutigliano, G., Riecher-Rössler, A., Simon, A.E., Mizuno, M., Lee, T.Y., Kwon, J.S., Lam, M.M.L., Perez, J., Keri, S., Amminger, P., Metzler, S., Kawohl, W., Rössler, W., Lee, J., Labad, J., Ziermans, T., An, S.K., Liu, C.C., Woodberry, K.A., Braham, A., Corcoran, C., McGorry, P., Yung, A.R., McGuire, P.K., 2016. Heterogeneity of psychosis risk within individuals at clinical high risk: A meta-analytical stratification. JAMA Psychiatry 73, 113–120. https://doi.org/10.1001/jamapsychiatry.2015.2324

Fusar-Poli, P., Stringer, D., M. S. Durieux, A., Rutigliano, G., Bonoldi, I., De Micheli, A., Stahl, D., 2019. Clinical-learning versus machine-learning for transdiagnostic prediction of psychosis onset in individuals at-risk. Transl. Psychiatry 9. https://doi.org/10.1038/s41398-019-0600-9

Glenthøj, L.B., Fagerlund, B., Hjorthøj, C., Jepsen, J.R.M., Bak, N., Kristensen, T.D., Wenneberg, C., Krakauer, K., Roberts, D.L., Nordentoft, M., 2016. Social cognition in patients at ultra-high risk for psychosis: What is the relation to social skills and functioning? Schizophr. Res. Cogn. 5, 21–27. https://doi.org/10.1016/j.scog.2016.06.004

Goghari, V.M., Brett, C., Tabraham, P., Johns, L., Valmaggia, L., Broome, M., Woolley, J., Bramon, E., Howes, O., Byrne, M., McGuire, P., 2014. Spatial working memory ability in individuals at ultra high risk for psychosis. J. Psychiatr. Res. 50, 100–105. https://doi.org/10.1016/j.jpsychires.2013.12.010

Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 153, 321–330.

Kambeitz-Ilankovic, L., Meisenzahl, E.M., Cabral, C., von Saldern, S., Kambeitz, J., Falkai, P., Möller, H.J., Reiser, M., Koutsouleris, N., 2016. Prediction of outcome in the psychosis prodrome using neuroanatomical pattern classification. Schizophr. Res. 173, 159–165. https://doi.org/10.1016/j.schres.2015.03.005

Keefe, R.S.E., Goldberg, T.E., Harvey, P.D., Gold, J.M., Poe, M.P., Coughenour, L., 2004. The Brief Assessment of Cognition in Schizophrenia: Reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr. Res. 68, 283–297. https://doi.org/10.1016/j.schres.2003.09.011

Keefe, R.S.E., Harvey, P.D., Goldberg, T.E., Gold, J.M., Walker, T.M., Kennel, C., Hawkins, K., 2008. Norms and standardization of the Brief Assessment of Cognition in Schizophrenia (BACS). Schizophr. Res. 102, 108–115. https://doi.org/10.1016/j.schres.2008.03.024

Kim, H.K., Park, H.Y., Seo, E., Bang, M., Song, Y.Y., Lee, S.Y., Kim, K.R., Park, J.Y., Kang, J.I., Lee, E., An, S.K., 2019. Factors associated with psychosocial functioning and outcome of individuals with recent-onset schizophrenia and at ultra-high risk for psychosis. Front. Psychiatry 10, 1–11. https://doi.org/10.3389/fpsyt.2019.00459

Koutsouleris, N., Borgwardt, S., Meisenzahl, E.M., Bottlender, R., Möller, H.J., Riecher-Rössler, A., 2012. Disease prediction in the at-risk mental state for psychosis using neuroanatomical biomarkers: Results from the fepsy study. Schizophr. Bull. 38, 1234–1246. https://doi.org/10.1093/schbul/sbr145

Koutsouleris, N., Kambeitz-Ilankovic, L., Ruhrmann, S., Rosen, M., Ruef, A., Dwyer, D.B., Paolini, M., Chisholm, K., Kambeitz, J., Haidl, T., Schmidt, A., Gillam, J., Schultze-Lutter, F., Falkai, P., Reiser, M., Riecher-Rössler, A., Upthegrove, R., Hietala, J., Salokangas, R.K.R., Pantelis, C., Meisenzahl, E., Wood, S.J., Beque, D., Brambilla, P., Borgwardt, S., 2018. Prediction Models of Functional Outcomes for Individuals in the Clinical High-Risk State for Psychosis or with Recent-Onset Depression: A Multimodal, Multisite Machine Learning Analysis. JAMA Psychiatry 75, 1156–1172. https://doi.org/10.1001/jamapsychiatry.2018.2165

Koutsouleris, N., Meisenzahl, E.M., Davatzikos, C., Bottlender, R., Frodl, T., Scheuerecker, J., Schmitt, G., Zetzsche, T., Decker, P., Reiser, M., Möller, H.J., Gaser, C., 2009. Use of neuroanatomical pattern classification to identify subjects in at-risk mental states of psychosis and predict disease transition. Arch. Gen. Psychiatry 66, 700–712. https://doi.org/10.1001/archgenpsychiatry.2009.62

Kraan, T., van Dam, D.S., Velthorst, E., de Ruigh, E.L., Nieman, D.H., Durston, S., Schothorst, P., van der Gaag, M., de Haan, L., 2015. Childhood trauma and clinical outcome in patients at ultra-high risk of transition to psychosis. Schizophr. Res. 169, 193–198. https://doi.org/10.1016/j.schres.2015.10.030

Lepage, M., Bodnar, M., Bowie, C.R., 2014. Neurocognition: Clinical and functional outcomes in schizophrenia. Can. J. Psychiatry 59, 5–12. https://doi.org/10.1177/070674371405900103

Lin, A., Wood, S.J., Nelson, B., Brewer, W.J., Spiliotacopoulos, D., Bruxner, A., Broussard, C., Pantelis, C., Yung, A.R., 2011. Neurocognitive predictors of functional outcome two to 13years after identification as ultra-high risk for psychosis. Schizophr. Res. 132, 1–7. https://doi.org/10.1016/j.schres.2011.06.014

McDonald, M., Christoforidou, E., Van Rijsbergen, N., Gajwani, R., Gross, J., Gumley, A.I., Lawrie, S.M., Schwannauer, M., Schultze-Lutter, F., Uhlhaas, P.J., 2019. Using online screening in the general population to detect participants at clinical high-risk for psychosis. Schizophr. Bull. 45, 600–609. https://doi.org/10.1093/schbul/sby069

Mechelli, A., Lin, A., Wood, S., McGorry, P., Amminger, P., Tognin, S., McGuire, P., Young, J., Nelson, B., Yung, A., 2017. Using clinical information to make individualized prognostic predictions in people at ultra high risk for psychosis. Schizophr. Res. 184, 32–38. https://doi.org/10.1016/j.schres.2016.11.047

Meyer, E.C., Carrión, R.E., Cornblatt, B.A., Addington, J., Cadenhead, K.S., Cannon, T.D., McGlashan, T.H., Perkins, D.O., Tsuang, M.T., Walker, E.F., Woods, S.W., Heinssen, R., Seidman, L.J., 2014. The relationship of neurocognition and negative symptoms to social and role functioning over time in individuals at clinical high risk in the first phase of the north american prodrome longitudinal study. Schizophr. Bull. 40, 1452–1461. https://doi.org/10.1093/schbul/sbt235

Millan, M.J., Andrieux, A., Bartzokis, G., Cadenhead, K., Dazzan, P., Fusar-Poli, P., Gallinat, J., Giedd, J., Grayson, D.R., Heinrichs, M., Kahn, R., Krebs, M.O., Leboyer, M., Lewis, D., Marin, O., Marin, P., Meyer-Lindenberg, A., McGorry, P., McGuire, P., Owen, M.J., Patterson, P., Sawa, A., Spedding, M., Uhlhaas, P., Vaccarino, F., Wahlestedt, C., Weinberger, D., 2016. Altering the course of schizophrenia: Progress and perspectives. Nat. Rev. Drug Discov. 15, 485–515. https://doi.org/10.1038/nrd.2016.28

Millman, Z.B., Gold, J.M., Mittal, V.A., Schiffman, J., 2019. The Critical Need for Help-Seeking Controls in Clinical High-Risk Research. Clin. Psychol. Sci. 7, 1171–1189. https://doi.org/10.1177/2167702619855660

Modinos, G., Kempton, M.J., Tognin, S., Calem, M., Porffy, L., Antoniades, M., Mason, A., Azis, M., Allen, P., Nelson, B., McGorry, P., Pantelis, C., Riecher-Rössler, A., Borgwardt, S., Bressan, R., Barrantes-Vidal, N., Krebs, M.O., Nordentoft, M., Glenthøj, B., Ruhrmann, S., Sachs, G., Rutten, B., Van Os, J., De Haan, L.,

Velthorst, E., Van Der Gaag, M., Valmaggia, L.R., McGuire, P., 2019. Association of Adverse Outcomes with Emotion Processing and Its Neural Substrate in Individuals at Clinical High Risk for Psychosis. JAMA Psychiatry 77, 190–200. https://doi.org/10.1001/jamapsychiatry.2019.3501

Moore, T.M., Reise, S.P., Gur, R.E., Hakonarson, H., Gur, R.C., 2015. Psychometric properties of the penn computerized neurocognitive battery. Neuropsychology 29, 235–246. https://doi.org/10.1037/neu0000093

Niendam, T.A., Bearden, C.E., Johnson, J.K., McKinley, M., Loewy, R., O'Brien, M., Nuechterlein, K.H., Green, M.F., Cannon, T.D., 2006. Neurocognitive performance and functional disability in the psychosis prodrome. Schizophr. Res. 84, 100–111. https://doi.org/10.1016/j.schres.2006.02.005

Ojala, M., Garriga, G.C., 2010. Permutation tests for studying classifier performance. J. Mach. Learn. Res. 11, 1833–1863.

Owen, M.J., Sawa, A., Mortensen, P.B., 2016. Schizophrenia. Lancet 388, 86–97. https://doi.org/10.1016/S0140-6736(15)01121-6

Ramyead, A., Studerus, E., Kometer, M., Uttinger, M., Gschwandtner, U., Fuhr, P., Riecher-Rössler, A., 2016. Prediction of psychosis using neural oscillations and machine learning in neuroleptic-naïve at-risk patients. World J. Biol. Psychiatry 17, 285–295. https://doi.org/10.3109/15622975.2015.1083614

Rekhi, G., Rapisarda, A., Lee, J., 2019. Impact of distress related to attenuated psychotic symptoms in individuals at ultra high risk of psychosis: Findings from the Longitudinal Youth at Risk Study. Early Interv. Psychiatry 13, 73–78. https://doi.org/10.1111/eip.12451

Salokangas, R.K.R., Heinimaa, M., From, T., Löyttyniemi, E., Ilonen, T., Luutonen, S., Hietala, J., Svirskis, T., von Reventlow, H.G., Juckel, G., Linszen, D., Dingemans, P., Birchwood, M., Patterson, P., Schultze-Lutter, F., Ruhrmann, S., Klosterkötter, J., McGorry, P.D., McGlashan, T.H., Knapp, M., van der Fliert, R., Klaassen, R., Picker, H., Neumann, M., Brockhaus-Dumke, A., Pukrop, R., Huttunen, J., Ristkari, T., Skeate, A., Gudlowski, Y., Ozgürdal, S., Witthaus, H., Lewis, S., Morrisson, A., 2014. Short-term functional outcome and premorbid adjustment in clinical high-risk patients. Results of the EPOS project. Eur. Psychiatry 29, 371–380. https://doi.org/10.1016/j.eurpsy.2013.10.003

Schmidt, S.J., Mueller, D.R., Roder, V., 2011. Social cognition as a mediator variable between neurocognition and functional outcome in schizophrenia: Empirical review and new results by structural equation modeling. Schizophr. Bull. 37. https://doi.org/10.1093/schbul/sbr079

Schultze-Lutter, F., 2009. Subjective symptoms of schizophrenia in research and the clinic: The basic symptom concept. Schizophr. Bull. 35, 5–8. https://doi.org/10.1093/schbul/sbn139

Schultze-Lutter, F., Addington, J., Ruhrmann, S., Klosterkötter, J., 2007. Schizophrenia Proneness Instrument-Adult Version (SPI-A). Giovanni Fioriti Editore, Rome, Italy.

Schultze-Lutter, F., Rahman, J., Ruhrmann, S., Michel, C., Schimmelmann, B.G., Maier, W., Klosterkötter, J., 2015. Duration of unspecific prodromal and clinical high risk states, and early help-seeking in first-admission psychosis patients. Soc. Psychiatry Psychiatr. Epidemiol. 50, 1831–1841. https://doi.org/10.1007/s00127-015-1093-3

Schultze-Lutter, F., Ruhrmann, S., Fusar-Poli, P., Bechdolf, A., Schimmelmann, B.G., Klosterkotter, J., 2012. Basic Symptoms and the Prediction of First-Episode Psychosis. Curr. Pharm. Des. 18, 351–357.

Sheehan, D. V, Lecrubier, Y., Sheehan, K., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 59, 22–33.

Uhlhaas, P.J., Gajwani, R., Gross, J., Gumley, A.I., Lawrie, S.M., Schwannauer, M., 2017. The Youth Mental Health Risk and Resilience Study (YouR-Study). BMC Psychiatry 17, 1–8. https://doi.org/10.1186/s12888-017-1206-5

Vieira, S., Gong, Q.Y., Pinaya, W.H.L., Scarpazza, C., Tognin, S., Crespo-Facorro, B., Tordesillas-Gutierrez, D., Ortiz-García, V., Setien-Suero, E., Scheepers, F.E., van Haren, N.E.M., Marques, T.R., Murray, R.M., David, A., Dazzan, P., McGuire, P., Mechelli, A., 2020. Using machine learning and structural neuroimaging to detect first episode psychosis: Reconsidering the evidence. Schizophr. Bull. 46, 17–26. https://doi.org/10.1093/schbul/sby189

Yung, A.R., Yuen, H.P., McGorry, P.D., Phillips, L.J., Kelly, D., Dell'Olio, M., Francey, S.M., Cosgrave, E.M., Killackey, E., Stanford, C., Godfrey, K., Buckby, J., 2005.

Mapping the onset of psychosis: The Comprehensive Assessment of At-Risk Mental States. Aust. N. Z. J. Psychiatry 39, 964–971. https://doi.org/10.1111/j.1440-1614.2005.01714.x

Chapter 2: Hippocampal structural alterations in early-stage psychosis: Specificity and relationship to clinical outcomes

Gina Brunner, Ruchika Gajwani, Joachim Gross, Andrew I. Gumley, Rajeev Krishnadas, Stephen M. Lawrie, Matthias Schwannauer, Frauke Schultze-Lutter, Alessio Fracasso*, Peter J. Uhlhaas*

* Equal contributions

Abstract

Hippocampal dysfunctions are a core feature of schizophrenia, but conflicting evidence exists whether volu-metric and morphological changes are present in early-stage psychosis and to what extent these deficits are related to clinical trajectories. In this study, we recruited individuals at clinical high risk for psychosis (CHR-P) (n = 108), patients with a first episode of psychosis (FEP) (n = 37), healthy controls (HC) (n = 70) as well as a psychiatric control group with substance abuse and affective disorders (CHR-N: n = 38). MRI-data at baseline were obtained and volumetric as well as vertex analyses of the hippocampus were carried out. Moreover, volumetric changes were examined in the amygdala, caudate, nucleus accumbens, pallidum, putamen and thalamus. In addition, we obtained follow-up functional and symptomatic assessments in CHR-P individuals to examine the question whether anatomical deficits at baseline predicted clinical trajectories. Our results show that the hippocampus is the only structure showing significant volumetric decrease in early-stage psychosis, with FEPs showing significantly smaller hippocampal volumes bilaterally alongside widespread shape changes in the vertex analysis. For the CHR-P group, volumetric decreases were confined to the left hippocampus. However, hippocampal alterations in the CHR-P group were not robustly associated with clinical outcomes, including the persistence of attenuated psychotic symptoms and functional trajectories. Accordingly, our findings highlight that dysfunctions in hippocampal anatomy are an important feature of early-stage psychosis which may, however, not be related to clinical outcomes in CHR-P participants.

Introduction

Psychotic disorders, such as schizophrenia (ScZ), have been associated with neuroanatomical changes, including grey matter (GM) alter-ations in cortical (Glahn et al., 2008) and subcortical regions (van Erp et al., 2016, Gutman et al., 2022), that have been related to negative symptoms (Walton et al., 2018) as well as to cognitive deficits (Pantelis and Nelson, 2019). In addition to cortical changes, reductions in the hippocampus, amygdala, thalamus and nucleus accumbens have been observed, while pallidum volume is increased in ScZ (van Erp et al., 2016). Volumetric changes in subcortical areas correlate with surface alterations that include both surface contractions and increases (Gutman et al., 2022).

Recent work has investigated the role of GM changes in participants at clinical high risk for psychosis (CHR-P) to identify biomarkers for early detection and prognosis (Jalbrzikowski et al., 2021). There is extensive evidence that ScZ is preceded by a prodromal phase of up to 5 years (Fusar-Poli et al., 2020a,b; Klosterkotter et al., 2001) that involves subtle alterations in cognition and functioning that could be mediated by changes in GM (Koutsouleris et al., 2010). Reductions in cortical GM have been identified in CHR-P individuals (Group, Jalbrzikowski et al. 2021; Zikidi et al., 2020), which may be related to transition to psy-chosis (Koutsouleris et al., 2009) as well as functional outcomes (Koutsouleris et al., 2018). Relationships with clinical outcomes are a particularly important issue as only a minority of CHR-P participants, approximately 25% over a three-year period (Pablo et al., 2021), will eventually transition to a first-episode of psychosis (FEP). While there is consistent evidence for cortical GM changes in CHR-P participants, evidence for a possible contribution of subcortical regions in emerging psychosis is less clear.

A region that has received particular attention during early-stage psychosis is the hippocampus (Provenzano et al., 2020). Previous studies suggested that abnormal functioning and anatomy of the hippocampus may constitute one of the earliest signs of psychosis (Lieber-man et al., 2018). Specifically, it has been proposed that dysregulated neurotransmission of glutamatergic circuitry may lead to excitotoxic effects (Lisman et al., 2008) and abnormal hippocampal

activation (Allen et al., 2015, 2021; Modinos et al., 2020a,b), resulting in volumetric reductions (Provenzano et al., 2020). Moreover, these changes may in turn drive functional and structural abnormalities in dopaminergic neurotransmission (Modinos et al., 2021; Stone et al., 2010), indicating that the hippocampus could play a key role in the pathophysiology of ScZ by triggering a cascade of events leading to wide-spread cortical and subcortical circuit changes. The subregion CA1 has received particular attention (Schobel et al., 2013), but there is also evidence for abnormalities in CA2 and CA3 (Baglivo et al., 2018).

Despite the prominent role of the hippocampus in ScZ, there is currently conflicting evidence whether hippocampal alterations are present in early-stage psychosis. In CHR-P participants, some studies have reported intact hippocampus volumes (Walter et al. 2016, 2020), while others have reported overall volumetric reductions (Ganzola et al., 2014; Harrisberger et al., 2016a,b,c; Wood et al., 2010), in particular in CA1 (Lieberman et al., 2018). Similarly, hippocampal hyperactivity, as reflected by elevated blood flow and glutamate levels, predicted tran-sition to psychosis in CHR-P participants (Bossong et al., 2019, Provenzano et al., 2020). In contrast, the majority of studies in FEP-patients have reported hippocampal reductions (Adriano et al., 2012; Borgwardt et al., 2007; Buehlmann et al., 2010; Lieberman et al., 2018; Phillips et al., 2002; Velakoulis et al., 2006), suggesting the possibility of progressive dysfunctions with illness stages.

To clarify the role of the hippocampus in early-stage psychosis, we performed volumetric and morphological analyses of the hippocampus and other subcortical structures (amygdala, caudate, nucleus accumbens, palladium, putamen, thalamus) in CHR-Ps and FEP-patients. This is because it is currently unclear whether anatomical alterations are specific to the hippocampus or whether subcortical regions, such as the nucleus accumbens, caudate (Sasabayashi et al., 2020), and thalamus (Harrisberger et al., 2016a), are also affected. Moreover, antipsychotic and antidepressant medication (APM/ADM) have previously been shown to affect subcortical volumes (Hashimoto et al., 2018). Accordingly, we also tested the effects of APM/ADM on anatomical variables in CHR-P and FEP-groups.

We also included a group of participants with affective and substance use disorders who did not meet CHR-P criteria (CHR-N) in addition to non-clinical

control participants (HC). There is evidence that hippocampal changes also occur in several other psychiatric syndromes, including major depressive disorder (Arnone et al., 2012) as well as substance abuse (Wilson et al., 2017; Wang et al., 2021) and there is substantial comorbidity between affective disorders, substance abuse and early-stage psychosis (Li et al., 2020; Wilson et al., 2017; Herniman et al., 2021). Finally, we investigated the relationship between hippocampal volumes and clinical features, including global functioning and cognition, and the persistence of attenuated psychotic symptoms (APS) to determine whether hippocampal changes correlate with clinical and functional outcomes in CHR-P participants.

Materials and methods

Participants

A total of 253 participants were recruited from the Youth Mental Health Risk and Resilience (YouR) Study (Uhlhaas et al., 2017) and divided into four groups: 1) 108 participants meeting CHR-P criteria, (2) 38 participants characterized by non-psychotic disorders, such as affective disorders (n = 11), anxiety disorders (n = 16), eating disorders (n = 1), and/or substance abuse (n = 10) (CHR-N), 3) 37 patients with FEP (15 antipsychotic-naïve) and, 4) 70 healthy control participants (HC) without an axis I diagnosis or family history of psychosis. Ages across groups ranged from 16 to 34 years.

CHR-P status at baseline was established by ultra-high risk criteria according to the Comprehensive Assessment of At Risk Mental States (CAARMS) Interview (Yung et al., 2005) and the Cognitive Disturbances (COGDIS) and Cognitive-Perceptive (COPER) basic symptoms criteria according to the Schizophrenia Proneness Instrument, Adult version (SPI-A (Schultze-Lutter et al., 2012). FEP patients were assessed with the Structured Clinical Interview for DSM-5 (SCID, First, 2014) and with the Positive and Negative Symptom Scale (PANSS, Kay et al., 1987). For all groups except FEP-patients, cognition was assessed with the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004).

The study was approved by the ethical committees of University of Glasgow and the NHS Research Ethical Committee Glasgow & Greater Clyde. All participants provided written informed consent.

MRI acquisition

We acquired T1-weighted MR images on a 3 T Siemens scanner using a 3D MPRAGE sequence with the following parameters: FoV: 256 × 256 × 176 mm3, voxel size: 1 × 1 × 1 mm3, TR: 2250 ms, TE: 2.6 ms, TI: 900 ms, FA: 9°.

Preprocessing

Pre-processing was performed using ANTs (http://stnava.github. io/ANTs/), AFNI (https://afni.nimh.nih.gov/), FSL (https://fsl.fmrib. ox.ac.uk/fsl/fslwiki) and custom functions in R (https://www.r-pro ject.org/). DICOM images were converted to nifti (.nii) files using the function dcm2niix_afni. T1-w volumes were up-sampled to 0.8 mm isotropic. Up-sampling was performed using the AFNI function 3dre-sample, using linear interpolation. Single-participant volumes were skull-stripped using the afni function 3dSkullStrip. The intensity of T1-w volumes was normalized to remove global inhomogeneities using the ANTs function N4BiasFieldCorrection. Volumes were normalized to Talairach space using the function @auto_tlrc and the corresponding affine transformations were stored for subsequent use. FSL FIRST was used to extract subcortical segmentations for the following structures: thalamus, putamen, pallidum, caudate, amygdala, hippocampus and nucleus accumbens. Lastly, we transformed the result of FSL segmen-tation back into the original single-participant space by inverting the affine transformation. The computation of subcortical volume was per-formed in the original single-participant space. We also obtained an estimate of total brain volume (TBV) from the brain mask obtained from 3dSkullStrip.

It is important to note that although Freesurfer has shown greater consistency with manual segmentations in pediatric and longitudinal data (Cover et al., 2016; Schoemaker et al., 2016), FSL-FIRST has consistently outperformed the non-longitudinal Freesurfer pipeline on hippocampal (Cover et al., 2016; Næss-Schmidt et al., 2016; Velasco-Annis et al., 2018) and other subcortical structures (Perlaki et al., 2017). We therefore chose FSL-FIRST to perform subcortical segmentations (see in Fig. 1). All images were visually inspected, whereby images with visible artifacts and poor quality segmentations (i. e. visibly inconsistent with how the image would have been segmented

manually) were excluded. Data from one CHR-P individual was excluded from all analyses due to motion artifacts.

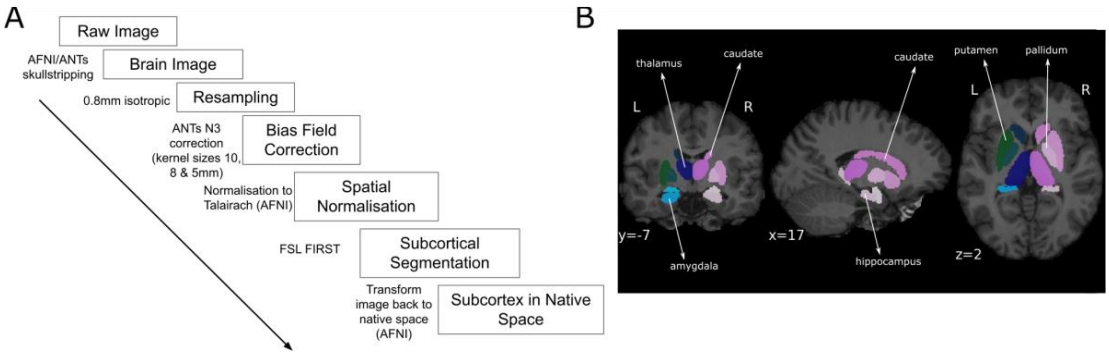


Figure 2-1 Analysis pipeline and example segmentation outcome from FSL FIRST. Panel A: flowchart reporting the preprocessing steps using AFNI and ANTs functions. B: subcortical segmentation example obtained from a single participant. The quality of all segmented images was determined by visual inspection.

Volumetric analysis

Volumetric measurements were extracted from the FSL segmentations and averaged across the two hemispheres for the following structures: thalamus, putamen, pallidum, caudate, amygdala, hippocampus, nucleus accumbens. We conducted a GLM analysis which tested for differences in volumes between HC and each clinical group with age and TBV being used as covariates. The following equation was used in R:

Subcortical volume ~ Group+TBV+age

The R function aov was additionally used to identify main effects of group. FDR correction was applied to correct for multiple comparisons; all analyses were conducted using the software R and the lme4 package. Analyses were also conducted for hemispheres and structures separately while controlling for years of education and handedness (Supplementary Table 1). In addition, we tested for the effects of antidepressant medication in the CHR-Ps and antipsychotic

medication in the FEP groups on subcortical volumes (Supplementary Tables 4 and 5).

Vertex analysis

Following our volumetric analysis, we used FSL to examine regional shape differences. While FSL does not directly extract subfield volumes, subfield-specific changes can be inferred from the location of shape deformations on the surface of each structure. Vertex analysis therefore allows us to determine where potential volumetric changes from the prior volumetric analysis likely originated from – i.e. whether they are regionally specific or widespread across a given subcortical structure. Surface meshes were extracted for each participant from the subcortical segmentations generated using FSL FIRST. Design matrices were generated for each pairwise group comparison and hemisphere separately.

We used the same covariates as for the linear models (i.e. total brain volume, age); covariate scores were mean-centered for the vertex analysis. FSL randomize was then used to generate 10,000 permutations (per comparison), and to compute the F-statistic and significance (FWE-corrected at the cluster level at a minimum cluster size of 3 voxels). Bonferroni-correction was additionally applied to correct for the mul-tiple comparisons between groups conducted.

For visualization purposes, the generated masks showing F-values were plotted in MNI space using the Python package nilearn. The masks were thresholded to only show F-values where the cluster p-value ≤ 0.05; analyses which returned no significant clusters were omitted from plotting.

Clinical Follow-Up

Participants meeting CHR-P criteria were reassessed at 3-, 6-, 9-, 12-, 18-, 24-, 30-, and 36-month intervals to examine the persistence of APS and functional outcomes, using the CAARMS interview. Based on past research (Allen et al., 2015; Modinos et al., 2019), GAF outcome cate-gories were split into good

(GFO) and poor functional outcomes (PFO) using a cutoff of GAF ≥ 65. For the follow-up analyses, we used GAF data from 6- and 12-months follow-ups.

Persistence of ultra-high risk criteria was operationalized by the continued presence of APS up to 12 months. In addition, transition to psychosis was assessed. We fitted binomial GLMs for each clinical outcome (i.e. APS persistence, functional outcomes, transition to psy-chosis) in the CHR-P group to investigate the relationship between hippocampal volumes and outcomes, using the same covariates (TBV, age) as our aforementioned linear models with the R package lme4.

Results

Demographic and clinical data

In the CHR-P group, n = 30 individuals showed persistent APS and n = 10 transitioned to psychosis (mean follow-up period to transition: 19.2 months). N = 78 CHR-Ps were characterized by GAF scores < 65 at baseline, n = 57 at 6 months follow-up, and n = 40 at 12-months follow-up. The groups showed differences in gender and age distribution, whereby the FEP group was slightly older and included more male participants. CHR-P individuals additionally showed significantly lower GAF, motor speed and total BACS scores than HC individuals (see Table 1).

Volumetric analysis

We conducted a general linear model (GLM) analysis for each subcortical structure. A significant effect of TBV was observed, indi-cating a positive scaling between subcortical structures volume and TBV (t-values ranging between 5.97 for the amygdala to 18.14 for the thal-amus, all $p > 0.05$, Bonferroni corrected). An effect of age was also observed for the thalamus and the hippocampus, indicating a positive scaling between volume and age (t of 3.56 and 2.95, respectively, $p < .05$, Bonferroni corrected).

Table 1: Demographics

	HC (N=70)	CHR-N (N=38)	CHR-P (N=108)	FEP (N=37)	Group effect	Post-hoc comparisons
Age (M, SD)	23.59 (3.87)	22.95 (4.66)	21.81 (4.46)	24.76 (4.15)	F=7.06, p < .001	HC < CHR-P FEP > CHR-P
Gender (F, %)	39 (55.71)	26 (68.42)	80 (74.07)	15 (40.54)	χ =17.05, p < .001	
Education (years)	16.65 (3.05)	16.46 (3.45)	15.30 (3.21)	16.20 (3.30)	F=2.58, p=.054	
Medication (n, %)				*		
None	70 (100)	23 (60.52)	50 (46.30)	4 (26.67)	-	-
Antidepressant	-	8 (21.05)	33 (30.56)	3 (20)	-	-
Antipsychotic	-	0 (0)	1 (0.92)	6 (40)	-	-
Other	-	7 (18.42)	30 (27.78)	7 (46.67)	-	-
CAARMS severity				*		
Total score (M, SD)	-	6.18 (6.21)	30.29 (4.64)	-	F = 45.33, p < .01	CHR-P > CHR-N CHR-P > HC
UTC	-	0.61 (1.15)	1.84 (1.93)	-	-	-
NBI	-	0.79 (1.04)	2.91 (1.76)	-	-	-
PA	-	0.97 (1.35)	2.87 (1.50)	-	-	-
DS	-	0.52 (0.89)	1.42 (1.38)	-	-	-
CHR category						
CAARMS only (APS/GFRD)	-	-	31	-	-	-
SPI-A only (COGDIS/COPER)	-	-	29	-	-	-
CAARMS + SPI-A	-	-	51	-	-	-
	HC (N=70)	CHR-N (N=38)	CHR-P (N=108)	FEP (N=37)	Group effect	Post-hoc comparisons
BACS						
Composite score	0.21 (0.78)	-0.05 (1.59)	-0.64 (1.67)	-	F=3.59, -p= .03	HC > CHR-P
Verbal memory	0.25 (1.0)	0.20 (1.73)	0.01 (1.27)	-	F=0.524, p= .59	-
Verbal fluency	0.07 (1.54)	-0.24 (1.01)	-0.03 (1.16)	-	F=,0.58 p= .56	-

Working memory (Digit sequencing)	0.19 (1.0)	0.29 (1.26)	0.05 (1.36)	-	F=0.39, p= .68	-
Motor speed (Token task)	0.0 (0.97)	-0.70 (1.0)	-1.10 (1.41)	-	F=9.60 p .< .01	HC > CHR-P
Executive functioning (Tower of London)	0.10 (0.79)	0.24 (1.25)	-0.16 (1.41)	-	F=,1.41 p= .32	HC > CHR-P
GAF0 (M, SD)	87.57 (6.49)	70.05 (12.76)	58.33 (13.83)	-	F=79.82, p < .01	HC > CHR-N HC > CHR-P CHR-N > CHR-P
GAF6 (M, SD)	-	57.73 (20.3)	58.8 (13.71)	-	-	
GAF12 (M, SD)	-	66.59 (20.32)	62.59 (14.52)	-	-	
N at follow-up (6m, 12m)	-	15, 20	88, 74	-	-	

Abbreviations: APS, attenuated psychotic symptoms; BACS, Brief Assessment of Cognition in Schizophrenia; CAARMS, Comprehensive Assessment of At Risk Mental States; COGDIS, Cognitive Disturbances, COGDIS, Cognitive-Perceptive Basic Symptoms criterion; HC, healthy controls; CHR-N, clinical risk-negative; CHR-P, clinical high-risk positive; FEP, first-episode psychosis; GAF, global assessment of functioning; SPI-A, Schizophrenia Proneness Instrument, Adult version; SD, standard deviation of the mean; AD, antidepressant; AP, antipsychotic.

Note: * data only available for 15 participants.

We observed a main effect of group on hippocampal volumes (F = 5.67, *p* <.01). A significant, bilateral reduction in hippocampal volume was found for FEPs vs. HCs (t = 3.75, p <.05, FDR corrected) (Fig. 2, Supplementary Table 1). The difference between CHR-Ps and HCs also was significant (t = 2.38, p =.017) before but not after FDR correction (p =.06). A reduction in volume was observed in the left (t = 2.69, p = 0.008, uncorrected) but not in the right hippocampus (t = 1.58, p = 0.116, uncorrected) in the CHR-P group compared to HCs. The difference between FEP and CHR-P groups was not significant (t = 1.8, p =.08).

No other subcortical structures were characterized by significant differences between clinical groups and HC (Fig. 2). Differences in the FEP group in the thalamus and amygdala as well as in the putamen in the CHR-P group showed p <.1, but were all nonsignificant at p <.05 after FDR correction (see Supplementary Table 1).

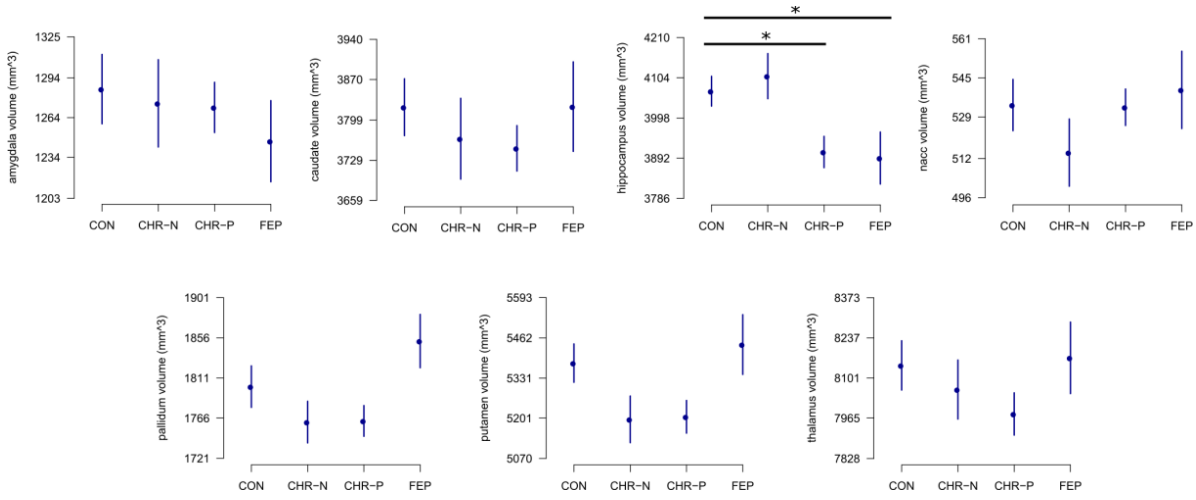


*Figure 2-2 Volumetric analysis, results. Average volumetric results for each subcortical structure across the control group (HC), clinical controls (CHR-N), clinical high-risk (CHR-P) and first-episode psychosis (FEP). Error bars indicate ±1 standard error of the mean (sem). Volumetric results are reported in cubic millimeters. *** indicate a significant difference between the groups, Bonferroni corrected, p < 0.05.*

Vertex analysis

Vertex analysis was limited to the hippocampus since this was the only subcortical structure that differed between groups (Fig. 3). The HC and FEP groups showed significant bilateral differences across the hip-pocampal surface (Peak cluster left: voxel 62, 106, 50 (MNI152 1 mm; p =.001, F = 16.12); peak cluster right: 116, 105, 50 (p =.0004, F = 18.91). In the CHR-P group, clusters with the highest F-values were primarily concentrated around the most anterior and posterior hippo-campus in both hemispheres. However, no differences between CHR-P and HC, or CHR-P and CHR-N groups were significant (Supplementary Table 3).

For the FEP and CHR-P groups, there was a significant difference in the anterior to mid-left hippocampus (p =.007, F = 10.17), with a peak cluster around voxel

120, 103, 61 (Fig. 3). No differences were observed in the right hemisphere (see Supplementary Table 3).

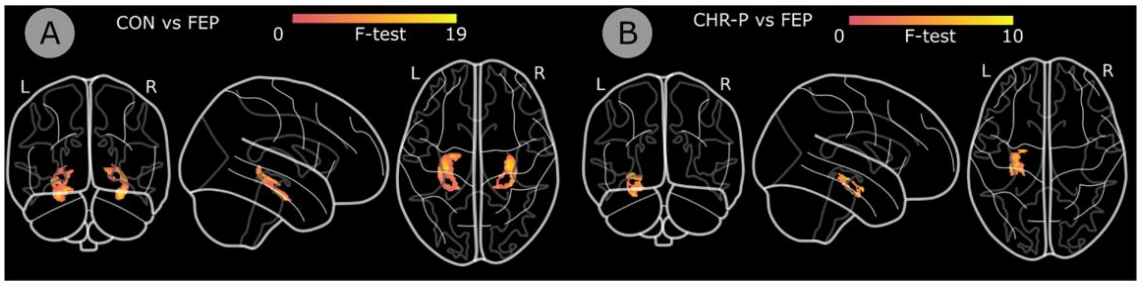


Figure 2-3. Vertex analysis at the level of the hippocampus. Hippocampal masks output by FSL showing the values of the F-statistic are overlaid onto a 1 mm MNI standard image. Panel A: the comparison between patients with a first-episode of psychosis (FEP) and healthy controls (HC) revealed significant shape differences. Panel B: the comparison between the clinical high-risk (CHR-P) and first episode (FEP) revealed significant shape differences in the anterior to mid-left hippocampus. No differences were observed in the right hemisphere.

Correlations with cognition and clinical measures

Hippocampal volumes did not show any significant correlations with global functioning (GAF), cognition (BACS total score and subscales), and symptom severity (CAARMS total and subscales, SPI-A severity) in the CHR-P group (see Supplementary Table 2). A relationship, however, was observed between left hippocampal volumes and GAF score at 12 months follow-up, but this was not significant after correction for multiple comparisons.

Subcortical volumes and clinical outcomes in CHR-P participants

We compared hippocampal volumetric data for CHR-P participants who continued to meet criteria for persistent APS at 12-month follow-up (APS-P: n = 32; APS-NP: n = 40). There were no significant differences between CHR-P subgroups (p =.14, t = -1.49). Moreover, a binomial GLM did not reveal a significant relationship between hippocampal volume and transition to psychosis (p >.10, see Supplementary Table 6). In addition, the relationship with good and poor functional outcomes

at baseline as well as at 6- and 12-months follow-up using logistic regression were explored. Mean hippocampus volume (averaged across hemispheres) did not show a significant association with GAF category at baseline (p =.58, uncorrected) or at 6 months (p =.33, uncorrected), but a relationship with GAF category at 12 months was detected (β = 0.0018, p =.036, Bonferroni-corrected) (Supplementary Table 6).

Medication effects on subcortical volumes

In the CHR-P group, ADM medication status did not show a significant relationship with any subcortical volumes in either hemisphere (all p > 0.1, uncorrected), including the hippocampus. Similarly, no effect was found in the FEP group for APM-status (Supplementary Table 5).

Discussion

The current study examined alterations in hippocampal volume and morphology during early-stage psychosis to address the specificity of hippocampal changes, relationship to illness stage as well as the link with clinical outcomes in CHR-P participants. We detected hippocampal volume-reductions in both CHR-P and FEP groups which were not pre-sent in psychiatric controls nor was any other subcortical structure characterized by anatomical deficits. Hippocampal volumes did not, however, robustly predict clinical and functional outcomes in CHR-P participants.

There is currently inconsistent evidence for hippocampus alterations in CHR-Ps. Although several studies have observed reduced hippocam-pus volumes (Borgwardt et al., 2007; Ganzola, Maziade & Duchesne, 2014; Harrisberger et al., 2016a,b,c; Sasabayashi et al., 2021; Wood et al., 2010), recent meta-analyses (Walter et al., 2016; Hinney et al., 2021) observed no robust evidence for volumetric reductions.

Reduced hippocampus volumes have been previously shown to predict transition to psychosis (Buehlmann et al., 2010; Provenzano et al., 2020, but see Hinney et al., 2020) as well as a persistence of APS (Ho et al., 2016, Ho et al., 2017a,b), especially in the hippocampal subregion CA1. In the current study, hippocampal volumes did not differ between CHR-P with persistent vs. non-

persistent APS nor were CHR-Ps who transitioned to psychosis characterized by exaggerated GM-reductions. However, there was a nonsignificant association between hippocampal volumes and GAF at 12 months but not at 6 months in the CHR-P group. Given the smaller number of follow-up data for CHR-Ps at 12 months, one possibility is that this effect is driven by attrition of participants.

In FEP patients, more robust deficits have been reported for both hippocampal volume and shape (Adriano et al., 2012; Borgwardt et al., 2007; Buehlmann et al., 2010; Lieberman et al., 2018; Phillips et al., 2002; Velakoulis et al., 2006), particularly in the anterior portion (McHugo et al., 2020; see also Haukvik et al., 2016). Interestingly, the extent of volume loss may be linked with the duration of untreated psychosis (Briend et al., 2020) and reduced hippocampal volume might be prognostic for clinical outcomes (McHugo et al., 2020).

In the current study, volumetric reductions in the FEP-group involved the bilateral hippocampus while in CHR-P participants defi-cits were confined to the left hemisphere. There is inconsistent evidence for the role of hemispheric differences in the hippocampus in early-stage psychosis. Some have observed changes in the left hemisphere that were associated with transition to psychosis (Buehlmann et al., 2010), FEP status (Baglivo et al., 2018; Velakoulis et al., 2006) and illness chronicity (Sasabayashi et al., 2021), while others did not report hemispheric differences in CHR-Ps (Harrisberger et al., 2016a,b,c) or in FEP-patients (Ho et al., 2017a,b).

Vertex analyses revealed widespread alterations in FEP-patients while in the CHR-P group, no significant differences were observed. Consistent with our findings, previous studies have found evidence for volumetric reductions in hippocampal subfields bilaterally in early psychosis, specifically CA2/3 and the subiculum (Baglivo et al., 2018; Vargas et al., 2018). On the other hand, illness progression has been associated with volumetric decline in CA1, CA2/3, DG, and (pre-) subiculum bilaterally (Vargas et al., 2018).

In contrasting with our data, however, others (e. g. Sasabayashi et al., 2021) have identified shared deficits between CHR-Ps and schizophrenia patients in CA1 as well as in the hippocampal tail. Accordingly, further longitudinal data will be required to determine the precise trajectory of hippocampal shape abnormalities from the CHR-P state to manifest psychosis and schizophrenia.

In the present study, CHR-Ps and FEPs showed an overlapping and specific deficit in hippocampal volume, providing support for the hypothesis that hippocampal dysfunctions may constitute a core signature of early-stage psychosis (e.g. Lieberman et al., 2018). Importantly, participants with substance abuse and affective disorders were not characterized by hippocampal volume loss, suggesting that the observed reductions may be specifically related to psychosis and not to other comorbid psychopathology (e.g. Cole et al., 2011; Santos et al., 2018). In addition, the hippocampal deficits in CHR-P and FEP-groups were not influenced by antipsychotic and antidepressant medication status.

The overlapping volumetric reductions in the hippocampus in both FEP and CHR-P groups indicate a potential role for hippocampal alterations in development of psychosis. However, the more pronounced hippocampal dysfunctions in both volume and shape in the FEP group suggest stage-specific differences that raises questions regarding the underlying mechanisms and origins. One possibility is that hippocampal dysfunctions are the result of prolonged psychosis and associated changes in hippocampus physiology involving elevated glutamatergic neurotransmission as previously proposed (e.g. Lieberman et al., 2018; Plitman et al., 2014). In addition, antipsychotic medication levels have been related to GM loss in schizophrenia (van Haren et al., 2008) as well as hippocampal shape changes (Gutman et al., 2022).

Finally, hippocampal deficits have been also found in individuals at high genetic risk (Ganzola, Maziade & Duchesne, 2014) as well as un-affected relatives of individuals with psychosis (e.g. Boos et al., 2007; Choi et al., 2022). Accordingly, it is conceivable that hippocampal abnormalities are driven partially by genetic susceptibility. To distinguish between these possibilities, further longitudinal studies are required in CHR-Ps and FEPs to identify the trajectory and contribution of anatomical and functional hippocampal alterations towards the development of psychosis as well as potential subgroups with distinct genetic contributions.

Several limitations must be considered in the interpretation of our findings. Firstly, hippocampal volume deficits in the CHR-P group did not reach statistical significance following corrections for multiple comparisons. Secondly, the number of transitions to FEP was too small to properly assess the relationship with hippocampal alterations.

Summary

Our study shows that CHR-P and FEP groups were characterized by a specific and overlapping deficit in hippocampal anatomy which was not observed in other subcortical structures, highlighting the importance of abnormalities in the hippocampus for understanding early stage-psychosis. However, volumetric abnormalities were not related to clinical and functional outcomes in CHR-P participants, suggesting that other biomarkers may be more promising for predicting clinical trajectories. Future studies should employ multi-modal neuroimaging approaches to characterize the functional consequences of abnormal hippocampus anatomy during early-stage psychosis.

Contributions

PJU is the principal investigator for the YouR study. PJU, SL and AG contributed to the conception and design of the study. PJU, RK, RG, MS and FSL contributed to the data collection. GB, PJU and AF analysed the data. GB, AF and PJU drafted the manuscript, with critical revision from SL, JG and FSL. All authors contributed to the interpretation of data, and revised the manuscript. All authors are responsible for the reported research, and have approved the manuscript as submitted.

All authors are responsible for the reported research, and have approved the manuscript as submitted.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: PJU has received research support from Lilly and Lundbeck outside the submitted work. SML has received a personal fee from Sunovion outside the submitted work. All other authors report no biomedical financial interests or potential conflicts of interest.

Acknowledgements

The investigators also acknowledge the support of the Scottish Mental Health Research Network (http://www.smhrn.org.uk) now called the NHS Research Scotland Mental Health Network (NRS MHN: http://www.nhsresearchscotland.org.uk/research-areas/mental-health) for providing assistance with participant recruitment, interviews and cognitive assessments. We would like to thank both the participants and patients who took part in the study and the research assistants of the YouR-study for supporting the recruitment and assessment of CHR-participants. G.B. is supported by the University of Glasgow Lord Kelvin-Adan Smith PhD scholarship. A.F. is supported by a grant from the Biotechnology and Biology research council (BBSRC, grant number: BB/S006605/1) and the Bial Foundation, Bial Foundation Grants Pro-gramme Grant id: A-29315, number: 203/2020, grant edition: G-15516.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103087.

References

Adriano, F., Caltagirone, C., Spalletta, G., 2012. Hippocampal volume reduction in first-episode and chronic schizophrenia: a review and meta-analysis. Neuroscientist 18 (2), 180–200.

Allen, P., Chaddock, C.A., Egerton, A., Howes, O.D., Barker, G., Bonoldi, I., Fusar-Poli, P., Murray, R., McGuire, P., 2015. Functional outcome in people at high risk for psychosis predicted by thalamic glutamate levels and prefronto-striatal activation. Schizophr. Bull. 41 (2), 429–439.

Allen, P., Hird, E.J., Orlov, N., Modinos, G., Bossong, M., Antoniades, M., Sampson, C., Azis, M., Howes, O., Stone, J., Perez, J., Broome, M., Grace, A.A., McGuire, P., 2021. Adverse clinical outcomes in people at clinical high-risk for psychosis related to altered interactions between hippocampal activity and glutamatergic function. Transl. Psychiatry 11 (1).

Arnone, D., McIntosh, A.M., Ebmeier, K.P., Munafo, M.R., Anderson, I.M., 2012. Magnetic resonance imaging studies in unipolar depression: systematic review and meta-regression analyses. Eur. Neuropsychopharmacol. 22 (1), 1–16.

Baglivo, V., Cao, B.o., Mwangi, B., Bellani, M., Perlini, C., Lasalvia, A., Dusi, N., Bonetto, C., Cristofalo, D., Alessandrini, F., Zoccatelli, G., Ciceri, E., Dario, L., Enrico, C., Francesca, P., Mazzi, F., Paolo, S., Balestrieri, M., Soares, J.C., Ruggeri, M., Brambilla, P., 2018. Hippocampal subfield volumes in patients with first-episode psychosis. Schizophr. Bull. 44 (3), 552–559.

Boos, H.B., Aleman, A., Cahn, W., Pol, H.H., Kahn, R.S., 2007. Brain volumes in relatives of patients with schizophrenia: a meta-analysis. Arch. Gen. Psychiatry 64 (3), 297–304.

Borgwardt, S.J., Riecher-Rossler, A., Dazzan, P., Chitnis, X., Aston, J., Drewe, M., Gschwandtner, U., Haller, S., Pflüger, M., Rechsteiner, E., D'Souza, M., Stieglitz, R.-D., Radü, E.-W., McGuire, P.K., 2007. Regional gray matter volume abnormalities in the at risk mental state. Biol. Psychiatry 61 (10), 1148–1156.

Bossong, M.G., Antoniades, M., Azis, M., Samson, C., Quinn, B., Bonoldi, I., Modinos, G., Perez, J., Howes, O.D., Stone, J.M., Allen, P., McGuire, P., 2019. Association of Hippocampal Glutamate Levels With Adverse Outcomes in Individuals at Clinical High Risk for Psychosis. JAMA Psychiatry 76 (2), 199–207.

Briend, F., Nelson, E.A., Maximo, O., Armstrong, W.P., Kraguljac, N.V., Lahti, A.C., 2020. Hippocampal glutamate and hippocampus subfield volumes in antipsychotic-naive first episode psychosis subjects and relationships to duration of untreated psychosis. Transl. Psychiatry 10 (1), 1–11.

Buehlmann, E., Berger, G.E., Aston, J., Gschwandtner, U., Pflueger, M.O., Borgwardt, S. J., Radue, E.-W., Riecher-Rossler, A., 2010. Hippocampus abnormalities in at risk mental states for psychosis? A cross-sectional high resolution region of interest magnetic resonance imaging study. J. Psychiatr. Res. 44 (7), 447–453.

Choi, S., Kim, M., Park, H., Kim, T., Moon, S.-Y., Lho, S.K., Lee, J., Kwon, J.S., 2022. Volume deficits in hippocampal subfields in unaffected relatives of schizophrenia patients with high genetic loading but without any psychiatric symptoms. Schizophr. Res. 240, 125–131.

Cole, J., Costafreda, S.G., McGuffin, P., Fu, C.H., 2011. Hippocampal atrophy in first episode depression: a meta-analysis of magnetic resonance imaging studies. J. Affect. Disord. 134 (1–3), 483–487.

Cover, K.S., van Schijndel, R.A., Versteeg, A., Leung, K.K., Mulder, E.R., Jong, R.A., Visser, P.J., Redolfi, A., Revillard, J., Grenier, B., Manset, D., Damangir, S., Bosco, P., Vrenken, H., van Dijk, B.W., Frisoni, G.B., Barkhof, F., 2016. Reproducibility of hippocampal atrophy rates measured with manual, FreeSurfer, AdaBoost, FSL/FIRST and the MAPS-HBSI methods in Alzheimer's disease. Psychiatry Res.: Neuroimaging 252, 26–35.

First, M.B., 2014. Structured clinical interview for the DSM (SCID). Encyclopedia Clin. Psychol. 1–6.

Fusar-Poli, P., Salazar de Pablo, G., Correll, C.U., Meyer-Lindenberg, A., Millan, M.J., Borgwardt, S., Galderisi, S., Bechdolf, A., Pfennig, A., Kessing, L.V., van Amelsvoort, T., Nieman, D.H., Domschke, K., Krebs, M.-O., Koutsouleris, N., McGuire, P., Do, K.Q., Arango, C., 2020a. Prevention of psychosis: advances in detection, prognosis, and intervention. JAMA Psychiatry 77 (7), 755.

Fusar-Poli, P., Salazar de Pablo, G., Correll, C.U., Meyer-Lindenberg, A., Millan, M.J., Borgwardt, S., Galderisi, S., Bechdolf, A., Pfennig, A., Kessing, L.V., van Amelsvoort, T., Nieman, D.H., Domschke, K., Krebs, M.-O., Koutsouleris, N., McGuire, P., Do, K.Q., Arango, C., 2020b. Prevention of psychosis: advances in detection, prognosis, and intervention. JAMA Psychiatry. 77 (7), 755.

Ganzola, R., Maziade, M., Duchesne, S., 2014. Hippocampus and amygdala volumes in children and young adults at high-risk of schizophrenia: research synthesis. Schizophr. Res. 156 (1), 76–86.

Glahn, D.C., Laird, A.R., Ellison-Wright, I., Thelen, S.M., Robinson, J.L., Lancaster, J.L., Bullmore, E., Fox, P.T., 2008. Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. Biol. Psychiatry 64 (9), 774–781.

Gutman, B.A., van Erp, T.G.M., Alpert, K., Ching, C.R.K., Isaev, D., Ragothaman, A., Jahanshad, N., Saremi, A., Zavaliangos-Petropulu, A., Glahn, D.C., Shen, L., Cong, S., Alnaes, D., Andreassen, O.A., Doan, N.T., Westlye, L.T., Kochunov, P., Satterthwaite, T.D., Wolf, D.H., Huang, A.J., Kessler, C., Weideman, A., Nguyen, D., Mueller, B.A., Faziola, L., Potkin, S.G., Preda, A., Mathalon, D.H., Bustillo, J., Calhoun, V., Ford, J.M., Walton, E., Ehrlich, S., Ducci, G., Banaj, N., Piras, F., Piras, F., Spalletta, G., Canales-Rodriguez, E.J., Fuentes-Claramonte, P., Pomarol-Clotet, E., Radua, J., Salvador, R., Sarro, S., Dickie, E.W., Voineskos, A., Tordesillas-Gutierrez, D., Crespo-Facorro, B., Setien-Suero, E., van Son, J.M., Borgwardt, S., Schonborn-Harrisberger, F., Morris, D., Donohoe, G., Holleran, L., Cannon, D., McDonald, C., Corvin, A., Gill, M., Filho, G.B., Rosa, P.G.P., Serpa, M.H., Zanetti, M. V., Lebedeva, I., Kaleda, V., Tomyshev, A., Crow, T., James, A., Cervenka, S., Sellgren, C.M., Fatouros-Bergman, H., Agartz, I., Howells, F., Stein, D.J., Temmingh, H., Uhlmann, A., de Zubicaray, G.I., McMahon, K.L., Wright, M., Cobia, D., Csernansky, J.G., Thompson, P.M., Turner, J.A., Wang, L., 2022. A meta-analysis of deep brain structural shape and asymmetry abnormalities in 2,833 individuals with schizophrenia compared with 3,929 healthy volunteers via the ENIGMA Consortium. Hum. Brain Mapp. 43 (1), 352–372.

Harrisberger, F., Buechler, R., Smieskova, R., Lenz, C., Walter, A., Egloff, L., Bendfeldt, K., Simon, A.E., Wotruba, D., Theodoridou, A., Rossler, W., Riecher-Rossler, A., Lang, U.E., Heekeren, K., Borgwardt, S., 2016a. Alterations in the

hippocampus and thalamus in individuals at high risk for psychosis. npj Schizophr. 2 (1).

Harrisberger, F., Smieskova, R., Vogler, C., Egli, T., Schmidt, A., Lenz, C., Simon, A.E., Riecher-Rossler, A., Papassotiropoulos, A., Borgwardt, S., 2016b. Impact of

polygenic schizophrenia-related risk and hippocampal volumes on the onset of psychosis. Transl. Psychiatry 6 (8) e868-e868.

Harrisberger, F., Buechler, R., Smieskova, R., Lenz, C., Walter, A., Egloff, L., Bendfeldt, K., Simon, A.E., Wotruba, D., Theodoridou, A., Rossler, W., Riecher-Rossler, A., Lang, U.E., Heekeren, K., Borgwardt, S., 2016c. Alterations in the

hippocampus and thalamus in individuals at high risk for psychosis. NPJ Schizophr 2, 16033.

Hashimoto, N., Ito, Y.M., Okada, N., Yamamori, H., Yasuda, Y., Fujimoto, M., Kudo, N., Takemura, A., Son, S., Narita, H., Yamamoto, M., Tha, K.K., Katsuki, A., Ohi, K., Yamashita, F., Koike, S., Takahashi, T., Nemoto, K., Fukunaga, M., Onitsuka, T., Watanabe, Y., Yamasue, H., Suzuki, M., Kasai, K., Kusumi, I., Hashimoto, R., 2018. The effect of duration of illness and antipsychotics on subcortical volumes in schizophrenia: Analysis of 778 subjects. NeuroImage: Clinical 17, 563–569.

Haukvik, U.K., Hartberg, C.B., Nerland, S., Jørgensen, K.N., Lange, E.H., Simonsen, C., Nesvåg, R., Dale, A.M., Andreassen, O.A., Melle, I., Agartz, I., 2016. No progressive brain changes during a 1-year follow-up of patients with first-episode psychosis. Psychol. Med. 46 (3), 589–598.

Herniman, S.E., Phillips, L.J., Wood, S.J., Cotton, S.M., Liemburg, E.J., Allott, K.A., 2021. Interrelationships between depressive symptoms and positive and negative symptoms of recent onset schizophrenia spectrum disorders: a network analytical approach. J. Psychiatr. Res. 140, 373–380.

Hinney, B., Walter, A., Aghlmandi, S., Andreou, C., Borgwardt, S., 2020. Does Hippocampal Volume Predict Transition to Psychosis in a High-Risk Group? A Meta-Analysis. Front Psychiatry 11, 614659.

Hinney, B., Walter, A., Aghlmandi, S., Andreou, C., Borgwardt, S., 2021. Does Hippocampal Volume Predict Transition to Psychosis in a High-Risk Group? A Meta-Analysis. Front. Psychiatry 11, 1582.

Ho, N.F., Holt, D.J., Cheung, M., Iglesias, J.E., Goh, A., Wang, M., Lim, J.KW., de Souza, J., Poh, J.S., See, Y.M., Adcock, A.R., Wood, S.J., Chee, M.WL., Lee, J., Zhou, J., 2017a. Progressive decline in hippocampal CA1 volume in individuals at ultra-high-risk for psychosis who do not remit: findings from the longitudinal youth at risk study. Neuropsychopharmacology 42 (6), 1361–1370.

Ho, N.F., Iglesias, J.E., Sum, M.Y., Kuswanto, C.N., Sitoh, Y.Y., De Souza, J., Hong, Z., Fischl, B., Roffman, J.L., Zhou, J., Sim, K., Holt, D.J., 2017b. Progression from selective to general involvement of hippocampal subfields in schizophrenia. Mol. Psychiatry 22 (1), 142–152.

Jalbrzikowski, M., Hayes, R.A., Wood, S.J., Nordholm, D., Zhou, J.H., Fusar-Poli, P., et al., 2021. Association of structural magnetic resonance imaging measures with psychosis onset in individuals at clinical high risk for developing psychosis: An ENIGMA working group mega-analysis. JAMA Psychiatry 78 (7), 753–766.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276.

Keefe, R.S., Goldberg, T.E., Harvey, P.D., Gold, J.M., Poe, M.P., Coughenour, L., 2004. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. Schizophr. Res. 68 (2–3),

283–297.

Klosterkotter, J., Hellmich, M., Steinmeyer, E.M., Schultze-Lutter, F., 2001. Diagnosing schizophrenia in the initial prodromal phase. Arch. Gen. Psychiatry 58 (2), 158–164.

Koutsouleris, N., Meisenzahl, E.M., Davatzikos, C., Bottlender, R., Frodl, T., Scheuerecker, J., Schmitt, G., Zetzsche, T., Decker, P., Reiser, M., Moller, H.J., Gaser, C., 2009. Use of neuroanatomical pattern classification to identify subjects in at-risk mental states of psychosis and predict disease transition. Arch. Gen. Psychiatry 66 (7), 700–712.

Koutsouleris, N., Patschurek-Kliche, K., Scheuerecker, J., Decker, P., Bottlender, R., Schmitt, G., Rujescu, D., Giegling, I., Gaser, C., Reiser, M., Moller, H.-J., Meisenzahl, E.M., 2010. Neuroanatomical correlates of executive dysfunction in the at-risk mental state for psychosis. Schizophr. Res. 123 (2-3), 160–174.

Koutsouleris, N., Kambeitz-Ilankovic, L., Ruhrmann, S., Rosen, M., Ruef, A., Dwyer, D.B., Paolini, M., Chisholm, K., Kambeitz, J., Haidl, T., Schmidt, A., Gillam, J., Schultze-Lutter, F., Falkai, P., Reiser, M., Riecher-Rossler, A., Upthegrove, R., Hietala, J., Salokangas, R.K.R., Pantelis, C., Meisenzahl, E., Wood, S.J., Beque, D., Brambilla, P., Borgwardt, S., 2018. Prediction Models of Functional Outcomes for Individuals in the Clinical High-Risk State for Psychosis or With Recent-Onset

Depression: A Multimodal, Multisite Machine Learning Analysis. JAMA Psychiatry 75 (11), 1156.

Li, W., Yang, Y., An, F.R., Zhang, L., Ungvari, G.S., Jackson, T., Yuan, Z., Xiang, Y.T., 2020. Prevalence of comorbid depression in schizophrenia: A meta-analysis of observational studies. J Affect Disord. 1 (273), 524–531. https://doi.org/10.1016/j. jad.2020.04.056.

Lieberman, J.A., Girgis, R.R., Brucato, G., Moore, H., Provenzano, F., Kegeles, L., Javitt, D., Kantrowitz, J., Wall, M.M., Corcoran, C.M., Schobel, S.A., Small, S.A., 2018. Hippocampal dysfunction in the pathophysiology of schizophrenia: a selective review and hypothesis for early detection and intervention. Mol. Psychiatry 23 (8), 1764–1772.

Lisman, J.E., Coyle, J.T., Green, R.W., Javitt, D.C., Benes, F.M., Heckers, S., Grace, A.A., 2008. Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. Trends Neurosci. 31 (5), 234–242.

McHugo, M., Armstrong, K., Roeske, M.J., Woodward, N.D., Blackford, J.U., Heckers, S., 2020. Hippocampal volume in early psychosis: a 2-year longitudinal study. Transl. Psychiatry 10 (1), 1–10.

Modinos, G., Kempton, M.J., Tognin, S., Calem, M., Porffy, L., Antoniades, M., Mason, A., Azis, M., Allen, P., Nelson, B., McGorry, P., Pantelis, C., Riecher-Rossler, A., Borgwardt, S., Bressan, R., Barrantes-Vidal, N., Krebs, M.-O., Nordentoft, M., Glenthøj, B., Ruhrmann, S., Sachs, G., Rutten, B., van Os, J., de Haan, L., Velthorst, E., van der Gaag, M., Valmaggia, L.R., McGuire, P., 2020a. Association of adverse outcomes with emotion processing and its neural substrate in individuals at clinical high risk for psychosis. JAMA Psychiatry 77 (2), 190.

Modinos, G., Allen, P., Zugman, A., Dima, D., Azis, M., Samson, C., Bonoldi, I., Quinn, B., Gifford, G.W.G., Smart, S.E., Antoniades, M., Bossong, M.G., Broome, M.R., Perez, J., Howes, O.D., Stone, J.M., Grace, A.A., McGuire, P., 2020b. Neural circuitry of novelty salience processing in psychosis risk: association with clinical outcome. Schizophr. Bull. 46 (3), 670–679.

Modinos, G., Richter, A., Egerton, A., Bonoldi, I., Azis, M., Antoniades, M., Bossong, M., Crossley, N., Perez, J., Stone, J.M., Veronese, M., Zelaya, F., Grace, A.A., Howes, O. D., Allen, P., McGuire, P., 2021. Interactions between hippocampal activity

and striatal dopamine in people at clinical high risk for psychosis: relationship to adverse outcomes. Neuropsychopharmacology 46 (8), 1468–1474.

Næss-Schmidt, E., Tietze, A., Blicher, J.U., Petersen, M., Mikkelsen, I.K., Coupe, P., Manjon, J.V., Eskildsen, S.F., 2016. Automatic thalamus and hippocampus segmentation from MP2RAGE: comparison of publicly available methods and implications for DTI quantification. Int. J. Comput. Assist. Radiol. Surg. 11 (11), 1979–1991.

Pantelis, C., Nelson, H.E., 2019. Cognitive functioning and symptomatology in schizophrenia: The role of frontal-subcortical systems. In: The neuropsychology of schizophrenia. Psychology Press, pp. 215–229.

Perlaki, G., Horvath, R., Nagy, S.A., Bogner, P., Doczi, T., Janszky, J., Orsi, G., 2017. Comparison of accuracy between FSL's FIRST and Freesurfer for caudate nucleus and putamen segmentation. Sci. Rep. 7 (1), 1–9.

Phillips, L., Velakoulis, D., Pantelis, C., Wood, S., Yuen, H., Yung, A., Desmond, P., Brewer, W., Mcgorry, P., 2002. Non-reduction in hippocampal volume is associated with higher risk of psychosis. Schizophr. Res. 58 (2-3), 145–158.

Plitman, E., Nakajima, S., de la Fuente-Sandoval, C., Gerretsen, P., Chakravarty, M.M., Kobylianskii, J., Chung, J.K., Caravaggio, F., Iwata, Y., Remington, G., Graff-Guerrero, A., 2014. Glutamate-mediated excitotoxicity in schizophrenia: a review. Eur. Neuropsychopharmacol. 24 (10), 1591–1605.

Provenzano, F.A., Guo, J., Wall, M.M., Feng, X., Sigmon, H.C., Brucato, G., First, M.B., Rothman, D.L., Girgis, R.R., Lieberman, J.A., Small, S.A., 2020. Hippocampal Pathology in Clinical High-Risk Patients and the Onset of Schizophrenia. Biol. Psychiatry 87 (3), 234–242.

Santos, M.A.O., Bezerra, L.S., Carvalho, A.R.M.R., Brainer-Lima, A.M., 2018. Global hippocampal atrophy in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. Trends Psychiatry Psychother. 40, 369–378.

Sasabayashi, D., Takayanagi, Y., Takahashi, T., Katagiri, N., Sakuma, A., Obara, C., Katsura, M., Okada, N., Koike, S., Yamasue, H., Nakamura, M., Furuichi, A., Kido, M., Nishikawa, Y., Noguchi, K., Matsumoto, K., Mizuno, M., Kasai, K.,

Suzuki, M., 2020. Subcortical Brain Volume Abnormalities in Individuals With an At-risk Mental State. Schizophr. Bull. 46 (4), 834–845.

Sasabayashi, D., Yoshimura, R., Takahashi, T., Takayanagi, Y., Nishiyama, S., Higuchi, Y., Mizukami, Y., Furuichi, A., Kido, M., Nakamura, M., Noguchi, K., Suzuki, M., 2021. Reduced Hippocampal Subfield Volume in Schizophrenia and Clinical High-Risk State for Psychosis. Front. Psychiatry 12.

Schobel, S.A., Chaudhury, N.H., Khan, U.A., Paniagua, B., Styner, M.A., Asllani, I., Inbar, B.P., Corcoran, C.M., Lieberman, J.A., Moore, H., Small, S.A., 2013. Imaging patients with psychosis and a mouse model establishes a spreading pattern of hippocampal dysfunction and implicates glutamate as a driver. Neuron 78 (1),

81–93.

Schoemaker, D., Buss, C., Head, K., Sandman, C.A., Davis, E.P., Chakravarty, M.M., Gauthier, S., Pruessner, J.C., 2016. Hippocampus and amygdala volumes from magnetic resonance images in children: Assessing accuracy of FreeSurfer and FSL against manual segmentation. Neuroimage 129, 1–14.

Schultze-Lutter, F., Ruhrmann, S., Fusar-Poli, P., Bechdolf, A., Schimmelmann, B.G., Klosterkotter, J., 2012. Basic symptoms and the prediction of first-episode psychosis. Curr. Pharm. Des. 18 (4), 351–357.

Stone, J.M., Howes, O.D., Egerton, A., Kambeitz, J., Allen, P., Lythgoe, D.J., O'Gorman, R.L., McLean, M.A., Barker, G.J., McGuire, P., 2010. Altered relationship between hippocampal glutamate levels and striatal dopamine function in subjects at ultra high risk of psychosis. Biol. Psychiatry 68 (7), 599–602.

Uhlhaas, P.J., Gajwani, R., Gross, J., Gumley, A.I., Lawrie, S.M., Schwannauer, M., 2017. The youth mental health risk and resilience study (YouR-Study). BMC Psychiatry 17 (1), 43.

van Erp, T.G.M., Hibar, D.P., Rasmussen, J.M., Glahn, D.C., Pearlson, G.D., Andreassen, O.A., Agartz, I., Westlye, L.T., Haukvik, U.K., Dale, A.M., Melle, I., Hartberg, C.B., Gruber, O., Kraemer, B., Zilles, D., Donohoe, G., Kelly, S., McDonald, C., Morris, D.W., Cannon, D.M., Corvin, A., Machielsen, M.W.J., Koenders, L., de Haan, L., Veltman, D.J., Satterthwaite, T.D., Wolf, D.H., Gur, R.C., Gur, R.E., Potkin, S.G., Mathalon, D.H., Mueller, B.A., Preda, A., Macciardi, F., Ehrlich, S., Walton, E., Hass, J., Calhoun, V.D., Bockholt, H.J., Sponheim, S.R., Shoemaker, J.M., van Haren, N.E.M., Pol, H.E.H., Ophoff, R.A., Kahn, R.S., Roiz-Santianez, R., Crespo-Facorro, B., Wang, L., Alpert, K.I., Jonsson, E.G., Dimitrova, R., Bois,

C., Whalley, H.C., McIntosh, A.M., Lawrie, S.M., Hashimoto, R., Thompson, P. M., Turner, J.A., 2016. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Mol. Psychiatry 21 (4), 547–553.

van Haren, N.E.M., Pol, H.E.H., Schnack, H.G., Cahn, W., Brans, R., Carati, I., Rais, M., Kahn, R.S., 2008. Progressive brain volume loss in schizophrenia over the course of the illness: evidence of maturational abnormalities in early adulthood. Biol. Psychiatry 63 (1), 106–113.

Vargas, T., Dean, D.J., Osborne, K.J., Gupta, T., Ristanovic, I., Ozturk, S., Turner, J., van Erp, T.G.M., Mittal, V.A., 2018. Hippocampal subregions across the psychosis spectrum. Schizophr. Bull. 44 (5), 1091–1099.

Velakoulis, D., Wood, S.J., Wong, M.T.H., McGorry, P.D., Yung, A., Phillips, L., Smith, D. e., Brewer, W., Proffitt, T., Desmond, P., Pantelis, C., 2006. Hippocampal and amygdala volumes according to psychosis stage and diagnosis: A magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra–high-risk individuals. Arch. Gen. Psychiatry 63 (2), 139.

Velasco-Annis, C., Akhondi-Asl, A., Stamm, A., Warfield, S.K., 2018. Reproducibility of brain MRI segmentation algorithms: empirical comparison of local MAP PSTAPLE, FreeSurfer, and FSL-FIRST. J. Neuroimaging 28 (2), 162–172.

Walter, A., Suenderhauf, C., Harrisberger, F., Lenz, C., Smieskova, R., Chung, Y., Cannon, T.D., Bearden, C.E., Rapp, C., Bendfeldt, K., Borgwardt, S., Vogel, T., 2016. Hippocampal volume in subjects at clinical high-risk for psychosis: a systematic review and meta-analysis. Neurosci. Biobehav. Rev. 71, 680–690.

Walton, E., Hibar, D.P., van Erp, T.G.M., Potkin, S.G., Roiz-Santianez, R., Crespo-Facorro, B., Suarez-Pinilla, P., van Haren, N.E.M., de Zwarte, S.M.C., Kahn, R.S., Cahn, W., Doan, N.T., Jørgensen, K.N., Gurholt, T.P., Agartz, I., Andreassen, O.A., Westlye, L.T., Melle, I., Berg, A.O., Morch-Johnsen, L., Færden, A., Flyckt, L., Fatouros-Bergman, H., Jonsson, E.G., Hashimoto, R., Yamamori, H., Fukunaga, M., Jahanshad, N., De Rossi, P., Piras, F., Banaj, N., Spalletta, G., Gur, R.E., Gur, R.C., Wolf, D.H., Satterthwaite, T.D., Beard, L.M., Sommer, I.E., Koops, S., Gruber, O., Richter, A., Kramer, B., Kelly, S., Donohoe, G., McDonald, C., Cannon, D.M., Corvin, A., Gill, M., Di Giorgio, A., Bertolino, A., Lawrie, S., Nickson, T., Whalley, H. C., Neilson, E., Calhoun, V.D., Thompson, P.M., Turner,

J.A., Ehrlich, S., 2018. Prefrontal cortical thinning links to negative symptoms in schizophrenia via the ENIGMA consortium. Psychol. Med. 48 (1), 82–94.

Wang, Y., Zuo, C., Wang, W., Xu, Q., Hao, L., 2021. Reduction in hippocampal volumes subsequent to heavy cannabis use: a 3-year longitudinal study. Psychiatry Res. 295, 113588.

Wilson, S., Bair, J.L., Thomas, K.M., Iacono, W.G., 2017. Problematic alcohol use and reduced hippocampal volume: a meta-analytic review. Psychol. Med. 47 (13), 2288–2301.

Wood, S.J., Kennedy, D., Phillips, L.J., Seal, M.L., Yücel, M., Nelson, B., Yung, A.R., Jackson, G., McGorry, P.D., Velakoulis, D., Pantelis, C., 2010. Hippocampal pathology in individuals at ultra-high risk for psychosis: a multi-modal magnetic resonance study. Neuroimage 52 (1), 62–68.

Yung, A.R., Yuen, H.P., McGorry, P.D., Phillips, L.J., Kelly, D., Dell'Olio, M., Francey, S. M., Cosgrave, E.M., Killackey, E., Stanford, C., Godfrey, K., Buckby, J., 2005. Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. Aust. N. Z. J. Psychiatry 39 (11–12), 964–971.

Zikidi, K., Gajwani, R., Gross, J., Gumley, A.I., Lawrie, S.M., Schwannauer, M., Schultze-Lutter, F., Fracasso, A., Uhlhaas, P.J., 2020. Grey-matter abnormalities in clinical high-risk participants for psychosis. Schizophrenia Res. 226, 120–128. https://doi. org/10.1016/j.schres.2019.08.034.

Chapter 3: Choroid plexus morphology in schizophrenia and early-stage psychosis: A cross-sectional study

Gina Brunner MSc, Ruchika Gajwani PhD, Joachim Gross PhD, Andrew Gumley PhD, Rosanne H. Timmerman MSc, Rebecca Taylor MSc, Rajeev Krishnadas PhD, Stephen M. Lawrie PhD, Matthias Schwannauer PhD, Frauke Schultze-Lutter PhD, Peter Uhlhaas PhD*, Alessio Fracasso PhD*

* these authors contributed equally to this work

Abstract

Background: The choroid plexus is an important structure contained within the ventricular system. Schizophrenia has been associated with morphological changes to the choroid plexus but the presence and extent of deficits at different illness stages is unclear. Methods: We examined choroid plexus volumes in participants at clinical high-risk for psychosis (N=110), participants with first-episode psychosis (N=37), participants with schizophrenia (N=28), clinical (N=38) and non-clinical controls (N=75). Automated segmentation (Gaussian mixture model) was used to estimate choroid plexus volumes from T1 MR images. We then conducted a linear model and Bayes factor analysis to investigate group differences, and assessed the relationship between choroid plexus volumes and clinical characteristics. Results: Schizophrenia patients were characterised by increased choroid plexus and ventricular volume while first-episode psychosis and clinical high-risk for psychosis participants showed no differences. However, choroid plexus volumes in schizophrenia patients did not significantly differ from controls when controlling for ventricular volume. Finally, choroid plexus volumes were not associated with clinical characteristics in any group. Conclusion: Our findings suggest that choroid plexus morphology is not affected in schizophrenia and early-stage psychosis. Previously reported choroid plexus abnormalities in schizophrenia patients are likely due to overall changes in ventricular volume.

Keywords: Psychosis, schizophrenia, choroid plexus, MRI

Introduction

The choroid plexus (CP) is contained within the ventricular system and primarily consists of an epithelial cell layer which is involved in the production of cerebrospinal fluid (CSF), and its capillary system maintains the blood-CSF barrier (Lun, Monuki, & Lehtinen, 2015). CP pathology such as papilloma, has been associated with major structural changes in the ventricular system (Fujimura et al., 2004) and may cause psychosis-like symptoms (Arasappa, Danivas, & Venkatasubramanian, 2013; Carson, Weingart, Guarnieri, & Fisher, 1997). CP function is further associated with the brain's inflammatory response (Karimy et al., 2017), dopaminergic states (Castellani et al., 2019), as well as learning (Arnaud et al., 2021; Zarif et al., 2018) and neuroplasticity (Falcao et al., 2012).

Abnormal CP functioning has been recently implicated in the pathophysiology of schizophrenia (SCZ), which is a severe psychotic disorder characterised by widespread neuroanatomical alterations (van Erp, Hibar, Rasmussen, Glahn, Pearlson, Andreassen, & Turner, 2016; Van Erp et al., 2018). The hippocampus and lateral ventricles have shown the largest volumetric changes in SCZ (van Erp, Hibar, Rasmussen, Glahn, Pearlson, Andreassen, & Turner, 2016; Van Erp et al., 2018). Several genes implicated in SCZ are also expressed in the CP and impact neuroplasticity (Balu & Coyle, 2011).

The onset of SCZ is preceded in the majority of cases by a clinical high-risk state for psychosis (CHR-P) characterized by attenuated psychotic symptoms (APS), self-reported cognitive deficits, functional impairments and anatomical alterations (Ellis, Walker, & Goldsmith, 2020; Yung et al., 2006; Zikidi et al., 2020). Approximately 22% of CHR-P individuals will transition to first-episode psychosis (FEP) within 2 years (G. S. de Pablo, Radua, Pereira, Bonoldi, Arienti, Besana, & Fusar-Poli, 2021). Increased inflammatory markers have been recently shown in CHR-P participants, although they did not predict transition to psychosis (Misiak et al., 2021)

In FEP, ventricular volumes are increased (Gallardo-Ruiz, Crespo-Facorro, Setien-Suero, & Tordesillas-Gutierrez, 2019; Steen, Mull, McClure, Hamer, & Lieberman, 2006), while CHR-P individuals have not consistently shown

ventricular alterations except for those who later convert to psychosis (Chung et al., 2015). Both FEP and CHR-P groups are characterized by decreased hippocampal volumes (Brunner et al., 2022; Gallardo-Ruiz et al., 2019; Velakoulis et al., 2006).

Recent investigations have reported increased CP volumes in schizophrenia as well as first-degree relatives (J. Huang et al., 2022; P. Lizano, Lutz, Ling, Lee, Eum, Bishop, & Keshavan, 2019). However, one study found changes to be confined to early stages of psychosis (within five years of diagnosis), but not later stages (Senay et al., 2023). In SCZ, CP volumes were found to correlate with stress and inflammatory markers but not clinical features (P. Lizano, Lutz, Ling, Lee, Eum, Bishop, & Keshavan, 2019; Zhou et al., 2020).

Increased CP volumes have been reported recently in CHR-P individuals, which correlated with inflammatory markers (D. Bannai et al., 2022b). However, there were significant effects of CP segmentation methods and differences in ventricular size were found to impact estimates of CP-volume (D. Bannai et al., 2022b; P. Lizano, Lutz, Ling, Lee, Eum, Bishop, & Keshavan, 2019). It is important to note that ventricles encompass the CP with robust positive correlations between ventricular size and CP volumes (P. Lizano, Lutz, Ling, Lee, Eum, Bishop, & Keshavan, 2019; Tamminga et al., 2021; Zhou et al., 2020).

In the current study, we investigated CP volumes in individuals with schizophrenia and in early-stage psychosis (CHR-P, FEP) to determine whether changes in CP morphology can be observed across illness stages and whether they are present independently of ventricular changes. To this end, we recruited a sample of 110 CHR-P, 37 FEP, and 28 patients with SCZ who were compared to non-clinical healthy controls (HC) and a clinical control group who did not meet CHR criteria (CHR-N). We included the CHR-N control group to control for potential effects of general psychopathology on CP volumes (N. Althubaity, Schubert, Martins, Yousaf, Nettis, Mondelli, & Veronese, 2022; Zhou et al., 2020). To investigate differences in CP morphology and its relationship with ventricular changes, we used linear models including ventricular volumes as a covariate. Moreover, we further incorporated a Bayesian analysis to estimate the confidence in our findings as the Bayes factor quantifies evidence in favour or against the null hypothesis tested (Keysers, Gazzola, & Wagenmakers, 2020).

Methods

Participants

A total of 289 participants from four clinical groups were recruited: 1) 110 participants meeting CHR-P criteria, 2) 38 participants not meeting CHR-P criteria but who met criteria for affective disorders (n = 11), anxiety disorders (n = 16), eating disorders (n = 1), and/or substance abuse (n = 10) (CHR-N), 3) 37 patients with FEP, 4) 28 participants with schizophrenia (SCZ), and 5) 75 healthy controls (HC) without an axis I diagnosis or family history of psychosis. All CHR-P, CHR-N, FEP and 38 HC subjects came from the Youth Mental Health Risk and Resilience (YouR) Study cohort (Uhlhaas et al., 2017).

CHR-P status was established using the Comprehensive Assessment of At Risk Mental States (CAARMS) high-risk criteria (Yung et al., 2006) and the Cognitive Disturbances (COGDIS) and Cognitive-Perceptive (COPER) basic symptoms criteria according to the Schizophrenia Proneness Instrument, Adult version (Schultze-Lutter et al., 2007). FEP and SCZ participants were assessed with the Structured Clinical Interview for DSM-5 (SCID) (First, 2014) and the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987). CHR-P, CHR-N and HC participants were assessed using the Brief Assessment of Cognition in Schizophrenia (BACS, Keefe et al. (2004).

The study was approved by the ethical committees of University of Glasgow and the NHS Research Ethical Committee Glasgow & Greater Clyde. All participants provided written informed consent.

MRI acquisition

YouR T1-weighted images were acquired using a Siemens 3T scanner using a 3D MPRAGE sequence with the following parameters: FoV: 256 × 256 × 176 mm3, voxel size: 1 × 1 × 1 mm3, TR: 2250 ms, TE: 2.6 ms, TI: 900 ms, FA: 9°. Data from the SCZ and n =37 HC participants were acquired on an Allegra 3T scanner using the following parameters: FoV: 256 mm3, voxel size: 1 × 1 × 1 mm3, TR: 2300 ms, TE: 3.93 ms.

MRI preprocessing and segmentation

All images were visually inspected for image quality and participants with visible artifacts or substantial anatomical abnormalities were excluded. One CHR-N participant was excluded due to a visible cerebellar abnormality.

CP segmentation was performed with Freesurfer (Fischl, 2012) recon-all and a Gaussian mixture model, GMM (Tadayon et al., 2020). While GMM-based segmentations have shown adequate accuracy in the past (D. Bannai et al., 2022b), the existing implementation (Tadayon et al., 2020) relies on a ventricle mask provided by Freesurfer – i.e. its accuracy may be diminished if this mask contains errors. Upon visual inspection, it was noted that the Freesurfer based ventricle mask could extend outside of the ventricle in the posterior portion, thus leading the GM segmentations to include grey and white matter. To address this problem, we used the AFNI (Cox, 1996) 3dseg tool to constrain this mask. Here, voxels with a > 0.75 probability of being CSF within the Freesurfer ventricle mask were kept and the remainder were excluded. GM-based CP segmentations were then computed within this restricted mask which was found to produce good accuracy in line with human inter-rater reliability (0.71).

In addition to GMM and Freesurfer, a randomly selected subset of 25 scans containing equal proportions of each group were manually segmented by three raters (GB, RE, RT) with substantial MRI experience. Dice coefficients were computed to assess the similarity of segmentations from each automated method with manual segmentations, and the similarity across different human raters (inter-rater reliability). We also report the Dice coefficient between manual rates and the GMM obtained from the original Freesurfer ventricular mask and the AFNI 3dseg ventricular mask. Qualitatively, it was noted that both Freesurfer and GMM segmentation masks showed similar shapes to manual segmentations, but Freesurfer segmentations were commonly shifted upwards or downwards which resulted in decreased overlap with manual segmentations compared with GMM segmentation masks.

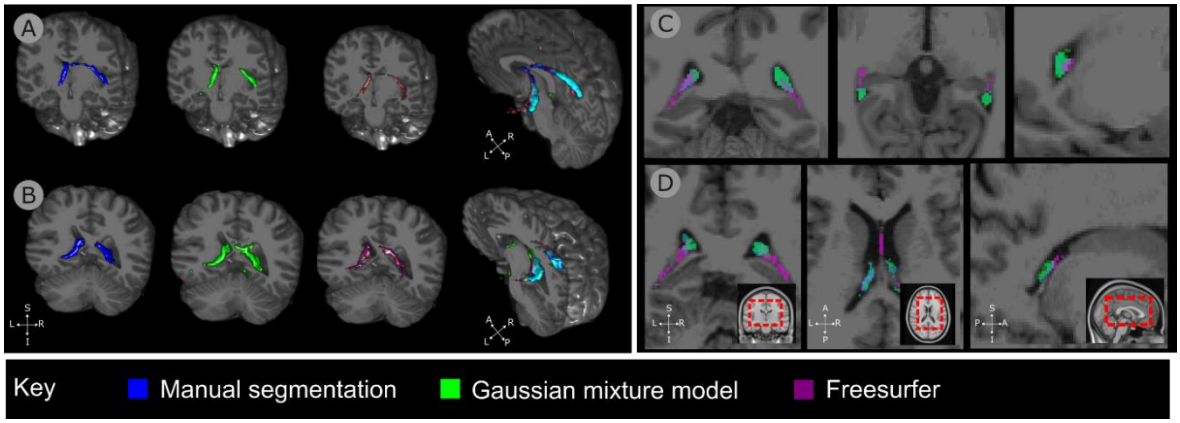


Figure 3-1. Manual, GMM, and Freesurfer (FS) segmentations for a selection of individual participants. Manual segmentation is shown in blue, GMM in green, and FS in pink colour. Panels A and B show 3D render for the three segmentation types separately, and overlayed (right) to show overlap, whereby blended colours represent overlap. Anatomical plane is shown in the cube at the bottom left of each panel. Panels C and D show a coronal, axial and sagittal slice with each segmentation type visible, whereby anatomical plane and direction are indicated at each side of the image, and at the bottom of each image in panel D. Images were visualised using FSLeyes (slices) and MRIcroGL (3D render).

Statistical methods

Statistical analyses were completed using R (https://www.r-project.org/). We fitted linear models using the lm function for R to investigate group differences in CP volume. CP volumes were averaged between the left and right hemisphere. The following equation was used (Equation 1):

(1.) CP volume ~ group * volume covariate + age

The primary volumetric covariate we used was ventricular volume as given by the volume of the ventricle masks, whereby the left and right hemispheres were averaged. We further fitted this model with total brain volume (TBV) as a covariate obtained from the Freesurfer brain mask. Both covariates were centred using the R scale function, with analyses completed using the original scale given in the supplement for completeness. We further applied bootstrapping with 5000 samples to obtain 95% confidence intervals.

We report both uncorrected CP volume analysis (Mann Whitney U) as well as models where ventricular volume is used as a covariate. The reasons for this

are twofold: Firstly, CP volumes correlate strongly with ventricular volumes (Tadayon et al., 2020). Secondly, differences in ventricular volume have frequently been identified in schizophrenia patients (van Erp, Hibar, Rasmussen, Glahn, Pearlson, Andreassen, & Turner, 2016). Reporting differences in CP volume without taking into consideration differences in ventricular or total brain volume (TBV) may therefore not reflect changes specific to the CP itself.

Furthermore, we fitted Bayesian linear models and obtained Bayes factors using the lmBF function from the BayesFactor package for R (Morey, Rouder, Jamil, & Morey, 2015). The model specification was identical to (Equation 1), whereby the chosen covariates were included in the null model. Models were fit separately for each group so that we could evaluate the evidential support for group effects compared to HC. We used BayesFactor default priors.

When describing our results, we use terminology previously introduced by Jeffreys regarding evidence in favour or against the null hypothesis (Jeffreys, 1939; Lee & Wagenmakers, 2013). More specifically, we use the terms 'weakly in favour/against', 'moderately in favour/against' and 'strongly in favour/against'. These corresponding to Bayes factors of <3, 3-10 and >10, respectively. Bayes factors can be reported as BF01 or BF10 (van Doorn et al., 2021), whereby larger values of the former indicate evidence in favour of the null over the alternative hypothesis, and vice versa. As both measures contain the same information, we only report the larger value for ease of readability.

We further assessed the relationship between CP volumes and clinical characteristics (CAARMS severity, GAF, BACS), as well as medication (antidepressants) in the CHR-P group. CAARMS severity, GAF scores, and BACS scores were correlated with CP volumes using Pearson's r, and GAF outcome was investigated with a GLM using a logistic link function which incorporated the covariates of age and ventricular volume. Here, a cut-off score of 65 (inclusive) was used to divide GAF scores into two outcome categories. Demographic information was compared across groups using ANOVA, chi-squared and post-hoc tests.

Results

Demographics

The groups differed regarding gender distribution (X=23.58, *p* <.001) and age (F=43.46, *p* < .001), whereby the FEP and SCZ groups tended to be older and included fewer female participants compared to controls. Compared to HC, CHR-Ps showed lower baseline GAF (F=79.65, *p* < .001) and reduced BACS composite, working memory, and motor task scores (*p*s < .05).

Table 1: Demographics and clinical information about the included sample

	HC (N=75)	CHR-N (N=38)	CHR-P (N=111)	FEP (N=39)	SCZ (N=30)	Group effect	Post-hoc comparisons
Age (M, SD)	24.68 (5.74)	22.95 (4.66)	21.9 (4.51)	25.0 (4.61)	37.53 (11.05)	F=43,46, p < .001	HC < CHR-P: p = .02; FEP > CHR-P: p = .05, SCZ > HC, CHR-N, CHR-P, FEP: ps < .001
Gender (F, %)	39 (52.0)	26 (68.42)	80 (72.07)	15 (38.46)	11 (36.66)	X=23.58, p <.001	
Education (years)	16.65 (3.05)	16.40 (3.47)	15.30 (3.21)	16.20 (3.30)	-	F=2.48, p=.062	NS
Medication (n, %)				*			
None	75 (100)	23 (60.52)	50 (45.05)	4 (10.26)	-	-	-
Antidepressant	-	8 (21.05)	33 (29.72)	3 (7.69)	-	-	-
Antipsychotic	-	0 (0)	1 (0.90)	6 (15.38)	-	-	-
Other	-	7 (18.42)	30 (27.03)	7 (17.95)	-	-	-

CAARMS severity				*			
Total score (M, SD)	-	6.18 (6.21)	29.75 (17.10)	-	-	F =161.14, p < .001	CHR-P > CHR-N: p < .001; CHR-P > HC: p < .001
UTC	-	0.61 (1.15)	1.83 (1.92)	-	-	-	-
NBI	-	0.79 (1.04)	2.84 (1.80)	-	-	-	-
PA	-	0.97 (1.35)	2.86 (1.50)	-	-	-	-
DS	-	0.53 (0.89)	1.43 (1.38)	-	-	-	-
CHR category							
CAARMS only (APS/GFRD)	-	-	31	-	-	-	-
SPI-A only (COGDIS/COPER)	-	-	29	-	-	-	-
CAARMS + SPI-A	-	-	51	-	-	-	-
BACS							
Composite score	0.21 (0.78)	-0.05 (1.59)	-0.64 (1.67)	-	-	F=3.59, -p= .03	HC > CHR-P: p = .044
Verbal memory	0.25 (1.0)	0.20 (1.73)	0.01 (1.27)	-	-	F=0.524, p= .59	-
Verbal fluency	0.07 (1.54)	-0.24 (1.01)	-0.03 (1.16)	-	-	F=,0.58 p= .56	-
Working memory (Digit sequencing)	0.19 (1.0)	0.29 (1.26)	0.05 (1.36)	-	-	F=0.39, p= .68	-
Motor speed (Token task)	0.0 (0.97)	-0.70 (1.0)	-1.10 (1.41)	-		F=9.60 p= .< .01	HC > CHR-P: p < .001

					-		
Executive functioning (Tower of London)	0.10 (0.79)	0.24 (1.25)	-0.16 (1.41)	-	-	F=,1.41 p= .32	HC > CHR-P, p < .001
GAF0 (M, SD)	87.57 (6.49)	70.05 (12.76)	58.28 (13.83)	-	-	F=79.65, p < .001	HC > CHR-N: p < .01; HC > CHR-P: p < .01; CHR-N > CHR-P: P < .01
GAF6 (M, SD)	-	57.73 (20.30)	59.01 (13.82)	-	-	-	
GAF12 (M, SD)	-	66.95 (20.32)	62.54 (14.48)	-	-	-	
N at follow-up (6m, 12m)	-	15, 20	91, 76	-	-	-	

Abbreviations: APS, attenuated psychotic symptoms; BACS, Brief Assessment of Cognition in Schizophrenia; CAARMS, Comprehensive Assessment of At Risk Mental States; COGDIS, Cognitive Disturbances, COGDIS, Cognitive-Perceptive Basic Symptoms criterion; HC, healthy controls; CHR-N, clinical risk-negative; CHR-P, clinical high-risk positive; FEP, first-episode psychosis; GAF, global assessment of functioning; SPI-A, Schizophrenia Proneness Instrument, Adult version; SD, standard deviation of the mean; AD, antidepressant; AP, antipsychotic

Note: * data only available for 15 subjects

Segmentation quality

Inter-rater Dice for manual segmentation included the highest Dice values and showed mean Dice of M=0.71, SD=0.13.

Mean Dice between manual and automated segmentations for GMM (M=0.71, SD=0.08) and Freesurfer (M=0.30, SD=0.07) were comparable to past observations (D. Bannai et al., 2022b). A Wilcoxon signed-rank test showed significantly higher Dice coefficients with manual segmentations compared to Freesurfer segmentations (W=300, $p < .001$) (Figure 2). Using GMM with the

default Freesurfer ventricle mask produced nonsignificant decreases in performance (M=0.70, SD=0.79), whereby GMM with the improved ventricle mask was used due to qualitative inspection.

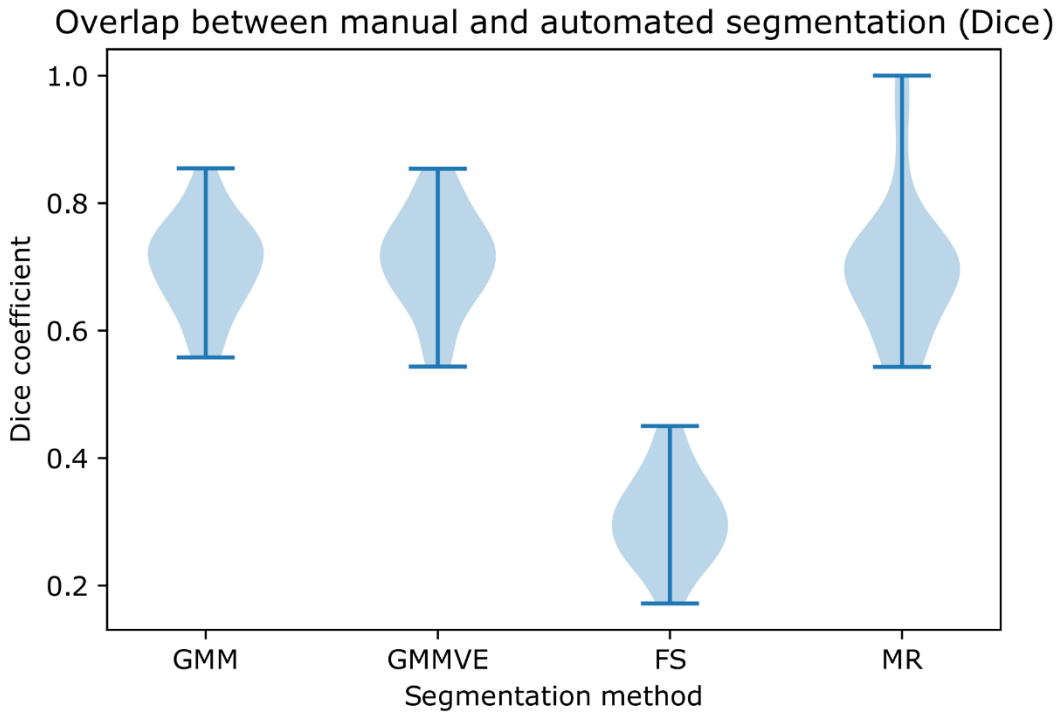


Figure 3-2. Distribution of Dice scores for GMM and Freesurfer segmentations. GMM: Gaussian mixture model; FS: Freesurfer; GMMVE: Gaussian mixture model with edited ventricle mask; MR: manual segmentation inter-rater reliability.

GMM segmentations were selected for statistical analyses based on performance. Full results including models fitted with the Freesurfer data can be found in the supplementary information.

Volumetric analysis

CP volumes showed a significant association with ventricular volume (t= 9.25, $p < .001$) but not age (t= 0.60, p=.55). The linear model did not show significant differences between HC and SCZ (t= 0.02, p=.98), FEP (t= -1.70, p=.09, 95%CI: -99.49, 6.15, whereby CIs are obtained from bootstrapping), CHR-P (t= -1.76, p=.08) and CHR-N (t= -0.59, p=.56).

Mann Whitney U testing (no covariates) showed increased ventricular (U = 605.0, *p* = .001) and CP volumes compared to HC (U = 780.0, *p* = .055) in SCZ patients; whereas FEP and CHR-P did not show an effect (*ps* > .05).

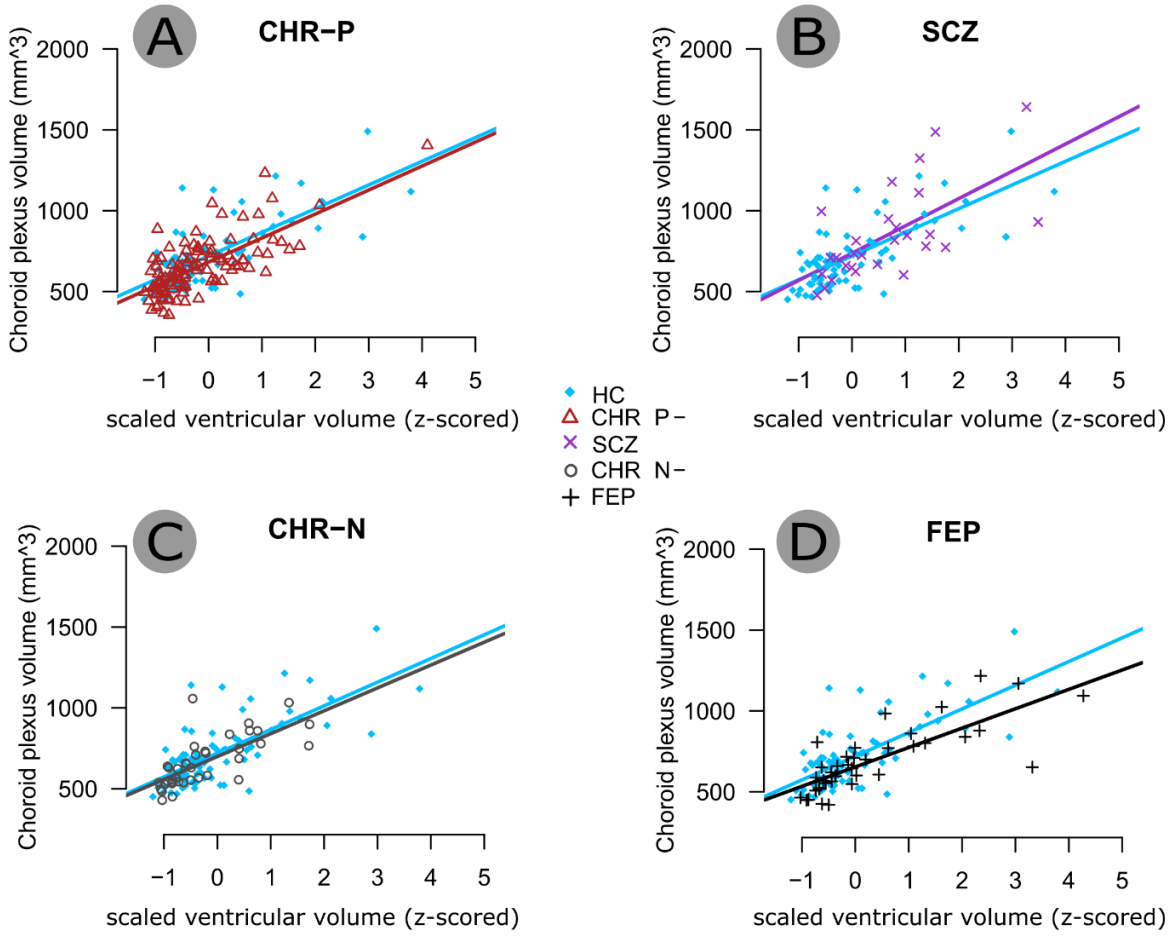


Figure 3-3. Linear associations between choroid plexus volumes and lateral ventricle volumes (centred) for each of the clinical groups, given with respect to the HC group.

A Bayesian analysis was conducted whereby models were fit separately for each group compared to controls. Bayes factors (BF01) are reported in accordance with Jeffrey's standards (Jeffreys, 1939; Lee & Wagenmakers, 2013). There was moderate to strong evidence in favour of the null model (no difference between CHR-P and HC) for the CHR-P group (BF01= 15.39 ±1.12%) and the CHR-N group (BF01= 28.98 ±1.17%). For the FEP group, the null model was weakly supported (2.69 ±2.61%). In the SCZ group, a BF01 of 3.815 ±1.2% weakly to moderately supported the null model.

Table 2. Model coefficients and BF01 for all groups. Mean posterior (10000 samples) and BF01 are taken from Bayesian linear models, t and p values are taken from frequentist testing. All models compare HC versus the clinical group listed, with HC at the intercept, and using ventricular volume and age as covariates. BF01 is pertaining to the model including group vs. the null model as described in Methods.

Model	Variable	Posterior (M, SD)	t	p	BF01
CHR-N	(Intercept)	701.908 (13.73)	18.09	<0.001	
	Group	-6.499 (13.01)	-0.59	0.557	28.98 ±1.17%
	VV	138.237 (16.48)	-	-	
	VV * Group	-5.925 (15.84)	-0.29	0.769	
	Age	2.647 (2.38)	0.60	0.551	
CHR-P	(Intercept)	684.343 (10.21)	18.09	<0.001	
	Group	-15.968 (10.24)	-1.76	0.080	15.39 ±1.12%
	VV	145.117 (11.48)	-	-	
	VV * Group	-1.254 (11.14)	-0.04	0.971	
	Age	2.238 (2.03)	0.60	0.551	
FEP	(Intercept)	715.579 (14.56)	18.09	<0.001	
	Group	-22.924 (14.02)	-1.70	0.090	2.69 ±2.61%
	VV	126.876 (12.59)	-	-	
	VV * Group	-17.606 (12.23)	-1.55	0.122	
	Age	2.145 (2.59)	0.60	0.551	
SCZ	(Intercept)	747.302 (17.988)	18.09	<0.001	
	Group	-5.785 (19.181)	0.02	0.984	3.815 ±1.2%
	VV	113.665 (16.981)	-	-	
	VV * Group	-29.532 (16.389)	-1.95	0.053	
	Age	1.545 (1.945)	0.60	0.551	

CP volumes and clinical characteristics and medication

There were no significant correlations between CP volume and CAARMS severity, GAF scores, or BACS (including subscales), each $p > .1$, uncorrected. Antidepressant medication was associated with decreased CP volumes in the CHR-P group ($t= -2.51$, $p=.013$) (see SI Material).

Discussion

The present study examined CP volumes in SCZ and early-stage psychosis to identify the pattern of deficits across illness stages, the relationship to ventricular changes as well as relationship with clinical characteristics. The CP is involved in several processes altered in psychosis, including inflammation (N. Althubaity, Schubert, Martins, Yousaf, Nettis, Mondelli, & Veronese, 2022; Karimy et al., 2017; P. Lizano, Lutz, Ling, Lee, Eum, Bishop, & Keshavan, 2019; Misiak et al., 2021), neuroplasticity (Zarif et al., 2018), and immunological processes mediated by its response to the dopamine system (Castellani et al., 2019; Williams, Macdonald, & Turkheimer, 2023). Previous studies reported volumetric increases in the CP in early-stage psychosis and schizophrenia (D. Bannai et al., 2022b; P. Lizano, Lutz, Ling, Lee, Eum, Bishop, & Keshavan, 2019; Senay et al., 2023; Zhou et al., 2020).

In the currently study, CP volumes were only increased in SCZ patients but not in the FEP or CHR-P groups. However, differences between SCZ patients and HC were not observed when controlling for ventricular volumes. Bayesian testing, which can be used to establish confidence in null findings (Keysers et al., 2020), provided further evidence against group differences. Moreover, we did not observe relationships between CP volumes and clinical characteristics for any group.

The CP is embedded within the ventricular space, and ventricular volume scales linearly with CP volume (D. Bannai et al., 2022a; P. Lizano, Lutz, Ling, Lee, Eum, Bishop, & Keshavan, 2019; Tadayon et al., 2020) which was also observed in the current study. Thus, when examining the CP in SCZ, it is crucial to account for potential differences in ventricular volume given the extensive evidence on ventricular enlargement in the disorder. Indeed, previous investigations investigating CP alterations in SCZ and early-stage psychosis suggest that the majority of group differences were no longer

significant after accounting for ventricular volumes (D. Bannai et al., 2022b; P. Lizano, Lutz, Ling, Lee, Eum, Bishop, & Keshavan, 2019; Senay et al., 2023).

Ventricular enlargement is among the largest and most frequently replicated anatomical alterations in psychosis (Svancer & Spaniel, 2021; van Erp, Hibar, Rasmussen, Glahn, Pearlson, Andreassen, & Turner, 2016; Van Erp et al., 2018). Increased ventricles have been observed in longitudinal studies of early-stage psychosis and have been associated with grey matter volume loss (Chung et al., 2017; Kempton, Stahl, Williams, & DeLisi, 2010). This enlargement is further linked with the duration of illness in SCZ and may be mediated by medication usage, treatment response and illness severity (Svancer & Spaniel, 2021). It has thus been suggested that ventricular enlargement may be a marker of neurodegeneration in chronic SCZ patients as ventricular differences are less prominent in early-stage psychosis (Chung et al., 2017; Svancer & Spaniel, 2021).

Consistent with previous findings (Ellis et al., 2020), our analyses did not show evidence for alterations in CP volume in the CHR-P, FEP, and SCZ groups when accounting for ventricular volumes, which suggests that anatomical deficits in the CP may be a secondary phenomenon of general neurodegenerative processes. The CP nonetheless remains a target of interest for SCZ and early-stage psychosis research. Although in vivo CP anatomy alone may not be a robust disease marker, recent advances in functional CP measurement using arterial spin labelling (ASL) and MRI/PET suggest that it is possible to study CP function and CSF flow dynamics (Mehta et al., 2022; Zhao, Taso, Dai, Press, & Alsop, 2020).

CP function is tied to the production of CSF (Lun et al., 2015) and accordingly may also be involved in the progressive increases in ventricular volume observed in psychosis. CP function is furthermore affected by dopamine activity (Castellani et al., 2019), which may affect CP microstructure especially in unmedicated schizophrenia (Williams et al., 2023).

In addition to investigating the impact of ventricular size on CP volumes, we also examined different segmentation methods since there is evidence indicating that the segmentation approach strongly affects CP volume estimates in early-stage psychosis (D. Bannai et al., 2022b) as well as other clinical groups (Tadayon et al., 2020). To address this issue, we manually segmented a subset of scans and compared those to Freesurfer and GMM

segmented images to evaluate their quality. Consistent with previous reports, we show that GMM segmentations yielded significantly more overlap with manual segmentation than Freesurfer (D. Bannai et al., 2022b; P. Lizano, Lutz, Ling, Lee, Eum, Bishop, & Keshavan, 2019; Tadayon et al., 2020). Importantly, Dice coefficients were similar to human inter-rater Dice coefficients. Thus, it is unlikely that our results are affected by systematic segmentation errors. However, we cannot exclude that small effects in CP volume (smaller than the margin of error of our measurement) could have eluded our detection. Further advancements in CP segmentation and possibly the use of other imaging modalities (see e.g. (Alkemade et al., 2022)) could provide more conclusive evidence regarding CP abnormalities in psychosis.

Conclusion

We investigated CP volumes in CHR-P, FEP and SCZ groups using different segmentation methods to examine the presence of changes in CP across different stages of psychosis. While increased CP volumes were observed in the SCZ, differences were not significant when taking into account ventricular volumes. Furthermore, we did not observe differences in CP volume in the CHR-P and FEP groups. Accordingly, we conclude that CP volumes are not a robust marker of psychosis and are likely a secondary consequence of broader anatomical changes to the ventricular system.

Acknowledgements

We would like to thank Frances Crabbe, MSc, Institute of Neuroscience and Psychology, University of Glasgow, Glasgow, Scotland for help in the acquisition of MEG/MRI-data. The investigators also acknowledge the support of the Scottish Mental Health Research Network (http://www.smhrn.org.uk), now called the NHS Research Scotland Mental Health Network (http://www.nhsresearchscotland.org.uk/research-areas/mental-health), for providing assistance with participant recruitment, interviews, and cognitive assessments. We thank both the participants and patients who took part in the study and the research assistants of the YouR-study for supporting the recruitment and assessment of CHR participants. This work was supported by the Max Planck Society.

Funding

The study was supported by the Medical Research Council (MR/L011689/1). This publication was supported by the University of Glasgow's Lord Kelvin/Adam Smith (LKAS) PhD Scholarship.

References

Alkemade, A., Bazin, P.-L., Balesar, R., Pine, K., Kirilina, E., Möller, H. E., . . . Bleys, R. L. (2022). A unified 3D map of microscopic architecture and MRI of the human brain. *Science advances, 8*(17), eabj7892.

Althubaity, N., Schubert, J., Martins, D., Yousaf, T., Nettis, M. A., Mondelli, V., & Veronese, M. (2022). Choroid plexus enlargement is associated with neuroinflammation and reduction of blood brain barrier permeability in depression. *NeuroImage: Clinical, 33*(10292), 6.

Arasappa, R., Danivas, V., & Venkatasubramanian, G. (2013). Choroid plexus papilloma presenting as schizophrenia: a case report. *The Journal of Neuropsychiatry and Clinical Neurosciences, 25*(1), E26-E27.

Arnaud, K., Moreira, V. O., Vincent, J., Dallerac, G., Dubreuil, C., Dupont, E., & Di Nardo, A. A. (2021). Choroid plexus APP regulates adult brain proliferation and animal behavior. *Life science alliance, 4*, 11.

Balu, D. T., & Coyle, J. T. (2011). Neuroplasticity signaling pathways linked to the pathophysiology of schizophrenia. *Neuroscience & Biobehavioral Reviews, 35*(3), 848-870.

Bannai, D., Reuter, M., Hegde, R., Hoang, D., Adhan, I., Gandu, S., & Lizano, P. (2022a). *Linking Choroid Plexus Enlargement with Plasma Analyte and Structural Phenotypes in Clinical High Risk for Psychosis. A Multisite Neuroimaging Study.*: bioRxiv.

Bannai, D., Reuter, M., Hegde, R., Hoang, D., Adhan, I., Gandu, S., & Lizano, P. (2022b). *Linking Choroid Plexus Enlargement with Plasma Analyte and Structural Phenotypes in Clinical High Risk for Psychosis. A Multisite Neuroimaging Study.* bioRxiv.

Brunner, G., Gajwani, R., Gross, J., Gumley, A. I., Krishnadas, R., Lawrie, S. M., . . . Uhlhaas, P. J. (2022). Hippocampal structural alterations in early-stage psychosis: Specificity and relationship to clinical outcomes. *NeuroImage: Clinical, 35*, 103087.

Carson, B. S., Weingart, J. D., Guarnieri, M., & Fisher, P. G. (1997). Third ventricular choroid plexus papilloma with psychosis: case report. *Journal of neurosurgery, 87*(1), 103-105.

Castellani, G., Contarini, G., Mereu, M., Albanesi, E., Devroye, C., D'Amore, C., & Papaleo, F. (2019). Dopamine-mediated immunomodulation affects choroid plexus function. *Brain, Behavior, and Immunity, 81*, 138-150.

Chung, Y., Haut, K. M., He, G., van Erp, T. G., McEwen, S., Addington, J., . . . Mathalon, D. H. (2017). Ventricular enlargement and progressive reduction of cortical gray matter are linked in prodromal youth who develop psychosis. *Schizophrenia Research, 189*, 169-174.

Chung, Y., Jacobson, A., He, G., van Erp, T. G., McEwen, S., Addington, J., . . . Mathalon, D. H. (2015). Prodromal symptom severity predicts accelerated gray matter reduction and third ventricle expansion among clinically high-risk youth developing psychotic disorders. *Complex Psychiatry, 1*(1), 13-22.

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical research, 29*(3), 162-173.

de Pablo, G. S., Radua, J., Pereira, J., Bonoldi, I., Arienti, V., Besana, F., & Fusar-Poli, P. (2021). Probability of transition to psychosis in individuals at clinical high risk: an updated meta-analysis. *JAMA psychiatry, 78*(9), 970-978.

Ellis, J. K., Walker, E. F., & Goldsmith, D. R. (2020). Selective review of neuroimaging findings in youth at clinical high risk for psychosis: on the path to biomarkers for conversion. *Frontiers in Psychiatry, 11*(56753), 4.

Falcao, A. M., Marques, F., Novais, A., Sousa, N., Palha, J. A., & Sousa, J. C. (2012). The path from the choroid plexus to the subventricular zone: go with the flow! *Frontiers in Cellular Neuroscience, 6*(34), 485-488.

First, M. B. (2014). Structured clinical interview for the DSM (SCID). *The encyclopedia of clinical psychology*, 1-6.

Fischl, B. (2012). FreeSurfer. *Neuroimage, 62*(2), 774-781.

Fujimura, M., Onuma, T., Kameyama, M., Motohashi, O., Kon, H., Yamamoto, K., . . . Tominaga, T. (2004). Hydrocephalus due to cerebrospinal fluid overproduction by bilateral choroid plexus papillomas. *Child's Nervous System, 20*, 485-488.

Gallardo-Ruiz, R., Crespo-Facorro, B., Setien-Suero, E., & Tordesillas-Gutierrez, D. (2019). Long-term grey matter changes in first episode psychosis: a systematic review. *Psychiatry investigation, 16*(5), 336.

Huang, J., Tong, J., Zhang, P., Zhou, Y., Li, Y., Tan, S., & Tan, Y. (2022). Elevated salivary kynurenic acid levels related to enlarged choroid plexus and severity of clinical phenotypes in treatment-resistant schizophrenia. *Brain, Behavior, and Immunity, 106*, 32-39.

Jeffreys, H. (1939). Theory of Probability.

Karimy, J. K., Zhang, J., Kurland, D. B., Theriault, B. C., Duran, D., Stokum, J. A., & Kahle, K. T. (2017). Inflammation-dependent cerebrospinal fluid hypersecretion by the choroid plexus epithelium in posthemorrhagic hydrocephalus. *Nature medicine, 23*(8), 997-1003.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin, 13*(2), 261-276.

Keefe, R. S., Goldberg, T. E., Harvey, P. D., Gold, J. M., Poe, M. P., & Coughenour, L. (2004). The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophrenia Research, 68*(2-3), 283-297.

Kempton, M. J., Stahl, D., Williams, S. C., & DeLisi, L. E. (2010). Progressive lateral ventricular enlargement in schizophrenia: a meta-analysis of longitudinal MRI studies. *Schizophrenia Research, 120*(1-3), 54-62.

Keysers, C., Gazzola, V., & Wagenmakers, E.-J. (2020). Using Bayes factor hypothesis testing in neuroscience to establish evidence of absence. *Nature neuroscience, 23*(7), 788-799.

Lee, M. D., & Wagenmakers, E.-J. (2013). Bayesian cognitive modeling: A practical course.

Lizano, P., Lutz, O., Ling, G., Lee, A. M., Eum, S., Bishop, J. R., & Keshavan, M. (2019). Association of choroid plexus enlargement with cognitive, inflammatory, and structural phenotypes across the psychosis spectrum. *American Journal of Psychiatry, 176*(7), 564-572.

Lun, M. P., Monuki, E. S., & Lehtinen, M. K. (2015). Development and functions of the choroid plexus--cerebrospinal fluid system. *Nature Reviews Neuroscience, 16*(8), 445-457.

Mehta, N. H., Suss, R. A., Dyke, J. P., Theise, N. D., Chiang, G. C., Strauss, S., . . . Babaria, V. (2022). Quantifying cerebrospinal fluid dynamics: A review of

human neuroimaging contributions to CSF physiology and neurodegenerative disease. *Neurobiology of Disease*, 105776.

Misiak, B., Bartoli, F., Carra, G., Stańczykiewicz, B., Gładka, A., Frydecka, D., & Miller, B. J. (2021). Immune-inflammatory markers and psychosis risk: A systematic review and meta-analysis. *Psychoneuroendocrinology, 127*, 10520.

Morey, R. D., Rouder, J. N., Jamil, T., & Morey, M. R. D. (2015). Package 'bayesfactor'. *URLh http://cran/r-projectorg/web/packages/BayesFactor/BayesFactor pdf i (accessed 1006 15)*.

Schultze-Lutter, F., Addington, J., Ruhrmann, S., & Klosterkötter, J. (2007). Schizophrenia proneness instrument, adult version (SPI-A). *Rome: Giovanni Fioriti*.

Senay, O., Seethaler, M., Makris, N., Yeterian, E., Rushmore, J., Cho, K. I. K., . . . Szczepankiewicz, F. (2023). A preliminary choroid plexus volumetric study in individuals with psychosis. *Human Brain Mapping, 44*(6), 2465-2478.

Steen, R. G., Mull, C., McClure, R., Hamer, R. M., & Lieberman, J. A. (2006). Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. *The British Journal of Psychiatry, 188*(6), 510-518.

Svancer, P., & Spaniel, F. (2021). Brain ventricular volume changes in schizophrenia. A narrative review. *Neuroscience Letters, 759*, 136065.

Tadayon, E., Moret, B., Sprugnoli, G., Monti, L., Pascual-Leone, A., Santarnecchi, E., & Initiative, A. s. D. N. (2020). Improving choroid plexus segmentation in the healthy and diseased brain: Relevance for Tau-PET imaging in dementia. *Journal of Alzheimer's Disease, 74*(4), 1057-1068.

Tamminga, C. A., Clementz, B. A., Pearlson, G., Keshavan, M., Gershon, E. S., Ivleva, E. I., & Gibbons, R. (2021). Biotyping in psychosis: using multiple computational approaches with one data set. *Neuropsychopharmacology, 46*(1), 143-155.

Uhlhaas, P. J., Gajwani, R., Gross, J., Gumley, A. I., Lawrie, S. M., & Schwannauer, M. (2017). The youth mental health risk and resilience study (YouR-Study). *BMC psychiatry, 17*, 1-8.

van Doorn, J., van den Bergh, D., Böhm, U., Dablander, F., Derks, K., Draws, T., . . . Haaf, J. M. (2021). The JASP guidelines for conducting and reporting a Bayesian analysis. *Psychonomic Bulletin & Review, 28*, 813-826.

van Erp, T. G., Hibar, D. P., Rasmussen, J. M., Glahn, D. C., Pearlson, G. D., Andreassen, O. A., & Turner, J. A. (2016). Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Molecular Psychiatry, 21*(4), 547-553.

Van Erp, T. G., Walton, E., Hibar, D. P., Schmaal, L., Jiang, W., Glahn, D. C., & Fatouros-Bergman, H. (2018). Cortical brain abnormalities in 4474 individuals with schizophrenia and 5098 control subjects via the enhancing neuro imaging genetics through meta analysis (ENIGMA) consortium. *Biological psychiatry, 84*(9), 644-654.

Velakoulis, D., Wood, S. J., Wong, M. T., McGorry, P. D., Yung, A., Phillips, L., . . . Desmond, P. (2006). Hippocampal and amygdala volumes according to psychosis stage and diagnosis: A magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra–high-risk individuals. *Archives of general psychiatry, 63*(2), 139-149.

Williams, M. R., Macdonald, C., & Turkheimer, F. E. (2023). Histological examination of choroid plexus epithelia changes in schizophrenia. *Brain, Behavior, and Immunity, 111*, 292-297.

Yung, A., Phillips, L., Yuen, H., & McGorry, P. (2006). Comprehensive assessment of at risk mental state. *Parkville Victoria: The PACE Clinic, ORYGEN Research Centre, University of Melbourne, Department of Psychiatry*.

Zarif, H., Nicolas, S., Guyot, M., Hosseiny, S., Lazzari, A., Canali, M. M., & Petit-Paitel, A. (2018). CD8+ T cells are essential for the effects of enriched environment on hippocampus-dependent behavior, hippocampal neurogenesis and synaptic plasticity. *Brain, Behavior, and Immunity, 69*, 235-254.

Zhao, L., Taso, M., Dai, W., Press, D. Z., & Alsop, D. C. (2020). Non-invasive measurement of choroid plexus apparent blood flow with arterial spin labeling. *Fluids and Barriers of the CNS, 17*, 1-11.

Zhou, Y. F., Huang, J. C., Zhang, P., Fan, F. M., Chen, S., Fan, H. Z., . . . Hong, L. E. (2020). Choroid Plexus Enlargement and Allostatic Load in Schizophrenia. *Schizophr Bull, 46*(3), 722-731. doi:10.1093/schbul/sbz100

Zikidi, K., Gajwani, R., Gross, J., Gumley, A. I., Lawrie, S. M., Schwannauer, M., . . . Uhlhaas, P. J. (2020). Grey-matter abnormalities in clinical high-risk participants for psychosis. *Schizophrenia research, 226*, 120-128.

Chapter 4: Altered connectivity of the hippocampus in cortico-subcortical networks in early psychosis

Gina Brunner MSc, Ruchika Gajwani PhD, Joachim Gross PhD, Andrew Gumley PhD, Rajeev Krishnadas PhD, Stephen M. Lawrie PhD, Matthias Schwannauer PhD, Frauke Schultze-Lutter PhD, Peter Uhlhaas PhD*, Alessio Fracasso PhD*

* these authors contributed equally to this work

Abstract

Background: Deficits in the hippocampus are a consistent finding in schizophrenia and have also been demonstrated in early-stage psychosis. Moreover, alterations in hippocampal anatomy and connectivity have been implicated in aberrant functional interactions in subcortical and cortical networks. However, the nature and extent of these alterations and their association with frontal and subcortical regions remain unclear.

Methods: To address these questions, we analysed resting state fMRI functional connectivity and graph properties in n=93 individuals at clinical high-risk for psychosis (CHR-P), n=26 patients with first-episode psychosis (FEP), n=31 individuals with affective disorders and substance abuse as well as n=58 healthy controls. We used novel denoising techniques and individually optimised functional connectivity matrices, which were compared across clinical groups. Finally, the centrality of the hippocampus as well as network segregation and integration were assessed using graph-based analysis.

Results: Both the FEP and CHR-P groups were characterised by reduced functional connectivity between the hippocampus and inferior frontal cortex albeit the differences in CHR-P individuals did not survive corrections for multiple comparisons. Compared to CHR-P, FEP show decreased centrality of the hippocampus but increased network segregation.

Conclusions: Our findings show decreased connectivity between the hippocampus and frontal cortex in early-stage psychosis, with FEP patients

showing stronger decreases in connectivity compared to CHR-Ps. Furthermore, network-based analyses highlight reduced centrality in FEPs compared to CHR-Ps, indicating reduced influence on the wider network. Thus, altered connectivity along the hippocampal-frontal axis could be a potential marker of illness stage in early-stage psychosis.

Introduction

Schizophrenia (ScZ) is a severe psychiatric disorder which is typically preceded by a prodromal phase, during which attenuated psychotic symptoms, functional deficits and cognitive impairments are present (Catalan et al., 2021; Fusar-Poli et al., 2013). These observations have led to the formulation of clinical high-risk for psychosis (CHR-P) criteria which are associated with a risk of developing first-episode psychosis (FEP) of approximately 25% over a three-year period (Gonzalo Salazar De Pablo, Radua, Pereira, Bonoldi, Arienti, Besana, Soardo, et al., 2021). CHR-P participants are characterized by both anatomical and functional brain changes (Fusar-Poli, 2012; Fusar-Poli, McGuire, & Borgwardt, 2012; Fusar-Poli et al., 2007). While some such alterations may be stable over time, others may potentially be progressive (Grace, 2012; J. Lieberman et al., 2018). Decreased hippocampal volumes are already observed in CHR-P participants (Brunner et al., 2022; Zikidi et al., 2020) and may predict transition to psychosis (Provenzano et al., 2020) and illness progression (Sasabayashi et al., 2021; Vargas et al., 2018).

The hippocampus is a crucial hub for subcortical and cortical networks and is characterized by extensive anatomical and functional connectivity (FC) with the frontal, occipital and temporal lobes as well as with sensory-motor regions and subcortical areas (Ezama, Hernández-Cabrera, Seoane, Pereda, & Janssen, 2021; Maller et al., 2019). Moreover, the hippocampus supports numerous cognitive functions, such as emotion regulation (Bubb, Kinnavane, & Aggleton, 2017; Pessoa, 2017), memory consolidation (Battaglia, Benchenane, Sirota, Pennartz, & Wiener, 2011), and social cognition (Montagrin, Saiote, & Schiller, 2018). Several of these domains are impaired in both CHR-Ps (Catalan et al., 2021) and ScZ patients (Bortolato, Miskowiak, Köhler, Vieta, & Carvalho, 2015). The hippocampus has shown decreased task-related activation in

combination with elevated baseline BOLD in early-stage psychosis in fMRI studies (McHugo et al., 2019) which could be due to excessive excitation and may cause volumetric changes (J. Lieberman et al., 2018).

At the circuit level, the hippocampus is involved in regulating striatal dopamine activity. N-methyl-D-aspartate (NMDA) receptor activation in the hippocampus causes the nucleus accumbens to inhibit the ventral pallidum via γ-aminobutyric acid (GABA) release, which in turn disinhibits the ventral tegmental area (Lisman et al., 2008; Lodge & Grace, 2006). In animal models of ScZ, lesions to the hippocampus during early development have been shown to induce disinhibition and behavioural deficits observed in ScZ patients (J. Lieberman et al., 2018). More specifically, it has been suggested that a loss of GABAergic interneurons and NMDA receptor dysfunction may increase baseline hippocampal excitation (Grace, 2012; J. Lieberman et al., 2018), resulting in elevated striatal dopamine activity (Grace, 2012). Excessive baseline excitation may compromise the anatomical integrity of both the hippocampus (Grace, 2012; J. Lieberman et al., 2018), and the frontal cortex (Bertolino et al., 2002; Lipska, Aultman, Verma, Weinberger, & Moghaddam, 2002), thus driving more widespread network changes surrounding the hippocampus (Sabaroedin et al., 2023).

Changes in functional connectivity between subcortical and cortical sites have been shown to predict the development of psychosis in CHR-P individuals (Anticevic et al., 2015) highlighting that investigations into large-scale functional networks may be important for understanding the development of psychosis. Furthermore, differences may exist across illness stages in cortical-subcortical networks (Sabaroedin et al., 2023). While the hippocampus has a pivotal role in such networks in theoretical and preclinical work (Grace, 2012; J. Lieberman et al., 2018), its role within the broader network in human neuroimaging remains an open question.

In the current study, we addressed this question through investigating alterations in functional connectivity between the hippocampus, subcortical and cortical regions in early-stage psychosis. Currently, the precise nature of the aberrant network interactions in early-stage psychosis remains unclear as both increased and decreased connectivity patterns have been demonstrated (Brunner et al., 2022; McHugo et al., 2019; Provenzano et al., 2020). In addition, evidence from graph theoretical studies has shown that that ScZ

patients show altered local but not global network organisation, which may correlate with illness severity (Kambeitz et al., 2016) (but see (Gao et al., 2023)). From a local network perspective, in CHR-P individuals, several frontal regions been shown to operate more in isolation compared to HC (Davies et al., 2023; R. R. Li et al., 2018; Lord et al., 2011). Global network properties on the other hand may be preserved (Lord et al., 2012).

Methods and Materials

Participants

A total of 289 participants from four clinical groups were included: 1) n=93 participants meeting CHR-P criteria, 2) n=31 participants not meeting CHR-P criteria but who met criteria for affective disorders (n = 11), anxiety disorders (n = 16), eating disorders (n = 1), and/or substance abuse (n = 10) (clinical high-risk negative, CHR-N, included as a clinical control group), 3) n=26 FEP patients, and 4) n=58 healthy controls (HC) without an axis I diagnosis or family history of psychosis. Measurements from a further 18 HC, 17 CHR-P, 7 CHR-N, and 11 FEP were recorded, but excluded due to either missing imaging data, clinically significant incidental findings, or poor image quality.

CHR-P status was established using the Comprehensive Assessment of At Risk Mental States (CAARMS) interview (Yung et al., 2006) and the Cognitive Disturbances (COGDIS) and Cognitive-Perceptive (COPER) basic symptoms criteria according to the Schizophrenia Proneness Instrument, Adult version (Schultze-Lutter et al., 2007). FEP patients were assessed with the Structured Clinical Interview for DSM-5 (SCID) (First, 2014) and the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987), and were required to have no more than one episode of psychosis, and a duration of illness of less than five years. CHR-P, CHR-N and HC participants were assessed using the Brief Assessment of Cognition in Schizophrenia battery (BACS)(Keefe et al., 2004).

The study was approved by the ethical committees of University of Glasgow and the NHS Research Ethical Committee Glasgow & Greater Clyde. All participants provided written informed consent.

MRI Acquisition

All images were acquired using a Siemens 3T scanner with a 32-channel head coil. T1-weighted images were acquired using a 3D MPRAGE sequence with the following parameters: FoV: $256 \times 256 \times 176$ mm^3, voxel size: $1 \times 1 \times 1$ mm^3, TR: 2250ms, TE: 2.6ms, TI: 900ms, FA: 9°. BOLD fMRI was acquired with an EP2D-PACE sequence using the following parameters: FoV, voxel size $3 \times 3 \times 3$ mm^3, TR: 2000ms, TE: 3ms, FA: 77°.

Neuroimaging Processing

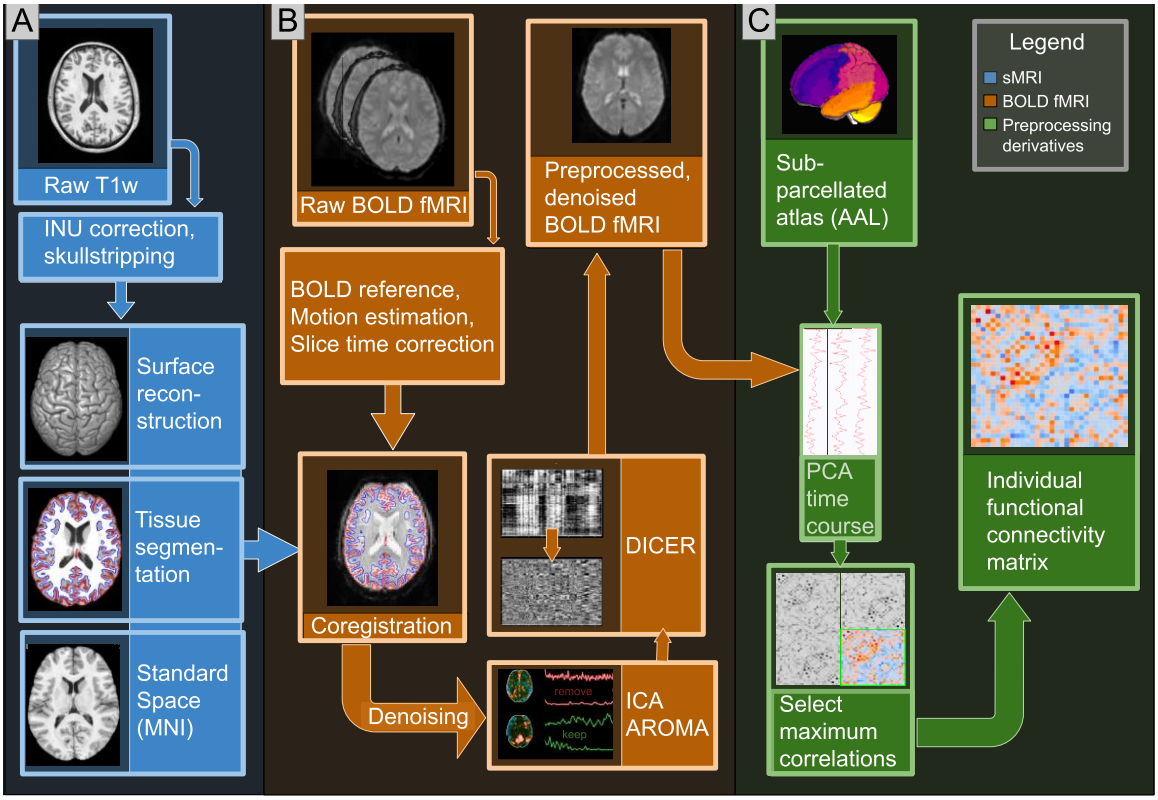


Figure 4-1: Schematic representation of the preprocessing pipeline. Preprocessing of anatomical (T1-weighted) data is shown in blue (panel A), following the standard fmriprep pipeline. BOLD fMRI preprocessing is shown in orange (panel B), and includes standard fmriprep preprocessing, as well as additional denoising steps (ICA-AROMA, DiCER). Shown are example topologies and time courses for a noise ICA component (red), and a component which was not rejected (green). The visualisation for DiCER shows two carpet plots, whereby the vertical axis reflects voxel location, and the horizontal axis shows changes in these voxels over time. The upmost carpet plot shows an image pre-DiCER, whereby the ordering of voxels is determined by DBSCAN clustering to visualise large signal deflections. The carpet plot below shows the same image and ordering post-DiCER, whereby the large signal deflections have been removed. Finally, derivatives of preprocessing are shown in green (panel C), whereby

time courses are extracted with PCA from AAL subparcellated regions (see text below), and the largest correlations per AAL region pair are retained for each subject, thus providing the outputs used for analysis. Abbreviations: sMRI, structural MRI; T1w, T1-weighted MRI; fMRI, functional MRI; AAL, automated anatomical labelling; DiCER, diffuse cluster estimation and regression; PCA, principal component analysis.

fmriprep preprocessing

We used fmriprep 21.0.2 (Esteban et al., 2019) to conduct anatomical and functional data processing. We primarily followed the fmriprep standard pipeline which is described fully in the Methods automatically generated by fmriprep, and can be found in Supplement Methods I. Several options differed from fmriprep defaults, specifically: we used 12 degrees of freedom during registration of BOLD to anatomical images, and used ICA-AROMA to reject noise components (Pruim et al., 2015). ICA-AROMA was chosen due to its ability to retain most data, unlike e.g. censoring approaches with similar denoising performance (Parkes, Fulcher, Yücel, & Fornito, 2018). ICA-AROMA uses a classifier on FSL MELODIC ICA components to identify and reject noise components, and has previously shown good performance in the removal of motion artifacts in resting state fMRI (Parkes et al., 2018).

Following fmriprep processing, we used ICA-AROMA regressors on the preprocessed BOLD images. In line with prior applications where ICA-AROMA regressors have been applied to data with less or no smoothing (Aquino et al., 2022), the regressors were applied to images smoothed with a 3mm FWHM Gaussian kernel as a final step.

Artifact correction

Clinical populations, such as schizophrenia patients, typically show increased head motion which can result in widespread fMRI signal deflections (Pardoe, Hiess, & Kuzniecky, 2016; N. Yao et al., 2017). This can increase local FC while diminishing long range FC (Van Dijk, Sabuncu, & Buckner, 2012), and may substantially impact case-control comparisons (Haar, Berman, Behrmann, & Dinstein, 2016; Parkes et al., 2018), graph metrics (Yan, Craddock, He, & Milham, 2013), and modelling results (Aquino et al., 2022). The most common

method for removing large signal deflections is global signal regression (GSR), which can remove global signal deflections and thereby strengthen fMRI-behavioural associations (J. Li, Kong, et al., 2019; Power, Plitt, Laumann, & Martin, 2017). However, GSR has been shown to introduce spurious negative correlations (Murphy, Birn, Handwerker, Jones, & Bandettini, 2009), or fail to remove some widespread signal deflections which likely reflect non-neuronal noise (Aquino, Fulcher, Parkes, Sabaroedin, & Fornito, 2020).

Diffuse Cluster Estimation and Regression (DiCER) is a novel method which uses DBSCAN clustering to identify clusters of widespread signal deflections in fMRI signals, and then using regression to remove it from the signal (Aquino et al., 2020). DICER attempts at regressing out anomalous clusters rather than the global signal, it is therefore more specific in its denoising than GSR, and captures signal deflections which do not affect all regions equally. As it has further been shown to improve measures of denoising quality such as FC distance dependence (Aquino et al., 2020), we therefore used DiCER to minimise the risk of false positive findings related to artifacts. All preprocessed scans were inspected using ordered carpet plots (Aquino et al., 2020), which allow for the visualisation of widespread signal deflections (see Figure 1, panel B).

Functional connectivity extraction

We used the NiPy ecosystem (Brett et al., 2009) and R to extract time courses and compute functional connectivity matrices. While the AAL atlas (Tzourio-Mazoyer et al., 2002) was used to provide a standardised set of anatomical regions, it has previously been observed that standardised atlases may fail to capture individual variation in functional connectivity (R. Kong, Yang, et al., 2021). To retain a set of regions comparable across subjects while retaining individual variability, we sub-parcellated each AAL region into 5 subregions using k-means clustering on the AAL atlas image ROI coordinates. We extracted time courses using the 1st principal component from each subregion as PCA has been found to yield more robust FC estimates (Anzellotti, Caramazza, & Saxe, 2017). Then, pairwise Pearson's correlations were computed for between all subregions in ROI pairs, and only the largest correlation (positive or negative) was retained for each pair.

Functional connectivity analysis

We analysed FC as given by the correlations between the hippocampus and all AAL regions in the medial, lateral, ventral and dorsal frontal cortex, amygdala, caudate, pallidum, putamen, and thalamus, based previous findings (Sabaroedin et al., 2023). FDR corrected T-tests were used to compare the obtained FC values between ROI pairs from each clinical group to HC.

Graph analysis

Graph generation and edge thresholding

The Python networkx package (Hagberg, Swart, & S Chult, 2008) was used to generate graph representations of individual FC matrices and to extract graph-theoretic metrics. We generated weighted, undirected graphs by using the FC correlation matrices described in the previous step to provide edge weights. Typically, this matrix is then thresholded to provide a sparse representation of network connectivity. While there is no consensus regarding the optimal threshold for graph representations of fMRI data, it has previously been reported that the choice of threshold can significantly impact case-control comparisons, including sign reversals of significant effects (Fornito, Zalesky, & Breakspear, 2013; van den Heuvel et al., 2017). To address these problems, we applied proportional thresholding multiple times, retaining the *n*th quantile from quantiles 1-10 at each step. By using quantiles (per subject), we ensure an equal number of connections for each graph at each step to ascertain that case-control differences will not be introduced by overall differences in FC, but by specific alterations to network function. Absolute FC values were used.

Graph metrics

Networkx was used to extract graph metrics for the left and right hippocampus, and local network properties. Based on prior findings in ScZ (Kambeitz et al., 2016), we focused on local efficiency as well as local clustering (node-level clustering coefficient) and betweenness centrality for the left and right hippocampus. Betweenness centrality was selected as a measure of the ability of the hippocampus to control information flow within the network as it measures the extent to which a given node is on the shortest path connecting other nodes with each other. The local clustering coefficient

and local efficiency measure network segregation and integration, respectively. As specified in the Networkx documentation, the former is calculated as *the geometric average of the subgraph edge weights*, while the latter is defined as *the average global efficiency of the subgraph induced by the neighbors of the node* (Networkx).

While metrics are reported at all quantiles to demonstrate the overall effects of thresholding, we restrict statistical testing to the 3rd to 7th quantile. At thresholds below the 3rd quantile, very few edge weights are removed, thus leaving in noisy, small correlations which can distort network properties. Conversely, a substantial proportion of participants' graph networks became disconnected at thresholds above the 7th quantile, i.e. there was no possible path from each node to every other node (for further details see Supplementary Material).

Within the range of thresholds selected for interpretation, t-tests were conducted to compare each clinical group to the HC group, with FDR correction applied across the number of quantiles.

Associations with Clinical and Behavioural Variables

ROIs with significant group differences were selected and Pearson's correlations were computed between FC and PANNS or CAARMS ratings (for FEP and CHR-P, respectively) as well as GAF scores.

Results

Demographics

Table 1: Clinical and demographics data for all included groups.

	HC (N=58)	CHR-N (N=31)	CHR-P (N=93)	FEP (N=26)	Group effect	Post-hoc comparisons
Age (M, SD)	24.017 (4.162)	23.19 (4.76)	21.58 (4.26)	24.22 (4.20)	F=5.12, p=.002	HC > CHR-P, FEP > CHR-P
Gender (F, %)	40 (58)	18 (58)	67 (72)	10 (38)	X=11.66, p<.01	-
Medication (n, %)						
Antidepressant	-	8 (25)	27 (29)	8 (30)	-	-
Antipsychotic	-	0 (0)	0 (0)	13 (50)	-	-
Neither	75 (100)	23 (74)	68 (73)	5 (19)	-	-
CAARMS severity						
Total score (M, SD)	-	5.06 (5.85)	32.46 (16.83)	-	t=9.24, p<.001	CHR-P > CHR-N
UTC	-	0.52 (1.12)	2.075 (1.95)	-	-	-
NBI	-	0.74 (1.06)	2.98 (1.78)	-	-	-
PA	-	0.71 (1.27)	2.84 (1.51)	-	-	-
CHR category		-				-
CAARMS only (APS/GFRD)	-	-	31	-	-	-
SPI-A only (COGDIS/COPER)	-	-	29	-	-	-
CAARMS + SPI-A	-	-	51	-	-	-
PANSS severity						
Total score (M, SD)	-	-	-	55.73 (20.11)	-	-
Positive	-	-	-	13.58 (7.05)	-	-
Negative	-	-	-	10.40 (4.29)	-	-
Cognitive	-	-	-	12.07 (3.33)	-	-

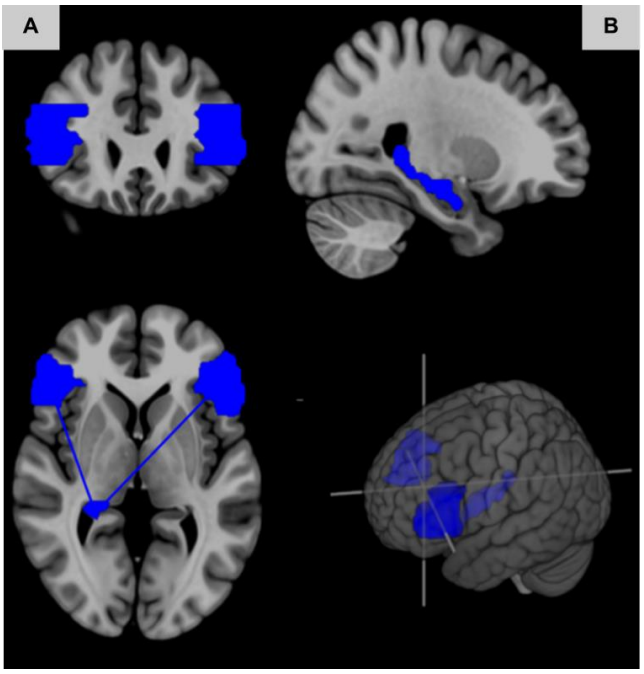
Global Functioning				*		
GAF (M, SD)	87.35 (7.15)	70.26 (12.95)	56.68 (11.85)	43.92 (15.45)	F=68.70, p<.001	HC > CHR-N, CHR-P, FEP, CHR-N > CHR-P, FEP, CHR-P > FEP

Abbreviations: APS, attenuated psychotic symptoms; BACS, Brief Assessment of Cognition in Schizophrenia; CAARMS, Comprehensive Assessment of At Risk Mental States; COGDIS, Cognitive Disturbances, COGDIS, Cognitive-Perceptive Basic Symptoms criterion; HC, healthy controls; CHR-N, clinical risk-negative; CHR-P, clinical high-risk positive; FEP, first-episode psychosis; GAF, global assessment of functioning; SPI-A, Schizophrenia Proneness Instrument, Adult version; SD, standard deviation of the mean; AD, antidepressant; AP, antipsychotic. Note: * data only available for 12 participants.

HC and FEP groups were older compared to CHR-Ps while the FEP group had fewer female participants and lower GAF scores.

Functional connectivity results

FEP patients showed significantly lower FC compared to HC between the hippocampus and inferior frontal cortex (pars triangularis) in the right hemisphere (t=-4.19, p_{FDR} =.0046, Figure 2). Furthermore, the FEP group showed reduced FC between the right hippocampus and ventrolateral prefrontal cortex (vlPFC, AAL region: inferior frontal cortex, pars triangularis) compared to CHR-Ps (t=-3.71, p_{FDR}=.023, Figure 2), as well as increased FC between the right hippocampus and right thalamus (t=3.47, p_{FDR}=.023). A reduction in FC between right hippocampus and vlPFC (left) was found when comparing HC and CHR-Ps, but this did not survive correction for multiple comparisons (t=-3.26, $p_{uncorr.}$=.0014, p_{FDR}=.086). CHR-N showed increased FC between the right hippocampus and right vlPFC (t=3.45, p_{FDR}=.054), as well as the right putamen (t=3.34, p_{FDR}=.054) (see Figure 3) Uncorrected results ($p_{uncorr.}$ < .02) can be found in Supplementary Material.



Contrast	ROI pair	t	p	p (FDR)
HC vs CHR-P	Hippocampus-R & Frontal-Inf-Tri-L	-3.26	0.0014	0.086
	Hippocampus-R & Amygdala-L	2.89	0.0046	0.14
HC vs FEP	Hippocampus-R & Frontal-Inf-Tri-R	-4.19	0.0001	0.0046 *
	Hippocampus-R & Frontal-Med-Orb-L	-2.60	0.013	0.22
CHR-P vs FEP	Hippocampus-R & Frontal-Inf-Tri-R	-3.71	0.0005	0.023 *
	Hippocampus-R & Thalamus-R	3.47	0.0007	0.023 *
HC vs CHR-N	Hippocampus-R & Frontal-Inf-Tri-L	3.45	0.0014	0.054
	Hippocampus-R & Putamen-R	3.34	0.0020	0.054
CHR-N vs FEP	Hippocampus-R & Frontal-Inf-Tri-R	-3.094	0.003	0.20
	Hippocampus-R & Frontal-Sup-R	-2.51	0.016	0.33
CHR-N vs CHR-P	Hippocampus-L & Caudate-L	3.06	0.0032	0.18
	Hippocampus-R & Pallidum-L	-2.82	0.0072	0.18

Figure 4-2: Results from the FC analysis. Panel A: Visualisation of loci of FC effects in FEP/CHR-P compared to HC. Shown are the right hippocampus and vlPFC (inferior frontal cortex, pars triangularis, left and right), whereby region masks are based on AAL regions. Regions are visualised in blue to indicate decreased FC. Panel B: Table showing the two largest effects per group comparison, including corrected (FDR) and uncorrected p-values, rounded to 2 significant figures. Significant (post FDR) effects are highlighted with an asterisk (*). Compared to HC, FEP show decreased FC between the hippocampus and vlPFC, which is seen for CHR-P prior to FDR correction only. Compared to CHR-P, FEP show decreased FC between hippocampus and vlPFC, and increased FC between hippocampus and thalamus.

Graph analysis

Compared to CHR-Ps, FEP patients had significantly decreased betweenness centrality of the right hippocampus (t=-4.73, p_{corr}=.0001, 4th quantile), but significantly increased local clustering in the left hippocampus (t=2.8, p_{corr} =.0075, 7th quantile; t=2.19, p_{corr} =.046, 5th quantile). FEP showed decreased betweenness centrality at the right hippocampus compared to HC (t=-2.44, p=.02, 4th quantile), but this was no longer significant after adjusting for multiple comparisons. There were no significant differences between CHR-P and HC, and no effects were seen for local efficiency (*p*s > .05).

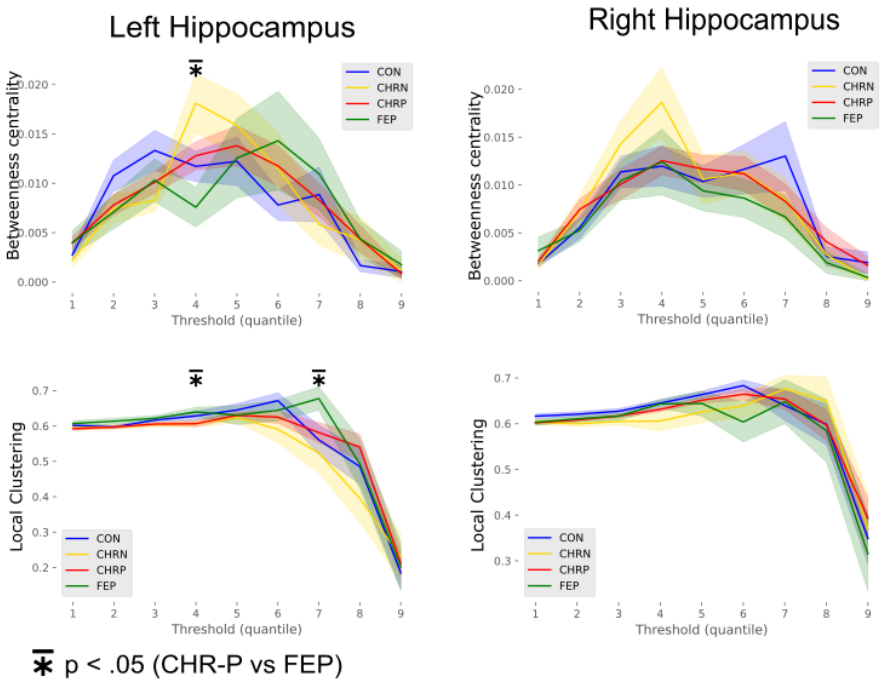


Figure 4-3: Betweenness centrality and local clustering for the left and right hippocampus. Shown are all thresholding quantiles (1-9), but statistical testing is restricted to quantiles 3-7. Highlighted (*) are significant differences between CHR-P and FEP, with the other groups not showing significant differences; shaded regions reflect one standard deviation from the mean. FEP showed significantly lower hippocampus betweenness centrality compared to CHR-P, and increased local clustering in the left hemisphere. Betweenness centrality indicates the extent to which the hippocampus is involved in information flow between different clusters within the network, and local clustering indicates the extent to which the immediate neighbours of the hippocampus are connected to each other.

Associations with Clinical and Behavioural Variables

A linear model showed decreased right hippocampal volumes in the FEP group (estimate: -203.20, t=-2.074, p=0.039) compared to controls, whereby total brain volume and age were used as covariates following our previous work. Hippocampal volumes were not significantly correlated with FC between right hippocampus and vlPFC (pars triangularis) in either hemisphere, neither betweenness centrality nor local clustering (*p*s > .05). Connectivity between the right hippocampus and vlPFC was not associated with betweenness

centrality or local clustering (using hemisphere and quantile where group differences were observed). Symptom severity (total PANNS scores) and functioning (GAF) did not show significant associations with either graph metrics or hippocampal FC with the vlPFC (as described above).

In FEP patients, antipsychotic medication (APM) was associated with increased FC between the right hippocampus and left vlPFC (pars triangularis): t=2.06, p=.049. There was no evidence for an effect of antidepressants on FC (hippocampus-vlPFC) or graph metrics (p > .05) in CHR-P.

Neither FC between the right hippocampus and vlPFC (pars triangularis, left and right) nor graph metrics were related to symptom severity (CAARMS), functioning (GAF), or right hippocampal volumes in CHR-P (ps > .05).

Discussion

We analysed functional connectivity and graph-based network properties in cortical-subcortical networks involving the hippocampus in early-stage psychosis using resting state fMRI. We found evidence for decreased functional connectivity between the right hippocampus and vlPFC in FEP patients. Compared to the CHR-P group, FEP patients showed increased connectivity between the right hippocampus and right thalamus. Moreover, APM was associated with increased FC between the right hippocampus and left vlPFC.

To our knowledge, this is the first study to investigate the role of the hippocampus within cortical-subcortical networks in early-stage psychosis using resting-state fMRI. Previous studies conducted whole brain analyses, highlighted different brain structures, or focused on different networks, such as the DMN, or structural connectivity. Consistent with previous research, we observed decreased functional connectivity between the hippocampus and inferior frontal cortex in early-stage psychosis (Benetti et al., 2009).

Interestingly, local clustering was increased in FEP patients compared to CHR-Ps, indicating that connectivity among the neighbouring brain areas was increased relative to the hippocampus. Moreover, we observed decreased centrality of the hippocampus in FEP patients, suggesting that the hippocampus is less embedded in the wider network. (Crossley et al., 2016). FEP patients have previously shown hypoconnectivity (Du et al., 2018), which is reflected anatomically in decreased hippocampal structural centrality

(Makowski et al., 2020). Together, these finding implicate the hippocampus as one contributing factor towards functional hypoconnectivity in early-stage psychosis. Preclinical and theoretical work suggests that impaired hippocampal regulatory function could induce elevated striatal dopaminergic activity which in turn increases activity in multiple regions (Grace, 2012; J. Lieberman et al., 2018; Lodge & Grace, 2006).

We did not observe significant reductions in local network integration in FEP patients or CHR-Ps. Previous studies have identified decreased local network integration in ScZ patients (Su, Hsu, Lin, & Lin, 2015). One reason for this difference may be our preprocessing pipeline, which did not use global signal regression and used individualised correlation matrices. The former has been shown to increase potentially spurious negative correlations in patients due to generally lower SNR (Aquino et al., 2020; Murphy et al., 2009; Saad et al., 2012), while the latter has been shown to decrease the number of significant case-control findings in ScZ (Levi et al., 2023).

Moreover, we did not identify correlations between hippocampal-frontal connectivity and symptom measures. This finding is consistent with previous work. For example, Samudra et al. did not report a relationship between hippocampal-frontal functional connectivity and PANSS scores in early-stage psychosis (Samudra et al., 2015), and this was also true at baseline in a longitudinal study (Alho et al., 2023).

In this work, we addressed several limitations typically found in functional connectivity analysis. First, an improved preprocessing pipeline to reduce the impact of noise (Aquino et al., 2020; Parkes et al., 2018) which tends to be larger in psychosis samples (Pardoe et al., 2016; Van Dijk et al., 2012; N. Yao et al., 2017). Furthermore, we used individually optimised functional connectivity matrices, which reduce individual variability in functional connectivity estimates (De La Vega, Yarkoni, Wager, & Banich, 2018; Gordon et al., 2017; Gratton et al., 2020; Samudra et al., 2015). Finally, we could show that observed alterations in functional connectivity were specific to psychosis in our sample. While reduced network connectivity has been observed in other psychiatric conditions, such as major depressive disorder (Sun et al., 2023), our CHR-N sample showed increased connectivity compared to FEP.

Limitations

Our FEP sample was relatively small. Moreover, the difference between CHR-P and HC in terms of hippocampal-vlPFC connectivity was no longer significant after correction for multiple comparisons. Moreover, there is currently no methodological consensus regarding graph measures (Fornito et al., 2013) which can limit generalisability (see e.g. (Gao et al., 2023)).

Conclusion

Resting state functional connectivity between the hippocampus and frontal cortex is decreased in early-stage psychosis. Using novel network-based analyses, our finding implicates the hippocampus as important factor in altered network organization, suggesting reduced involvement in the information flow between connected cortical and subcortical networks. Thus, altered connectivity along the hippocampal-frontal axis could be a potential biomarker of early-stage psychosis.

To further elucidate the nature and mechanisms of alterations in hippocampal networks in psychosis, future work could investigate the role of neurotransmitter systems in generating these network alterations using MR spectroscopy or PET imaging. This may connect our human findings to past theoretical and preclinical work which highlights an important role for dopaminergic and glutamatergic transmission (Grace, 2012; J. Lieberman et al., 2018; Lodge & Grace, 2006).

Acknowledgements

Dr. Uhlhaas has received research support from Lilly and Lundbeck outside the submitted work. Dr. Rajeev Krishnadas was supported by the Neurosciences Foundation. Drs. Fracasso, Gajwani, Gross, Gumley, Krishanadas, Lawrie, Schwannauer, Schultze-Lutter, and Ms Brunner reported no biomedical financial interests or potential conflicts of interest. Ms Brunner was supported by the University of Glasgow Lord-Kelvin-Adam-Smith scholarship.

References

Alho, J., Lahnakoski, J. M., Panula, J. M., Rikandi, E., Mäntylä, T., Lindgren, M., . . . Raij, T. T. (2023). Hippocampus-centered network is associated with positive symptom alleviation in patients with first-episode psychosis. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 8*(12), 1197-1206.

Anticevic, A., Haut, K., Murray, J. D., Repovs, G., Yang, G. J., Diehl, C., . . . Goodyear, B. (2015). Association of thalamic dysconnectivity and conversion to psychosis in youth and young adults at elevated clinical risk. *JAMA psychiatry, 72*(9), 882-891.

Anzellotti, S., Caramazza, A., & Saxe, R. (2017). Multivariate pattern dependence. *PLoS computational biology, 13*(11), e1005799.

Aquino, K. M., Fulcher, B., Oldham, S., Parkes, L., Gollo, L., Deco, G., & Fornito, A. (2022). On the intersection between data quality and dynamical modelling of large-scale fMRI signals. *Neuroimage, 256*, 119051.

Aquino, K. M., Fulcher, B. D., Parkes, L., Sabaroedin, K., & Fornito, A. (2020). Identifying and removing widespread signal deflections from fMRI data: Rethinking the global signal regression problem. *Neuroimage, 212*, 116614.

Battaglia, F. P., Benchenane, K., Sirota, A., Pennartz, C. M., & Wiener, S. I. (2011). The hippocampus: hub of brain network communication for memory. *Trends in cognitive sciences, 15*(7), 310-318.

Benetti, S., Mechelli, A., Picchioni, M., Broome, M., Williams, S., & McGuire, P. (2009). Functional integration between the posterior hippocampus and prefrontal cortex is impaired in both first episode schizophrenia and the at risk mental state. *Brain, 132*(9), 2426-2436.

Bertolino, A., Roffman, J. L., Lipska, B. K., Van Gelderen, P., Olson, A., & Weinberger, D. R. (2002). Reduced N-acetylaspartate in prefrontal cortex of adult rats with neonatal hippocampal damage. *Cerebral cortex, 12*(9), 983-990.

Bortolato, B., Miskowiak, K. W., Köhler, C. A., Vieta, E., & Carvalho, A. F. (2015). Cognitive dysfunction in bipolar disorder and schizophrenia: a systematic review of meta-analyses. *Neuropsychiatric disease and treatment*, 3111-3125.

Brett, M., Taylor, J., Burns, C., Millman, K., Perez, F., Roche, A., . . . D'Esposito, M. (2009). NIPY: an open library and development framework for FMRI data analysis. *Neuroimage*(47), S196.

Brunner, G., Gajwani, R., Gross, J., Gumley, A. I., Krishnadas, R., Lawrie, S. M., . . . Uhlhaas, P. J. (2022). Hippocampal structural alterations in early-stage psychosis: Specificity and relationship to clinical outcomes. *NeuroImage: Clinical, 35*, 103087.

Bubb, E. J., Kinnavane, L., & Aggleton, J. P. (2017). Hippocampal–diencephalic–cingulate networks for memory and emotion: An anatomical guide. *Brain and neuroscience advances, 1*, 2398212817723443.

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

Crossley, N. A., Mechelli, A., Ginestet, C., Rubinov, M., Bullmore, E. T., & McGuire, P. (2016). Altered hub functioning and compensatory activations in the connectome: a meta-analysis of functional neuroimaging studies in schizophrenia. *Schizophrenia bulletin, 42*(2), 434-442.

Davies, C., Martins, D., Dipasquale, O., McCutcheon, R., De Micheli, A., Ramella-Cravaro, V., . . . Oliver, D. (2023). Connectome dysfunction in patients at clinical high risk for psychosis and modulation by oxytocin. *medRxiv*, 2023.2003. 2017.23286528.

De La Vega, A., Yarkoni, T., Wager, T. D., & Banich, M. T. (2018). Large-scale meta-analysis suggests low regional modularity in lateral frontal cortex. *Cerebral Cortex, 28*(10), 3414-3428.

De Pablo, G. S., Radua, J., Pereira, J., Bonoldi, I., Arienti, V., Besana, F., . . . Catalan, A. (2021). Probability of transition to psychosis in

individuals at clinical high risk: an updated meta-analysis. *JAMA psychiatry, 78*(9), 970-978.

Du, Y., Fryer, S. L., Fu, Z., Lin, D., Sui, J., Chen, J., . . . Loewy, R. L. (2018). Dynamic functional connectivity impairments in early schizophrenia and clinical high-risk for psychosis. *Neuroimage, 180*, 632-645.

Esteban, O., Markiewicz, C. J., Blair, R. W., Moodie, C. A., Isik, A. I., Erramuzpe, A., . . . Snyder, M. (2019). fMRIPrep: a robust preprocessing pipeline for functional MRI. *Nature methods, 16*(1), 111-116.

Ezama, L., Hernández-Cabrera, J. A., Seoane, S., Pereda, E., & Janssen, N. (2021). Functional connectivity of the hippocampus and its subfields in resting-state networks. *European Journal of Neuroscience, 53*(10), 3378-3393.

First, M. B. (2014). Structured clinical interview for the DSM (SCID). *The encyclopedia of clinical psychology*, 1-6.

Fornito, A., Zalesky, A., & Breakspear, M. (2013). Graph analysis of the human connectome: promise, progress, and pitfalls. *Neuroimage, 80*, 426-444.

Fusar-Poli, P. (2012). Voxel-wise meta-analysis of fMRI studies in patients at clinical high risk for psychosis. *Journal of Psychiatry and Neuroscience, 37*(2), 106-112.

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rössler, A., Schultze-Lutter, F., . . . Seidman, L. J. (2013). The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA psychiatry, 70*(1), 107-120.

Fusar-Poli, P., McGuire, P., & Borgwardt, S. (2012). Mapping prodromal psychosis: a critical review of neuroimaging studies. *European Psychiatry, 27*(3), 181-191.

Fusar-Poli, P., Perez, J., Broome, M., Borgwardt, S., Placentino, A., Caverzasi, E., . . . Barale, F. (2007). Neurofunctional correlates of vulnerability to psychosis: a systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews, 31*(4), 465-484.

Gao, Z., Xiao, Y., Zhu, F., Tao, B., Yu, W., & Lui, S. (2023). The whole-brain connectome landscape in patients with schizophrenia: A systematic review and meta-analysis of graph theoretical characteristics. *Neuroscience & biobehavioral reviews*, 105144.

Gordon, E. M., Laumann, T. O., Gilmore, A. W., Newbold, D. J., Greene, D. J., Berg, J. J., . . . Sun, H. (2017). Precision functional mapping of individual human brains. *Neuron, 95*(4), 791-807. e797.

Grace, A. A. (2012). Dopamine system dysregulation by the hippocampus: implications for the pathophysiology and treatment of schizophrenia. *Neuropharmacology, 62*(3), 1342-1348.

Gratton, C., Kraus, B. T., Greene, D. J., Gordon, E. M., Laumann, T. O., Nelson, S. M., . . . Petersen, S. E. (2020). Defining individual-specific functional neuroanatomy for precision psychiatry. *Biological psychiatry, 88*(1), 28-39.

Haar, S., Berman, S., Behrmann, M., & Dinstein, I. (2016). Anatomical abnormalities in autism? *Cerebral cortex, 26*(4), 1440-1452.

Hagberg, A., Swart, P., & S Chult, D. (2008). *Exploring network structure, dynamics, and function using NetworkX*. Retrieved from

Kambeitz, J., Kambeitz-Ilankovic, L., Cabral, C., Dwyer, D. B., Calhoun, V. D., Van Den Heuvel, M. P., . . . Malchow, B. (2016). Aberrant functional whole-brain network architecture in patients with schizophrenia: a meta-analysis. *Schizophrenia Bulletin, 42*(suppl_1), S13-S21.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia bulletin, 13*(2), 261-276.

Keefe, R. S., Goldberg, T. E., Harvey, P. D., Gold, J. M., Poe, M. P., & Coughenour, L. (2004). The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophrenia research, 68*(2-3), 283-297.

Kong, R., Yang, Q., Gordon, E., Xue, A., Yan, X., Orban, C., . . . Holmes, A. (2021). Individual-specific areal-level parcellations improve

functional connectivity prediction of behavior. *Cerebral Cortex, 31*(10), 4477-4500.

Levi, P. T., Chopra, S., Pang, J. C., Holmes, A., Gajwani, M., Sassenberg, T. A., . . . Fornito, A. (2023). The effect of using group-averaged or individualized brain parcellations when investigating connectome dysfunction in psychosis. *Network Neuroscience, 7*(4), 1228-1247.

Li, J., Kong, R., Liégeois, R., Orban, C., Tan, Y., Sun, N., . . . Yeo, B. T. (2019). Global signal regression strengthens association between resting-state functional connectivity and behavior. *Neuroimage, 196*, 126-141.

Li, R. R., Lyu, H. L., Liu, F., Lian, N., Wu, R. R., Zhao, J. P., & Guo, W. B. (2018). Altered functional connectivity strength and its correlations with cognitive function in subjects with ultra-high risk for psychosis at rest. *CNS Neuroscience & Therapeutics, 24*(12), 1140-1148.

Lieberman, J., Girgis, R., Brucato, G., Moore, H., Provenzano, F., Kegeles, L., . . . Corcoran, C. (2018). Hippocampal dysfunction in the pathophysiology of schizophrenia: a selective review and hypothesis for early detection and intervention. *Molecular psychiatry, 23*(8), 1764-1772.

Lipska, B. K., Aultman, J. M., Verma, A., Weinberger, D. R., & Moghaddam, B. (2002). Neonatal damage of the ventral hippocampus impairs working memory in the rat. *Neuropsychopharmacology, 27*(1), 47-54.

Lisman, J. E., Coyle, J. T., Green, R. W., Javitt, D. C., Benes, F. M., Heckers, S., & Grace, A. A. (2008). Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends in neurosciences, 31*(5), 234-242.

Lodge, D. J., & Grace, A. A. (2006). The hippocampus modulates dopamine neuron responsivity by regulating the intensity of phasic neuron activation. *Neuropsychopharmacology, 31*(7), 1356-1361.

Lord, L.-D., Allen, P., Expert, P., Howes, O., Broome, M., Lambiotte, R., . . . Turkheimer, F. E. (2012). Functional brain networks before the onset of psychosis: a prospective fMRI study with graph theoretical analysis. *NeuroImage: Clinical, 1*(1), 91-98.

Lord, L.-D., Allen, P., Expert, P., Howes, O., Lambiotte, R., McGuire, P., . . . Turkheimer, F. E. (2011). Characterization of the anterior cingulate's role in the at-risk mental state using graph theory. *Neuroimage, 56*(3), 1531-1539.

Makowski, C., Lewis, J. D., Khundrakpam, B., Tardif, C. L., Palaniyappan, L., Joober, R., . . . Chakravarty, M. M. (2020). Altered hippocampal centrality and dynamic anatomical covariance of intracortical microstructure in first episode psychosis. *Hippocampus, 30*(10), 1058-1072.

Maller, J. J., Welton, T., Middione, M., Callaghan, F. M., Rosenfeld, J. V., & Grieve, S. M. (2019). Revealing the hippocampal connectome through super-resolution 1150-direction diffusion MRI. *Scientific reports, 9*(1), 2418.

McHugo, M., Talati, P., Armstrong, K., Vandekar, S. N., Blackford, J. U., Woodward, N. D., & Heckers, S. (2019). Hyperactivity and reduced activation of anterior hippocampus in early psychosis. *American Journal of Psychiatry, 176*(12), 1030-1038.

Montagrin, A., Saiote, C., & Schiller, D. (2018). The social hippocampus. *Hippocampus, 28*(9), 672-679.

Murphy, K., Birn, R. M., Handwerker, D. A., Jones, T. B., & Bandettini, P. A. (2009). The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? *Neuroimage, 44*(3), 893-905.

Networkx. Networkx Documentation.

Pardoe, H. R., Hiess, R. K., & Kuzniecky, R. (2016). Motion and morphometry in clinical and nonclinical populations. *Neuroimage, 135*, 177-185.

Parkes, L., Fulcher, B., Yücel, M., & Fornito, A. (2018). An evaluation of the efficacy, reliability, and sensitivity of motion correction

strategies for resting-state functional MRI. *Neuroimage, 171*, 415-436.

Pessoa, L. (2017). A network model of the emotional brain. *Trends in cognitive sciences, 21*(5), 357-371.

Power, J. D., Plitt, M., Laumann, T. O., & Martin, A. (2017). Sources and implications of whole-brain fMRI signals in humans. *Neuroimage, 146*, 609-625.

Provenzano, F. A., Guo, J., Wall, M. M., Feng, X., Sigmon, H. C., Brucato, G., . . . Lieberman, J. A. (2020). Hippocampal pathology in clinical high-risk patients and the onset of schizophrenia. *Biological psychiatry, 87*(3), 234-242.

Pruim, R. H., Mennes, M., van Rooij, D., Llera, A., Buitelaar, J. K., & Beckmann, C. F. (2015). ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. *Neuroimage, 112*, 267-277.

Saad, Z. S., Gotts, S. J., Murphy, K., Chen, G., Jo, H. J., Martin, A., & Cox, R. W. (2012). Trouble at rest: how correlation patterns and group differences become distorted after global signal regression. *Brain connectivity, 2*(1), 25-32.

Sabaroedin, K., Tiego, J., & Fornito, A. (2023). Circuit-based approaches to understanding corticostriatothalamic dysfunction across the psychosis continuum. *Biological Psychiatry, 93*(2), 113-124.

Samudra, N., Ivleva, E. I., Hubbard, N. A., Rypma, B., Sweeney, J. A., Clementz, B. A., . . . Tamminga, C. A. (2015). Alterations in hippocampal connectivity across the psychosis dimension. *Psychiatry Research: Neuroimaging, 233*(2), 148-157.

Sasabayashi, D., Yoshimura, R., Takahashi, T., Takayanagi, Y., Nishiyama, S., Higuchi, Y., . . . Nakamura, M. (2021). Reduced hippocampal subfield volume in schizophrenia and clinical high-risk state for psychosis. *Frontiers in Psychiatry, 12*, 642048.

Schultze-Lutter, F., Addington, J., Ruhrmann, S., & Klosterkötter, J. (2007). Schizophrenia proneness instrument, adult version (SPI-A). *Rome: Giovanni Fioriti*.

Su, T.-W., Hsu, T.-W., Lin, Y.-C., & Lin, C.-P. (2015). Schizophrenia symptoms and brain network efficiency: A resting-state fMRI study. *Psychiatry Research: Neuroimaging, 234*(2), 208-218.

Sun, N., Liu, M., Liu, P., Zhang, A., Yang, C., Liu, Z., . . . Zhang, K. (2023). Abnormal cortical-striatal-thalamic-cortical circuit centered on the thalamus in MDD patients with somatic symptoms: Evidence from the REST-meta-MDD project. *Journal of affective disorders, 323*, 71-84.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., . . . Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage, 15*(1), 273-289.

van den Heuvel, M. P., de Lange, S. C., Zalesky, A., Seguin, C., Yeo, B. T., & Schmidt, R. (2017). Proportional thresholding in resting-state fMRI functional connectivity networks and consequences for patient-control connectome studies: Issues and recommendations. *Neuroimage, 152*, 437-449.

Van Dijk, K. R., Sabuncu, M. R., & Buckner, R. L. (2012). The influence of head motion on intrinsic functional connectivity MRI. *Neuroimage, 59*(1), 431-438.

Vargas, T., Dean, D. J., Osborne, K. J., Gupta, T., Ristanovic, I., Ozturk, S., . . . Mittal, V. A. (2018). Hippocampal subregions across the psychosis spectrum. *Schizophrenia bulletin, 44*(5), 1091-1099.

Yan, C.-G., Craddock, R. C., He, Y., & Milham, M. P. (2013). Addressing head motion dependencies for small-world topologies in functional connectomics. *Frontiers in human neuroscience, 7*, 910.

Yao, N., Winkler, A. M., Barrett, J., Book, G. A., Beetham, T., Horseman, R., . . . Mathias, S. (2017). Inferring pathobiology from structural MRI in schizophrenia and bipolar disorder: modeling head motion and neuroanatomical specificity. *Human brain mapping, 38*(8), 3757-3770.

Yung, A., Phillips, L., Yuen, H., & McGorry, P. (2006). Comprehensive assessment of at risk mental state. *Parkville Victoria: The PACE*

Clinic, ORYGEN Research Centre, University of Melbourne, Department of Psychiatry.

Zikidi, K., Gajwani, R., Gross, J., Gumley, A. I., Lawrie, S. M., Schwannauer, M., . . . Uhlhaas, P. J. (2020). Grey-matter abnormalities in clinical high-risk participants for psychosis. *Schizophrenia research, 226*, 120-128.

Chapter 5: General Discussion

Summary of Results

In this thesis, behavioural, neuroanatomical, and functional neuroimaging markers of emerging and early-stage psychosis were identified.

In Chapter 1, the relationship between cognitive tests and functional outcomes in CHR-P individuals was assessed using machine learning approaches. Based on previous research using patients as their own baseline, the models informed by cognitive data were compared to simpler models using only baseline functioning measures as predictors of functional outcomes. Here, models informed by cognition were able to predict functional outcomes with adequate accuracy, but their performance was not better than models informed only by baseline functioning. This suggests that functioning follows a predictable course from baseline, and its prediction is not improved by incorporating cognitive markers.

In Chapter 2, the subcortex and hippocampus were analysed anatomically in terms of volume, and, where volumetric differences were identified, shape. CHR-P and FEP groups were analysed, as well as a clinical control group (CHR-N) to assess the specificity of potential findings to psychosis. Decreased hippocampal volumes were observed in psychosis but not the CHR-N group, which indicated specificity to psychosis. Other subcortical structures on the other hand were unaffected. Hippocampal shape deformations were seen across the hippocampal surface bilaterally in FEP patients, while volumetric contractions were more regionally specific and smaller in magnitude in the CHR-P group. However, hippocampal volume did not show an association with clinical or cognitive features in either group.

In Chapter 3, the choroid plexus was analysed in CHR-P, CHR-N, FEP, and ScZ individuals as a possible contributor to ventricular alterations in psychosis. Here, we refined an existing protocol for choroid plexus segmentation, and determined that it performed on par with manual segmentation by inspecting inter-rater overlap among humans, and overlap with the automated segmentation method. Freesurfer, a popular segmentation method which was used in previous research, showed very low overlap with manual segmentations and produced different statistical results to our chosen segmentation method. Using this improved protocol, a conventional

frequentist analysis showed no evidence for alterations in choroid plexus volume in either psychosis group. Further strengthening this, an additional Bayesian analysis provided evidence against group differences, which suggests that choroid plexus volumes are not a reliable marker of psychosis at any stage of illness.

In Chapter 4, functional connectivity was analysed. Prominent theoretical frameworks assign a key role to the hippocampus in cortical-subcortical networks, but this has not been investigated empirically in early-stage and emerging psychosis yet. Based on this gap in the literature, investigated this using fMRI. We identified lower functional connectivity between the hippocampus and inferior frontal cortex in psychosis, whereby this effect was stronger in the early-stage psychosis group. The centrality of the hippocampus differed between the two illness stages, but neither graph metrics nor functional connectivity showed an association with clinical measures or hippocampal volumes.

The key implications of our findings will now be discussed for each analysis, and potential future studies based on our findings will be described.

Cognition and Functional Outcomes: Implications and Future Directions

Psychosis is characterised by cognitive difficulties at all stages of illness, including the clinical at-risk stage. Our CHR-P sample had lower total BACS scores as well as lower processing and motor speed, although they were not impaired on other individual tasks. Compared to HC, CHR-P individuals had significantly worse baseline GAF scores, indicative of lower overall functioning. Because functioning relates to an individual's need for support, predicting future functioning is particularly of interest when trying to allocate future treatments or support. Clinical outcomes are diverse and not known at the stage of CHR-P (G. S. de Pablo, Radua, Pereira, Bonoldi, Arienti, Besana, & Fusar-Poli, 2021; Gonzalo Salazar De Pablo et al., 2022), so being able to predict future need for support could therefore aid clinical decision-making.

Machine learning models are particularly well suited for this, as trained models can be provided to e.g. clinicians or other researchers, and a prediction can be returned for any new samples fed into a pre-fit model (Koutsouleris et al.,

2018; Young, Kempton, & McGuire, 2016). In some instances, incorporating machine learning predictions may yield improved outcome predictions in psychosis compared to clinical expertise alone (Fusar-Poli et al., 2019).

In our sample, machine learning models informed by cognitive markers could predict functional outcomes (as measured via the GAF scale) with above-chance accuracy. However, functional outcomes were best predicted by models informed by baseline functioning measures – this suggests that GAF scores either follow a reliable trajectory following baseline, or that they simply do not change very much. As can be seen in Supplement 1, the latter was the case in our dataset. This is consistent with past evidence (Koutsouleris et al., 2018), although here typically the ability of other markers to also contribute has been highlighted rather than the fact that functioning is predictive of itself over time. Functioning itself being the strongest predictor of future functioning scores does not negate the association between cognitive variables and functional outcomes. However, it implies that the use of complex models informed by cognitive variables may not be warranted at this stage. Arguably, the complexity of a model should be justified by sufficient improvements in performance over simpler variants, especially if their use may require additional training for clinical staff who are not necessarily experienced in incorporating machine learning models into their clinical decision-making processes.

The utility of baseline functioning in predicting its future course also has important clinical implications – it is often assumed that the primary clinical outcome that should be monitored in CHR-P individuals is transition to psychosis, and that individuals who do not transition may not require treatment. However, most individuals with poor functioning at baseline also presented with poor functional outcomes many months later in our sample. Not only were CHR-P individuals unlikely to recover GAF scores over time, but the majority of them also presented with low GAF scores at all assessment time points. It can thus be proposed that CHR-P individuals with poor functioning should be offered help by default, rather than wait for either transition to psychosis or for individuals to get better over time.

GAF scores represent a mixture of different components, including symptom severity, social life, or occupational/educational functioning (Hall, 1995). Due to this, it is possible for individuals with substantially different constellations of

these different factors to be rated the same. For instance, an individual who experiences frequent psychotic symptoms but is successful in their career may be assigned to the same GAF outcome category as an individual who experiences much milder symptoms, but whose symptoms preclude them from engaging in work or education. GF-Role and GF-Social are designed to separate these different contributions by rating them separately. However, we observed the variance in GF scores on either subscale to be very low, which ultimately rendered them unsuitable as an outcome variable. Future research may benefit from the development of improved clinical tools to assess functioning. Based on our observations, these tools should be able to separate different aspects of functioning such as symptom severity and occupational success, and they should not be as coarse as GF-Role and Social to ensure that there will be statistical variance that can be analysed. While it is an assumption that there is more true variability in functioning in the CHR-P population than GF Role and Social indicated in our sample, arguably the range of outcomes after CHR-P baseline supports this assumption - see e.g. (G. S. de Pablo, Radua, Pereira, Bonoldi, Arienti, Besana, & Fusar-Poli, 2021; Gonzalo Salazar De Pablo et al., 2022; Solmi, Soardo, et al., 2023).

In summary, cognitive variables and functioning show an association in our CHR-P sample, who were cognitively and functionally impaired. However, future functioning is best predicted by baseline functioning measures because scores change little over time, which suggests that early intervention should be given at the CHR-P stage.

Anatomical Markers of Psychosis

In the anatomical domain, we investigated the hippocampus and subcortex, as well as the choroid plexus and the ventricular system. Here, the hippocampus showed shrinkage in early-stage psychosis, whereas the choroid plexus was not altered volumetrically at any stage of illness.

Not only did we not find evidence for volumetric differences in the choroid plexus in any illness stage in psychosis, but a Bayesian analysis also indicated evidence against group differences when ventricular volume was used as a covariate. Volumetric enlargement relative to HC was observed in the ScZ group prior to such correction, but this finding is of limited importance. This is

because the ScZ group also showed enlarged ventricles - and it is known that the size of the choroid plexus scales with the ventricular system, just as e.g. grey matter structures typically scale with total brain size.

Recent advances in choroid plexus segmentation have revealed relatively low quality of Freesurfer-based segmentations (D. Bannai et al., 2022b; Tadayon et al., 2020), on the basis of which some past studies have reported volumetric differences (Paulo Lizano, Lutz, Ling, Lee, Eum, Bishop, Kelly, et al., 2019). Consistent with our findings, a recent study also found that the statistical results varied depending on the choice of segmentation algorithm (Deepthi Bannai et al., 2024). This highlights the importance of quality assurance of segmentations for any volumetric analysis, even for commonly used software packages such as Freesurfer.

Our findings further highlight the utility of incorporating different statistical approaches, such as Bayesian analysis, to obtain a more complete understanding of the results. Bayesian analysis in particular can be used to improve our understanding of null findings, which, in a frequentist framework, as such cannot tell us whether the data was simply uninformative regarding the presence of an effect (i.e. a simple replication failure), or may in fact provide evidence against it (Dienes, 2014). Some previous studies have reported null findings in a frequentist framework in some psychotic disorders as well as CHR-P individuals, (Deepthi Bannai et al., 2024; Paulo Lizano, Lutz, Ling, Lee, Eum, Bishop, Kelly, et al., 2019), although the meaning of these results has remained unclear up until now. To my knowledge, we are the first to also report Bayesian analysis of choroid plexus volumes, demonstrating that our dataset was not uninformative regarding the question of volumetric differences, but indeed provided evidence against them.

Overall, this suggests that the choroid plexus volume is unlikely to be a robust marker of psychosis. The choroid plexus may still be mechanistically involved in the alterations to the ventricular system in psychosis, but this contribution is not evident through volumetric changes. Future research may instead assess the function of the choroid plexus, as this could be a more promising avenue to identifying origins of ventricular changes in psychosis. For more information on measuring choroid plexus function, see e.g. (Mehta et al., 2022; Zhao et al., 2020).

While choroid plexus volumes are rejected as a candidate marker of psychosis, we find decreased hippocampal volumes to be a marker specific to early-stage psychosis. No change to hippocampal volumes is seen in the clinical control group, and any (non-significant) changes from the HC group are in the opposite direction to the effects identified in early-stage psychosis. Furthermore, we find evidence that shape deformities are more regionally confined in the CHR-P group, but they are seen across the hippocampal surface in the FEP group.

It should be noted that the volumetric differences in the CHR-P group were ultimately not statistically significant after correction, thus no strong claims can be made about this group. Numerically, the difference between CHR-P and HC is comparable to that between FEP and HC, which is consistent with past findings, whereby not all find such differences to be statistically significant (Buehlmann et al., 2010; Ganzola, Maziade, & Duchesne, 2014; J. Lieberman et al., 2018; Provenzano et al., 2020; Velakoulis et al., 2006; Walter et al., 2016; Wood et al., 2010). Particularly if volumetric contractions are potentially confined to small subregions within the hippocampus, overall volumetric changes may be too small to be reliably detected at samples of our size. This suggests that a shape analysis should be performed on a larger sample; whereby the use of Bayesian statistics (as e.g. in Chapter 3) could clarify the meaning of null findings if they occur.

Furthermore, the number of transitions to psychosis was too small in our sample to assess the relationship between transition and morphometry in either brain structure (n=14 [13% of the sample included in the volumetric analysis, 9% of the total sample]). Very large CHR-P cohorts are likely required to capture a sufficiently sized group of transitions, which may be of interest to future research.

To summarise our anatomical findings, we found evidence for decreased hippocampal volumes in early-stage psychosis, but evidence against choroid plexus volume changes across illness stages. The role of the hippocampus will thus be discussed further.

The Role of the Hippocampus in Psychosis: Causes, Implications and Future Directions

Converging evidence from multiple neuroimaging modalities (see Chapter 2 and 4) point to hippocampal alterations being markers of psychosis in our sample. In early-stage psychosis, the hippocampus had significantly decreased volumes, as well as decreased functional connectivity with the inferior frontal cortex. Numerically, both anatomical and functional changes were larger in early-stage psychosis than in CHR-P, which may suggest that these markers are indicative of not only risk but also early disease processes. Further evidence for differences between illness stages came from the network analysis, which suggested that the functional organisation of the hippocampus within a cortical-subcortical network may differ between early-stage psychosis and CHR-P. Both our anatomical and functional neuroimaging observations are broadly consistent with previous findings (J. Lieberman et al., 2018; Provenzano et al., 2020; Wood et al., 2010), although this leaves open the question why hippocampal changes are seen in psychosis and how they may emerge.

Neurodevelopmental theories suggest that susceptibility to psychosis may emerge early in life (Gilmore, 2010).The development of hippocampal volumes may be particularly susceptible to stress, particularly early life stress (Humphreys et al., 2019; Larosa & Wong, 2022), which is commonly evident via adverse childhood experiences in individuals with psychotic disorders (Rosenberg, Lu, Mueser, Jankowski, & Cournos, 2007). Genetic risk factors may contribute to hippocampal abnormalities in psychosis, and this is further associated with subcortical volumes (Smeland et al., 2018). Alterations in gene expression could be another contributing factor (Heckers & Konradi, 2010), and abnormal development and function can be induced with infections in animal models (Ducharme, Lowe, Goutagny, & Williams, 2012), which appears consistent with the increase in psychosis risk associated with prenatal infection (Khandaker, Zimbron, Lewis, & Jones, 2013). This implies that the antecedents of the effects we detected may occur at developmentally very early stages, long even before the onset of the prodromal phase. Given the differences we observed between CHR-P and FEP regarding e.g. network organisation surrounding the hippocampus, this suggests that disease-relevant processes in the hippocampus may nonetheless occur at these stages (as

opposed to much earlier in development). Future work may assess individuals longitudinally, and explore whether alterations in functional network organisation or hippocampal volumes can be mitigated at earlier stages of illness. Such research may help clarify if early developmental changes inevitably cause pathological changes to occur in later developmental stages such as adolescence/early adulthood, or if they only represent a risk factor which can be mitigated given appropriate interventions.

Furthermore, previous studies and theoretical works have addressed possible mechanisms of hippocampal change in early-stage psychosis. Here, neurodegenerative views suggest a decline during active phases of illness (Keshavan, 1999; J. A. Lieberman, 1999). Although this is not something that could be measured directly in our sample, animal models suggest that abnormal activity in the hippocampus and volumetric decline may be linked through a process of excitotoxicity (Grace, 2012; J. Lieberman et al., 2018). We did not observe a significant association between hippocampal volumes and either functional connectivity or network properties, which, while not supporting this view, is also not inconsistent with it. Our sample was cross-sectional, whereas the excitotoxicity hypothesis of the relationship between hippocampal activity and volumes in psychosis deals with longitudinal changes, so that longitudinal data is required thoroughly test it. It is further worth noting that not all individuals in the CHR-P group are truly in the prodromal phase of psychosis, as the majority of them did not transition to psychosis at the time of the final assessment. Another contributing factor to the lack of association between measures of hippocampal function and anatomy could thus lie in the fact that the disease process of psychosis may have been underway in relatively few CHR-P individuals, so that the CHR-P group as a whole is less likely to show an effect. That is, since most CHR-P individuals did not transition to psychosis, they were not in a state of emerging psychosis. However, this is speculative, and the question whether CHR-P individuals who transition and those who don’t are in some sense qualitatively different at baseline is outside the scope of this thesis. Exploring whether psychosis risk and early disease processes differ qualitatively or only in magnitude may be of interest to future work.

Besides the assessment of longitudinal changes, another future avenue of interest is highlighted by this work. The glutamate hypothesis of psychosis proposes that NMDA receptor hypofunction contributes to changes in

hippocampal activity in the early stages of illness (Farber, 2003; Grace, 2012). An fMRI protocol as used in the present work could be combined in future research with imaging modalities that are sensitive to neurotransmitters, such as magnetic resonance spectroscopy (MRS) or positron emission tomography (PET). Here, researchers could assess whether regional changes in glutamate activity show a relationship with the functional connectivity between the hippocampus and inferior frontal cortex, or the role of the hippocampus in the cortical-subcortical network as measured for example with betweenness centrality.

The hippocampus has further been described in relation to dopamine hyperactivity in psychosis. Here, animal models suggest that the aforementioned changes in hippocampal activity cause disinhibition, which in turn causes striatal dopamine activity to be abnormally elevated and gives rise to aberrant salience (Grace, 2012; Lodge & Grace, 2006; Winton-Brown et al., 2014). Interestingly, we did not observe changes to functional connectivity between hippocampus and subcortical regions. Subcortical regions did also not show volumetric changes in the anatomical analysis, so we do not find evidence to support proposed links between hippocampus and striatal regions in our sample. Similarly to proposed future investigations of glutamate function in psychosis, MRS or PET imaging could be used to image dopamine in striatal regions specifically to determine whether the hippocampal changes our work highlights show an association with, for instance, dopamine receptor occupancy in early-stage and emerging psychosis, relating our work to previous investigations on dopamine receptor occupancy in ScZ (Abi-Dargham et al., 2000).

While the hippocampus has been an important ROI in both past empirical and theoretical work (see e.g. (Grace, 2012; Lodge & Grace, 2006)), our investigations make a novel contribution to this body of literature by highlighting the following aspects. In the anatomical domain, we compare hippocampal volumes and shape across illness stages in early-stage and emerging psychosis, and we establish that, at least in our sample, the identified alterations are specific to psychosis as they are not observed in the clinical control group, CHR-N. These aspects are also incorporated into the fMRI analysis, which is also novel to my knowledge. Furthermore, we draw from the latest developments in fMRI preprocessing designed to address artifacts which are known to be more common in patients (Pardoe et al., 2016;

Parkes et al., 2018; N. Yao et al., 2017), and the use of which has previously been shown to affect case-control comparisons (Aquino et al., 2020; Parkes et al., 2018).

In summary, we thus provide novel evidence to support existing frameworks postulating an important role for the hippocampus in early-stage and emerging psychosis. Our work points to several promising lines of research which could be conducted in the future to enhance our understanding of the role of the hippocampus in psychosis.

Multimodal Characteristics of Psychosis: Associations between Behavioural, Anatomical, and Functional Markers of Psychosis

Multimodal analysis can reveal markers of psychosis from different angles and levels of analysis, and highlight relationships between the different data modalities. Furthermore, it can highlight information that is shared across different modalities, as well as information which is unique and may thus expand our understanding of psychosis.

Early-stage and emerging psychosis were characterised by both behavioural and neuroanatomical/functional alterations in our sample. Consistent with previous evidence, CHR-P and FEP individuals showed some cognitive impairments and reduced global functioning (Glenthøj et al., 2016; Lin et al., 2011; Niendam et al., 2006; Schaefer et al., 2013). Many normal cognitive functions rely at least in part on the hippocampus, including e.g. memory formation, spatial navigation, or even emotional cognition (Battaglia et al., 2011; Shohamy & Turk-Browne, 2013). Changes in hippocampal baseline activation have further been associated with differences in cognitive performance on cognitive tasks (McHugo et al., 2019). As past theoretical and preclinical work further shows associations between excessive baseline excitation in the hippocampus and decreased volumes (J. Lieberman et al., 2018), one might therefore expect to observe relationships between hippocampal variables and behavioural measures.

While the hippocampus shows both anatomical and functional alterations in our early-stage psychosis samples, we consistently found no association between either neuroimaging modality and cognitive or clinical markers. Hippocampal volumes as well as the role of the hippocampus in the cortical-

subcortical network showed a relationship with illness stage, but did not demonstrate associations with clinical features such as symptom severity or persistence of attenuated psychotic symptoms within each stage. The observed alterations were however specific to psychosis in our data, suggesting that they characterise early-stage psychosis but are not prognostic of clinical course or outcomes.

On the flip side, this also implies that the features captured by each data modality contain unique information about psychosis. Thus, this provides support for a multimodal approach, as each chapter addressing a different data modality also provides new markers for early-stage and emerging psychosis. Future modelling work could assess the extent to which information from these modalities may be synergistic in predicting clinical outcomes – that is, can the unique contributions from each modality be combined in a way which improves predictive performance over separate analyses? In the case of such prediction models, the use of features which already contain significant correlations would be less advantageous, as at least some of this shared information would be redundant and could cause problems with collinearity in model fitting.

Future studies may draw from our work and measure e.g. hippocampal volumes as well as hippocampal function and role in the cortical-subcortical network to predict transition to psychosis from CHR-P. Because the proportion of transitions to psychosis has significantly decreased in recent years compared to earlier samples (Gonzalo Salazar De Pablo, Radua, Pereira, Bonoldi, Arienti, Besana, Soardo, et al., 2021), large samples will likely be required to detect effects associated with transition. Problems such as overfitting, which are commonly found in individualised prediction models fitted on smaller datasets, could be mitigated this way (Schnack & Kahn, 2016; Vieira et al., 2020; Vieira, Pinaya, & Mechelli, 2017). Recent methodological advances in e.g. convolutional neural networks incorporating graphs may further aid in the analysis of multimodal data by not only qualitatively comparing their findings, but by actively fusing the modalities during analysis (Z. Kong, Sun, et al., 2021). We chose not to use such methods in the present work due to our sample size, but future research could build on our work described in Chapter 4 by analysing the same network multimodally, in a large, multi-centre sample.

This thesis thus makes advances to psychosis research by highlighting markers which could be particularly useful in future multimodal prediction models.

This thesis further indicates that, at least in our dataset, the identified markers are specific to psychosis as they were not observed in our clinical control group (CHR-N). At face value, this may be at odds with previous studies which have reported hippocampal volume loss in conditions other than psychosis (Cole et al., 2011; Kempton et al., 2011; Videbech & Ravnkilde, 2004; Wilson et al., 2017). However, individuals with psychosis were not directly compared to these other conditions in these samples.

It should be noted that our clinical control group was relatively small, so that future investigations into the specificity of hippocampal volume reductions, shape changes, and function in a cortical-subcortical network to psychosis are warranted. In such future studies, the relationship between various markers of general psychopathology versus features of psychosis and our identified brain markers should further be analysed. For instance, hippocampal volumes could be correlated with PANSS scores, but also with the severity of MDD or anxiety symptom severity in a clinical control group. This may help determine whether any potential relationships between behavioural and brain markers are specific to psychosis, or are also evident in other psychiatric conditions.

Limitations

Several limitations should be considered when interpreting our findings, particularly regarding sample size and data availability, specificity to psychosis, outcomes in the CHR-P group, individualised prediction methods, and the cross-sectional design. Suggestions are given about how future studies may address these limitations.

Sample sizes in the CHR-N, FEP, and ScZ groups were smaller than in the CHR-P and HC groups, which may have limited our ability to identify effects in these groups. We were also unable to assess the relationship between clinical variables such as symptom severity and neuroimaging features in the FEP and ScZ groups due to limited data availability. In the ScZ group, fMRI data was unavailable, so we were not able to analyse potential changes in hippocampal function in this group. Hippocampal alterations have been proposed to play a

causal role in generating aberrant salience (Grace, 2012; Heckers & Konradi, 2010; Winton-Brown et al., 2014), but our data cannot directly address this important hypothesis. The relationship between the hippocampal markers we identified and symptom severity in the FEP and ScZ groups should be assessed in future studies.

Data availability should also be considered in the interpretation of our findings that cognitive and hippocampal changes were specific to psychosis rather than reflective of general psychopathology (see chapters 1, 2, 4). The CHR-N group were assessed with the same clinical instruments as the CHR-P group, which indicated whether criteria were met across multiple disorders (e.g. generalised anxiety disorder), but did not provide detailed information about severity outwith psychosis-related symptoms. Thus, we cannot exclude the possibility that overall psychopathology was lower in this group compared to CHR-P, which could have contributed to the differences between these groups. It should also be noted that the extent to which severity can be compared across different diagnostic categories is a matter of debate, with some suggesting that psychosis should be considered more severe in principle (Caspi et al., 2014; Kotov et al., 2017).

Analysis of the CHR-P group was also limited by data availability. Transition to psychosis is an important clinical outcome in this group, but it was omitted from analysis in this thesis because we considered the number of CHR-P individuals who transitioned in our dataset too small (<10%). This low rate is in keeping with a current downward trend in transition rates described in Chapter 0 (G. S. de Pablo, Radua, Pereira, Bonoldi, Arienti, Besana, & Fusar-Poli, 2021), which indicates that future studies may need to collect CHR-P samples much larger than ours to capture a sufficiently large transitioned group.

A related problem is that the CHR-P cohort as a whole likely show a mixture of risk, compensatory, and resilience markers regarding transition to psychosis (de Wit et al., 2016; Thakkar et al., 2023), and clinical outcomes are highly heterogenous (G. S. de Pablo, Radua, Pereira, Bonoldi, Arienti, Besana, & Fusar-Poli, 2021; Gonzalo Salazar De Pablo et al., 2022). We cannot exclude the possibility that some differences between HC and CHR-P identified in this thesis are the result of e.g. compensatory mechanisms as opposed to psychosis risk. An analysis of transitioners versus non-transitioners in future

studies could therefore clarify which aspect of the CHR-P group our identified markers best capture. Furthermore, it is not yet clear whether even those who transition to psychosis can be regarded as a homogenous group, as evidence for distinct subtypes exists, which may be transdiagnostic (Cowan & Mittal, 2021; Lalousis et al., 2022). This thesis did not include data-driven analysis to identify subgroups in the CHR-P group, so it is not possible to state whether the alterations we identified are characteristic of CHR-P as a whole, or are driven by a particular subgroup.

In clinical research, one major limitation of traditional statistical analysis is that it does not directly enable individualised prediction. Machine learning, however, is capable of this (Dwyer, Falkai, & Koutsouleris, 2018; Janssen, Mourão-Miranda, & Schnack, 2018). While we aimed to take advantage of this in Chapter 1, machine learning analysis is not included in Chapters 2-4. Preliminary machine learning analysis of the neuroimaging data (not included in thesis) showed unstable model performance, indicative of overfitting. This is a known problem in the machine learning analysis of neuroimaging data and may be due to sample size(Schnack & Kahn, 2016; Vieira et al., 2021). There is no hard rule to determine when a given sample is suitable for machine learning analysis, although more subtle and complex patterns generally require larger sample sizes (Rajput, Wang, & Chen, 2023). Our sample was thus likely too small to generate individualised predictions from the neuroimaging data.

Nested cross-validation, whereby hyperparameters are optimised in addition to model parameters, often outperforms simple k-fold cross validation, and has been recommended for machine learning model optimisation (Bates, Hastie, & Tibshirani, 2024; Cearns, Hahn, & Baune, 2019). In Chapter 1, we chose k-fold cross validation and therefore did not optimise hyperparameters as this failed to show a benefit (see e.g. (Wainer & Cawley, 2021). It is therefore possible that models with optimised hyperparameters may outperform our simple GAF model, and this should be assessed in future studies.

In the theoretical frameworks we draw from, the hippocampus may undergo longitudinal changes across illness stages, particularly at the onset of psychosis (Grace, 2012; J. Lieberman et al., 2018; Moghaddam & Javitt, 2012). This suggests that changes such as volume loss may occur between the CHR-P and FEP stages. Our data is consistent with this, but cannot directly

confirm longitudinal effects due to the cross-sectional design. This is an important limitation, and longitudinal neuroimaging studies of CHR-P cohorts will be required to directly to test the longitudinal predictions of these frameworks.

In summary, the conclusions that can be drawn from this thesis are limited by sample size and data availability, as well as the inferential and predictive limitations of the design used. Future studies may further advance our understanding of early-stage and emerging psychosis by collecting longitudinal neuroimaging data, and ensuring that sufficient clinical information is collected for all groups. To enable analysis of transition to psychosis in the CHR-P group as well as individualised prediction modelling, larger samples will be required in future studies.

Conclusion

Early-stage and emerging psychosis are characterised by impairments in cognitive function and global functioning, and these problems are unlikely to improve over time without support. Concurrently, these individuals show altered function and volume of the hippocampus, and this distinguished psychosis from other psychopathology in our sample. More specifically, hippocampus volumes were decreased, and functional connectivity between the hippocampus and inferior frontal cortex was also lower in early-stage psychosis. Furthermore, early-stage and emerging psychosis differ from each other in terms of the magnitude of anatomical and functional changes to the hippocampus. Its role in a cortical-subcortical network further differs between illness stages.

The markers identified in each data modality are unique, and do not show significant associations with one another. On the one hand, this means that we cannot conclude from this thesis what the behavioural/clinical implications of our neuroimaging results are. While a disadvantage at first glance, there is also an important advantage to this: identifying unique markers is useful for future predictive modelling studies, as they can draw from the multimodal markers we identified without facing problems due to collinearity. This thesis thus makes a novel contribution to the field by identifying promising

neuroanatomical and functional neuroimaging markers for predictive modelling studies of emerging and early-stage psychosis.

References

Abi-Dargham, A., Rodenhiser, J., Printz, D., Zea-Ponce, Y., Gil, R., Kegeles, L. S., . . . Van Heertum, R. L. (2000). Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proceedings of the National Academy of Sciences, 97*(14), 8104-8109.

Addington, J., Piskulic, D., Liu, L., Lockwood, J., Cadenhead, K. S., Cannon, T. D., . . . Seidman, L. J. (2017). Comorbid diagnoses for youth at clinical high risk of psychosis. *Schizophrenia research, 190*, 90-95.

Adityanjee, Aderibigbe, Y. A., Theodoridis, D., & Vieweg, W. V. R. (1999). Dementia praecox to schizophrenia: the first 100 years. *Psychiatry and Clinical neurosciences, 53*(4), 437-448.

Adriano, F., Spoletini, I., Caltagirone, C., & Spalletta, G. (2010). Updated meta-analyses reveal thalamus volume reduction in patients with first-episode and chronic schizophrenia. *Schizophrenia research, 123*(1), 1-14.

Alho, J., Lahnakoski, J. M., Panula, J. M., Rikandi, E., Mäntylä, T., Lindgren, M., . . . Raij, T. T. (2023). Hippocampus-centered network is associated with positive symptom alleviation in patients with first-episode psychosis. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 8*(12), 1197-1206.

Ali, S., Santomauro, D., Ferrari, A. J., & Charlson, F. (2022). Excess mortality in severe mental disorders: A systematic review and meta-regression. *Journal of psychiatric research, 149*, 97-105.

Alkemade, A., Bazin, P.-L., Balesar, R., Pine, K., Kirilina, E., Möller, H. E., . . . Bleys, R. L. (2022). A unified 3D map of microscopic architecture and MRI of the human brain. *Science advances, 8*(17), eabj7892.

Allen, P., Chaddock, C. A., Egerton, A., Howes, O. D., Bonoldi, I., Zelaya, F., . . . McGuire, P. (2016). Resting hyperperfusion of the hippocampus, midbrain, and basal ganglia in people at high risk for psychosis. *American Journal of Psychiatry, 173*(4), 392-399.

Althubaity, N., Schubert, J., Martins, D., Yousaf, T., Nettis, M. A., Mondelli, V., . . . Dima, D. (2022). Choroid plexus enlargement is associated with neuroinflammation and reduction of blood brain barrier permeability in depression. *NeuroImage: Clinical, 33*, 102926.

Althubaity, N., Schubert, J., Martins, D., Yousaf, T., Nettis, M. A., Mondelli, V., & Veronese, M. (2022). Choroid plexus enlargement is associated with neuroinflammation and reduction of blood brain barrier permeability in depression. *NeuroImage: Clinical, 33*(10292), 6.

American Psychiatric Association, D., & Association, A. P. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (Vol. 5): American psychiatric association Washington, DC.

Andreou, C., & Borgwardt, S. (2020). Structural and functional imaging markers for susceptibility to psychosis. *Molecular psychiatry, 25*(11), 2773-2785.

Anticevic, A., Haut, K., Murray, J. D., Repovs, G., Yang, G. J., Diehl, C., . . . Goodyear, B. (2015). Association of thalamic dysconnectivity and conversion to psychosis in youth and young adults at elevated clinical risk. *JAMA psychiatry, 72*(9), 882-891.

Anzellotti, S., Caramazza, A., & Saxe, R. (2017). Multivariate pattern dependence. *PLoS computational biology, 13*(11), e1005799.

Aquino, K. M., Fulcher, B., Oldham, S., Parkes, L., Gollo, L., Deco, G., & Fornito, A. (2022). On the intersection between data quality and dynamical modelling of large-scale fMRI signals. *Neuroimage, 256*, 119051.

Aquino, K. M., Fulcher, B. D., Parkes, L., Sabaroedin, K., & Fornito, A. (2020). Identifying and removing widespread signal deflections from fMRI data: Rethinking the global signal regression problem. *Neuroimage, 212*, 116614.

Arasappa, R., Danivas, V., & Venkatasubramanian, G. (2013). Choroid plexus papilloma presenting as schizophrenia: a case report. *The Journal of Neuropsychiatry and Clinical Neurosciences, 25*(1), E26-E27.

Arnaud, K., Moreira, V. O., Vincent, J., Dallerac, G., Dubreuil, C., Dupont, E., & Di Nardo, A. A. (2021). Choroid plexus APP regulates adult brain proliferation and animal behavior. *Life science alliance, 4*, 11.

Asami, T., Bouix, S., Whitford, T. J., Shenton, M. E., Salisbury, D. F., & McCarley, R. W. (2012). Longitudinal loss of gray matter volume in patients with first-episode schizophrenia: DARTEL automated analysis and ROI validation. *Neuroimage, 59*(2), 986-996.

Balu, D. T., & Coyle, J. T. (2011). Neuroplasticity signaling pathways linked to the pathophysiology of schizophrenia. *Neuroscience & Biobehavioral Reviews, 35*(3), 848-870.

Bannai, D., Reuter, M., Hegde, R., Hoang, D., Adhan, I., Gandu, S., & Lizano, P. (2022a). *Linking Choroid Plexus Enlargement with Plasma Analyte and Structural Phenotypes in Clinical High Risk for Psychosis. A Multisite Neuroimaging Study.*: bioRxiv.

Bannai, D., Reuter, M., Hegde, R., Hoang, D., Adhan, I., Gandu, S., & Lizano, P. (2022b). *Linking Choroid Plexus Enlargement with Plasma Analyte and Structural Phenotypes in Clinical High Risk for Psychosis. A Multisite Neuroimaging Study.* bioRxiv.

Bannai, D., Reuter, M., Hegde, R., Hoang, D., Adhan, I., Gandu, S., . . . Chung, Y. (2024). Linking enlarged choroid plexus with plasma analyte and structural phenotypes in clinical high risk for psychosis: A multisite neuroimaging study. *Brain, Behavior, and Immunity, 117*, 70-79.

Bates, S., Hastie, T., & Tibshirani, R. (2024). Cross-validation: what does it estimate and how well does it do it? *Journal of the American Statistical Association, 119*(546), 1434-1445.

Battaglia, F. P., Benchenane, K., Sirota, A., Pennartz, C. M., & Wiener, S. I. (2011). The hippocampus: hub of brain network communication for memory. *Trends in cognitive sciences, 15*(7), 310-318.
Bell, D. (1965). Comparison of amphetamine psychosis and schizophrenia. *The British Journal of Psychiatry, 111*(477), 701-707.
Benes, F. M. (2009). Neural circuitry models of schizophrenia: is it dopamine, GABA, glutamate, or something else? *Biological psychiatry, 65*(12), 1003-1005.
Benetti, S., Mechelli, A., Picchioni, M., Broome, M., Williams, S., & McGuire, P. (2009). Functional integration between the posterior hippocampus and prefrontal cortex is impaired in both first episode schizophrenia and the at risk mental state. *Brain, 132*(9), 2426-2436.
Berger, G., Wood, S., Velakoulis, D., Ang, A., Brewer, W., Phillips, L., . . . McGorry, P. (2007). Ventricle volumes in emerging psychosis. A cross-sectional and longitudinal MRI study. *European Psychiatry, 22*(S1), S30-S31.
Bertolino, A., Roffman, J. L., Lipska, B. K., Van Gelderen, P., Olson, A., & Weinberger, D. R. (2002). Reduced N-acetylaspartate in prefrontal cortex of adult rats with neonatal hippocampal damage. *Cerebral cortex, 12*(9), 983-990.
Bhati, M. T. (2013). Defining psychosis: the evolution of DSM-5 schizophrenia spectrum disorders. *Current psychiatry reports, 15*, 1-7.
Bhattacahrjee, D., Singh, N. K., Rai, A. K., Kumar, P., Verma, A., & Munda, S. K. (2011). Sociological understanding of psychiatric illness: An appraisal. *Delhi Psychiatry Journal, 14*(1).
Björklund, A., & Dunnett, S. B. (2007). Dopamine neuron systems in the brain: an update. *Trends in neurosciences, 30*(5), 194-202.
Bleuler, M. (1931). Schizophrenia: review of the work of prof. eugen bleuler. *Archives of Neurology & Psychiatry, 26*(3), 610-627.
Boly, M., Gosseries, O., Massimini, M., & Rosanova, M. (2016). Functional neuroimaging techniques. In *The Neurology of Conciousness* (pp. 31-47): Elsevier.
Boos, H. B., Aleman, A., Cahn, W., Pol, H. H., & Kahn, R. S. (2007). Brain volumes in relatives of patients with schizophrenia: a meta-analysis. *Archives of general psychiatry, 64*(3), 297-304.
Bortolato, B., Miskowiak, K. W., Köhler, C. A., Vieta, E., & Carvalho, A. F. (2015). Cognitive dysfunction in bipolar disorder and schizophrenia: a systematic review of meta-analyses. *Neuropsychiatric disease and treatment*, 3111-3125.
Brett, M., Taylor, J., Burns, C., Millman, K., Perez, F., Roche, A., . . . D'Esposito, M. (2009). NIPY: an open library and development framework for FMRI data analysis. *Neuroimage*(47), S196.
Brunner, G., Gajwani, R., Gross, J., Gumley, A. I., Krishnadas, R., Lawrie, S. M., . . . Uhlhaas, P. J. (2022). Hippocampal structural alterations in early-stage psychosis: Specificity and relationship to clinical outcomes. *NeuroImage: Clinical, 35*, 103087.

Bubb, E. J., Kinnavane, L., & Aggleton, J. P. (2017). Hippocampal–diencephalic–cingulate networks for memory and emotion: An anatomical guide. *Brain and neuroscience advances, 1*, 2398212817723443.

Buehlmann, E., Berger, G. E., Aston, J., Gschwandtner, U., Pflueger, M. O., Borgwardt, S. J., . . . Riecher-Rössler, A. (2010). Hippocampus abnormalities in at risk mental states for psychosis? A cross-sectional high resolution region of interest magnetic resonance imaging study. *Journal of psychiatric research, 44*(7), 447-453.

Bürgy, M. (2008). The concept of psychosis: historical and phenomenological aspects. *Schizophrenia bulletin, 34*(6), 1200-1210.

Carrión, R. E., Goldberg, T. E., McLaughlin, D., Auther, A. M., Correll, C. U., & Cornblatt, B. A. (2011). Impact of neurocognition on social and role functioning in individuals at clinical high risk for psychosis. *American Journal of Psychiatry, 168*(8), 806-813.

Carrión, R. E., McLaughlin, D., Goldberg, T. E., Auther, A. M., Olsen, R. H., Olvet, D. M., . . . Cornblatt, B. A. (2013). Prediction of functional outcome in individuals at clinical high risk for psychosis. *JAMA psychiatry, 70*(11), 1133-1142.

Carson, B. S., Weingart, J. D., Guarnieri, M., & Fisher, P. G. (1997). Third ventricular choroid plexus papilloma with psychosis: case report. *Journal of neurosurgery, 87*(1), 103-105.

Caspi, A., Houts, R. M., Belsky, D. W., Goldman-Mellor, S. J., Harrington, H., Israel, S., . . . Poulton, R. (2014). The p factor: one general psychopathology factor in the structure of psychiatric disorders? *Clinical psychological science, 2*(2), 119-137.

Castellani, G., Contarini, G., Mereu, M., Albanesi, E., Devroye, C., D'Amore, C., & Papaleo, F. (2019). Dopamine-mediated immunomodulation affects choroid plexus function. *Brain, Behavior, and Immunity, 81*, 138-150.

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

Cattarinussi, G., Grimaldi, D. A., & Sambataro, F. (2023). Spontaneous brain activity alterations in first-episode psychosis: a meta-analysis of functional Magnetic Resonance Imaging studies. *Schizophrenia bulletin, 49*(6), 1494-1507.

Cearns, M., Hahn, T., & Baune, B. T. (2019). Recommendations and future directions for supervised machine learning in psychiatry. *Translational psychiatry, 9*(1), 271.

Chung, Y., Haut, K. M., He, G., van Erp, T. G., McEwen, S., Addington, J., . . . Mathalon, D. H. (2017). Ventricular enlargement and progressive reduction of cortical gray matter are linked in prodromal youth who develop psychosis. *Schizophrenia research, 189*, 169-174.

Chung, Y., Jacobson, A., He, G., van Erp, T. G., McEwen, S., Addington, J., . . . Mathalon, D. H. (2015). Prodromal symptom severity predicts accelerated gray matter reduction and third ventricle

expansion among clinically high-risk youth developing psychotic disorders. *Complex Psychiatry, 1*(1), 13-22.
Cole, J., Costafreda, S. G., McGuffin, P., & Fu, C. H. (2011). Hippocampal atrophy in first episode depression: a meta-analysis of magnetic resonance imaging studies. *Journal of affective disorders, 134*(1-3), 483-487.
Cowan, H. R., & Mittal, V. A. (2021). Transdiagnostic dimensions of psychiatric comorbidity in individuals at clinical high risk for psychosis: a preliminary study informed by HiTOP. *Frontiers in Psychiatry, 11*, 614710.
Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical research, 29*(3), 162-173.
Crespo-Facorro, B., Such, P., Nylander, A.-G., Madera, J., Resemann, H. K., Worthington, E., . . . Newton, R. (2021). The burden of disease in early schizophrenia–a systematic literature review. *Current medical research and opinion, 37*(1), 109-121.
Crossley, N. A., Mechelli, A., Ginestet, C., Rubinov, M., Bullmore, E. T., & McGuire, P. (2016). Altered hub functioning and compensatory activations in the connectome: a meta-analysis of functional neuroimaging studies in schizophrenia. *Schizophrenia bulletin, 42*(2), 434-442.
Davies, C., Martins, D., Dipasquale, O., McCutcheon, R., De Micheli, A., Ramella-Cravaro, V., . . . Oliver, D. (2023). Connectome dysfunction in patients at clinical high risk for psychosis and modulation by oxytocin. *medRxiv*, 2023.2003. 2017.23286528.
de la Salle, S., Shah, D., Choueiry, J., Bowers, H., McIntosh, J., Carroll, B., . . . Knott, V. (2021). N-methyl-d-aspartate receptor antagonism modulates P300 event-related potentials and associated activity in salience and central executive networks. *Pharmacology Biochemistry and Behavior, 211*, 173287.
De La Vega, A., Yarkoni, T., Wager, T. D., & Banich, M. T. (2018). Large-scale meta-analysis suggests low regional modularity in lateral frontal cortex. *Cerebral Cortex, 28*(10), 3414-3428.
de Pablo, G. S., Radua, J., Pereira, J., Bonoldi, I., Arienti, V., Besana, F., & Fusar-Poli, P. (2021). Probability of transition to psychosis in individuals at clinical high risk: an updated meta-analysis. *JAMA psychiatry, 78*(9), 970-978.
De Pablo, G. S., Radua, J., Pereira, J., Bonoldi, I., Arienti, V., Besana, F., . . . Catalan, A. (2021). Probability of transition to psychosis in individuals at clinical high risk: an updated meta-analysis. *JAMA psychiatry, 78*(9), 970-978.
De Pablo, G. S., Soardo, L., Cabras, A., Pereira, J., Kaur, S., Besana, F., . . . Solmi, M. (2022). Clinical outcomes in individuals at clinical high risk of psychosis who do not transition to psychosis: a meta-analysis. *Epidemiology and psychiatric sciences, 31*, e9.
de Wit, S., Wierenga, L. M., Oranje, B., Ziermans, T. B., Schothorst, P. F., van Engeland, H., . . . Durston, S. (2016). Brain development in adolescents at ultra-high risk for psychosis: longitudinal changes related to resilience. *NeuroImage: Clinical, 12*, 542-549.

Del Fabro, L., Schmidt, A., Fortea, L., Delvecchio, G., D'Agostino, A., Radua, J., . . . Brambilla, P. (2021). Functional brain network dysfunctions in subjects at high-risk for psychosis: a meta-analysis of resting-state functional connectivity. *Neuroscience & biobehavioral reviews, 128*, 90-101.

Desalegn, D., Girma, S., & Abdeta, T. (2020). Quality of life and its association with psychiatric symptoms and socio-demographic characteristics among people with schizophrenia: A hospital-based cross-sectional study. *Plos one, 15*(2), e0229514.

Di Biase, M. A., Cetin-Karayumak, S., Lyall, A. E., Zalesky, A., Cho, K. I. K., Zhang, F., . . . Bouix, S. (2021). White matter changes in psychosis risk relate to development and are not impacted by the transition to psychosis. *Molecular psychiatry, 26*(11), 6833-6844.

Dienes, Z. (2014). Using Bayes to get the most out of non-significant results. *Frontiers in psychology, 5*, 85883.

Du, Y., Fryer, S. L., Fu, Z., Lin, D., Sui, J., Chen, J., . . . Loewy, R. L. (2018). Dynamic functional connectivity impairments in early schizophrenia and clinical high-risk for psychosis. *Neuroimage, 180*, 632-645.

Ducharme, G., Lowe, G. C., Goutagny, R., & Williams, S. (2012). Early alterations in hippocampal circuitry and theta rhythm generation in a mouse model of prenatal infection: implications for schizophrenia. *Plos one, 7*(1), e29754.

Dwyer, D. B., Falkai, P., & Koutsouleris, N. (2018). Machine learning approaches for clinical psychology and psychiatry. *Annual review of clinical psychology, 14*(1), 91-118.

Eggers, A. E. (2013). A serotonin hypothesis of schizophrenia. *Medical hypotheses, 80*(6), 791-794.

Ellis, J. K., Walker, E. F., & Goldsmith, D. R. (2020). Selective review of neuroimaging findings in youth at clinical high risk for psychosis: on the path to biomarkers for conversion. *Frontiers in Psychiatry, 11*(56753), 4.

Ellison-Wright, I., Glahn, D. C., Laird, A. R., Thelen, S. M., & Bullmore, E. (2008). The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. *American Journal of Psychiatry, 165*(8), 1015-1023.

Eslami, A., Jahshan, C., & Cadenhead, K. S. (2011). Disorganized symptoms and executive functioning predict impaired social functioning in subjects at risk for psychosis. *The Journal of neuropsychiatry and clinical neurosciences, 23*(4), 457-460.

Esteban, O., Markiewicz, C. J., Blair, R. W., Moodie, C. A., Isik, A. I., Erramuzpe, A., . . . Snyder, M. (2019). fMRIPrep: a robust preprocessing pipeline for functional MRI. *Nature methods, 16*(1), 111-116.

Ezama, L., Hernández-Cabrera, J. A., Seoane, S., Pereda, E., & Janssen, N. (2021). Functional connectivity of the hippocampus and its subfields in resting-state networks. *European Journal of Neuroscience, 53*(10), 3378-3393.

Falcao, A. M., Marques, F., Novais, A., Sousa, N., Palha, J. A., & Sousa, J. C. (2012). The path from the choroid plexus to the

subventricular zone: go with the flow! *Frontiers in Cellular Neuroscience, 6*(34), 485-488.
Fan, F., Xiang, H., Tan, S., Yang, F., Fan, H., Guo, H., . . . Tan, Y. (2019). Subcortical structures and cognitive dysfunction in first episode schizophrenia. *Psychiatry Research: Neuroimaging, 286*, 69-75.
Farber, N. B. (2003). The NMDA receptor hypofunction model of psychosis. *Annals of the New York Academy of Sciences, 1003*(1), 119-130.
First, M. B. (2014). Structured clinical interview for the DSM (SCID). *The encyclopedia of clinical psychology*, 1-6.
Fischl, B. (2012). FreeSurfer. *Neuroimage, 62*(2), 774-781.
Fornito, A., Zalesky, A., & Breakspear, M. (2013). Graph analysis of the human connectome: promise, progress, and pitfalls. *Neuroimage, 80*, 426-444.
Fornito, A., Zalesky, A., & Bullmore, E. (2016). Fundamentals of brain network analysis.
Fujihara, K. (2023). Beyond the GABA hypothesis of schizophrenia. *Frontiers in Cellular Neuroscience*.
Fujimura, M., Onuma, T., Kameyama, M., Motohashi, O., Kon, H., Yamamoto, K., . . . Tominaga, T. (2004). Hydrocephalus due to cerebrospinal fluid overproduction by bilateral choroid plexus papillomas. *Child's Nervous System, 20*, 485-488.
Fusar-Poli, P. (2012). Voxel-wise meta-analysis of fMRI studies in patients at clinical high risk for psychosis. *Journal of Psychiatry and Neuroscience, 37*(2), 106-112.
Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rössler, A., Schultze-Lutter, F., . . . Seidman, L. J. (2013). The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA psychiatry, 70*(1), 107-120.
Fusar-Poli, P., McGuire, P., & Borgwardt, S. (2012). Mapping prodromal psychosis: a critical review of neuroimaging studies. *European Psychiatry, 27*(3), 181-191.
Fusar-Poli, P., Perez, J., Broome, M., Borgwardt, S., Placentino, A., Caverzasi, E., . . . Barale, F. (2007). Neurofunctional correlates of vulnerability to psychosis: a systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews, 31*(4), 465-484.
Fusar-Poli, P., Smieskova, R., Serafini, G., Politi, P., & Borgwardt, S. (2014). Neuroanatomical markers of genetic liability to psychosis and first episode psychosis: a voxelwise meta-analytical comparison. *The World Journal of Biological Psychiatry, 15*(3), 219-228.
Fusar-Poli, P., Stringer, D., MS Durieux, A., Rutigliano, G., Bonoldi, I., De Micheli, A., & Stahl, D. (2019). Clinical-learning versus machine-learning for transdiagnostic prediction of psychosis onset in individuals at-risk. *Translational psychiatry, 9*(1), 259.
Gallardo-Ruiz, R., Crespo-Facorro, B., Setien-Suero, E., & Tordesillas-Gutierrez, D. (2019). Long-term grey matter changes in first episode psychosis: a systematic review. *Psychiatry investigation, 16*(5), 336.

Ganella, E. P., Seguin, C., Pantelis, C., Whittle, S., Baune, B. T., Olver, J., . . . Zalesky, A. (2018). Resting-state functional brain networks in first-episode psychosis: A 12-month follow-up study. *Australian & New Zealand Journal of Psychiatry, 52*(9), 864-875.
Ganzola, R., Maziade, M., & Duchesne, S. (2014). Hippocampus and amygdala volumes in children and young adults at high-risk of schizophrenia: research synthesis. *Schizophrenia research, 156*(1), 76-86.
Gao, Z., Xiao, Y., Zhu, F., Tao, B., Yu, W., & Lui, S. (2023). The whole-brain connectome landscape in patients with schizophrenia: A systematic review and meta-analysis of graph theoretical characteristics. *Neuroscience & biobehavioral reviews*, 105144.
Gilmore, J. H. (2010). Understanding what causes schizophrenia: a developmental perspective. In (Vol. 167, pp. 8-10): Am Psychiatric Assoc.
Giraldo-Chica, M., & Woodward, N. D. (2017). Review of thalamocortical resting-state fMRI studies in schizophrenia. *Schizophrenia research, 180*, 58-63.
Glahn, D. C., Laird, A. R., Ellison-Wright, I., Thelen, S. M., Robinson, J. L., Lancaster, J. L., . . . Fox, P. T. (2008). Meta-analysis of gray matter anomalies in schizophrenia: application of anatomic likelihood estimation and network analysis. *Biological psychiatry, 64*(9), 774-781.
Glenthøj, L. B., Fagerlund, B., Hjorthøj, C., Jepsen, J. R., Bak, N., Kristensen, T. D., . . . Nordentoft, M. (2016). Social cognition in patients at ultra-high risk for psychosis: what is the relation to social skills and functioning? *Schizophrenia Research: Cognition, 5*, 21-27.
Gordon, E. M., Laumann, T. O., Gilmore, A. W., Newbold, D. J., Greene, D. J., Berg, J. J., . . . Sun, H. (2017). Precision functional mapping of individual human brains. *Neuron, 95*(4), 791-807. e797.
Grace, A. A. (2012). Dopamine system dysregulation by the hippocampus: implications for the pathophysiology and treatment of schizophrenia. *Neuropharmacology, 62*(3), 1342-1348.
Gratton, C., Kraus, B. T., Greene, D. J., Gordon, E. M., Laumann, T. O., Nelson, S. M., . . . Petersen, S. E. (2020). Defining individual-specific functional neuroanatomy for precision psychiatry. *Biological psychiatry, 88*(1), 28-39.
Haar, S., Berman, S., Behrmann, M., & Dinstein, I. (2016). Anatomical abnormalities in autism? *Cerebral cortex, 26*(4), 1440-1452.
Hadley, J. A., Nenert, R., Kraguljac, N. V., Bolding, M. S., White, D. M., Skidmore, F. M., . . . Lahti, A. C. (2014). Ventral tegmental area/midbrain functional connectivity and response to antipsychotic medication in schizophrenia. *Neuropsychopharmacology, 39*(4), 1020-1030.
Hagberg, A., Swart, P., & S Chult, D. (2008). *Exploring network structure, dynamics, and function using NetworkX*. Retrieved from
Haijma, S. V., Van Haren, N., Cahn, W., Koolschijn, P. C. M., Hulshoff Pol, H. E., & Kahn, R. S. (2013). Brain volumes in schizophrenia: a

meta-analysis in over 18 000 subjects. *Schizophrenia bulletin, 39*(5), 1129-1138.
Hall, R. C. (1995). Global assessment of functioning: a modified scale. *Psychosomatics, 36*(3), 267-275.
Hamilton, H. K., Boos, A. K., & Mathalon, D. H. (2020). Electroencephalography and event-related potential biomarkers in individuals at clinical high risk for psychosis. *Biological psychiatry, 88*(4), 294-303.
Harrisberger, F., Buechler, R., Smieskova, R., Lenz, C., Walter, A., Egloff, L., . . . Theodoridou, A. (2016). Alterations in the hippocampus and thalamus in individuals at high risk for psychosis. *NPJ schizophrenia, 2*(1), 1-6.
Harrisberger, F., Smieskova, R., Vogler, C., Egli, T., Schmidt, A., Lenz, C., . . . Borgwardt, S. (2016). Impact of polygenic schizophrenia-related risk and hippocampal volumes on the onset of psychosis. *Translational psychiatry, 6*(8), e868-e868.
Heckers, S., & Konradi, C. (2010). Hippocampal pathology in schizophrenia. *Behavioral neurobiology of schizophrenia and its treatment*, 529-553.
Ho, B.-C., & Magnotta, V. (2010). Hippocampal volume deficits and shape deformities in young biological relatives of schizophrenia probands. *Neuroimage, 49*(4), 3385-3393.
Howes, O. D., & Kapur, S. (2009). The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophrenia bulletin, 35*(3), 549-562.
Huang, J., Tong, J., Zhang, P., Zhou, Y., Li, Y., Tan, S., & Tan, Y. (2022). Elevated salivary kynurenic acid levels related to enlarged choroid plexus and severity of clinical phenotypes in treatment-resistant schizophrenia. *Brain, Behavior, and Immunity, 106*, 32-39.
Huang, X., Fox, K., Ribeiro, J., & Franklin, J. (2018). Psychosis as a risk factor for suicidal thoughts and behaviors: a meta-analysis of longitudinal studies. *Psychological medicine, 48*(5), 765-776.
Humphreys, K. L., King, L. S., Sacchet, M. D., Camacho, M. C., Colich, N. L., Ordaz, S. J., . . . Gotlib, I. H. (2019). Evidence for a sensitive period in the effects of early life stress on hippocampal volume. *Developmental Science, 22*(3), e12775.
Hýža, M., Kuhn, M., Češková, E., Ustohal, L., & Kašpárek, T. (2016). Hippocampal volume in first-episode schizophrenia and longitudinal course of the illness. *The World Journal of Biological Psychiatry, 17*(6), 429-438.
Jablensky, A. (2010). The diagnostic concept of schizophrenia: its history, evolution, and future prospects. *Dialogues in clinical neuroscience, 12*(3), 271-287.
Jackson, D. M., & Westlind-Danielsson, A. (1994). Dopamine receptors: molecular biology, biochemistry and behavioural aspects. *Pharmacology & therapeutics, 64*(2), 291-370.
Jaco, E. G. (1954). The social isolation hypothesis and schizophrenia. *American Sociological Review, 19*(5), 567-577.
Jalbrzikowski, M., Hayes, R. A., Wood, S. J., Nordholm, D., Zhou, J. H., Fusar-Poli, P., . . . Kwak, Y. B. (2021). Association of structural

magnetic resonance imaging measures with psychosis onset in individuals at clinical high risk for developing psychosis: an ENIGMA working group mega-analysis. *JAMA psychiatry, 78*(7), 753-766.
Janssen, R. J., Mourão-Miranda, J., & Schnack, H. G. (2018). Making individual prognoses in psychiatry using neuroimaging and machine learning. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 3*(9), 798-808.
Jeffreys, H. (1939). Theory of Probability.
Kambeitz, J., Kambeitz-Ilankovic, L., Cabral, C., Dwyer, D. B., Calhoun, V. D., Van Den Heuvel, M. P., . . . Malchow, B. (2016). Aberrant functional whole-brain network architecture in patients with schizophrenia: a meta-analysis. *Schizophrenia bulletin, 42*(suppl_1), S13-S21.
Kapur, S., & Seeman, P. (2000). Antipsychotic agents differ in how fast they come off the dopamine D2 receptors. Implications for atypical antipsychotic action. *Journal of Psychiatry and Neuroscience, 25*(2), 161.
Karimy, J. K., Zhang, J., Kurland, D. B., Theriault, B. C., Duran, D., Stokum, J. A., & Kahle, K. T. (2017). Inflammation-dependent cerebrospinal fluid hypersecretion by the choroid plexus epithelium in posthemorrhagic hydrocephalus. *Nature medicine, 23*(8), 997-1003.
Kaufmann, T., Skåtun, K. C., Alnæs, D., Doan, N. T., Duff, E. P., Tønnesen, S., . . . Lagerberg, T. V. (2015). Disintegration of sensorimotor brain networks in schizophrenia. *Schizophrenia bulletin, 41*(6), 1326-1335.
Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia bulletin, 13*(2), 261-276.
Keefe, R. S., Goldberg, T. E., Harvey, P. D., Gold, J. M., Poe, M. P., & Coughenour, L. (2004). The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophrenia research, 68*(2-3), 283-297.
Kempton, M. J., Salvador, Z., Munafò, M. R., Geddes, J. R., Simmons, A., Frangou, S., & Williams, S. C. (2011). Structural neuroimaging studies in major depressive disorder: meta-analysis and comparison with bipolar disorder. *Archives of general psychiatry, 68*(7), 675-690.
Kempton, M. J., Stahl, D., Williams, S. C., & DeLisi, L. E. (2010). Progressive lateral ventricular enlargement in schizophrenia: a meta-analysis of longitudinal MRI studies. *Schizophrenia Research, 120*(1-3), 54-62.
Keshavan, M. S. (1999). Development, disease and degeneration in schizophrenia: a unitary pathophysiological model. *Journal of psychiatric research, 33*(6), 513-521.
Keysers, C., Gazzola, V., & Wagenmakers, E.-J. (2020). Using Bayes factor hypothesis testing in neuroscience to establish evidence of absence. *Nature neuroscience, 23*(7), 788-799.

Khandaker, G. M., Zimbron, J., Lewis, G., & Jones, P. (2013). Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. *Psychological medicine, 43*(2), 239-257.

Kong, R., Yang, Q., Gordon, E., Xue, A., Yan, X., Orban, C., . . . Holmes, A. (2021). Individual-specific areal-level parcellations improve functional connectivity prediction of behavior. *Cerebral Cortex, 31*(10), 4477-4500.

Kong, Z., Sun, L., Peng, H., Zhan, L., Chen, Y., & He, L. (2021). Multiplex graph networks for multimodal brain network analysis. *arXiv preprint arXiv:2108.00158*.

Kotov, R., Krueger, R. F., Watson, D., Achenbach, T. M., Althoff, R. R., Bagby, R. M., . . . Clark, L. A. (2017). The Hierarchical Taxonomy of Psychopathology (HiTOP): A dimensional alternative to traditional nosologies. *Journal of abnormal psychology, 126*(4), 454.

Koutsouleris, N., Kambeitz-Ilankovic, L., Ruhrmann, S., Rosen, M., Ruef, A., Dwyer, D. B., . . . Haidl, T. (2018). Prediction models of functional outcomes for individuals in the clinical high-risk state for psychosis or with recent-onset depression: a multimodal, multisite machine learning analysis. *JAMA psychiatry, 75*(11), 1156-1172.

Kraepelin, E. (1919). *Dementia praecox and paraphrenia*: Livingstone.

Kraguljac, N. V., Srivastava, A., & Lahti, A. C. (2013). Memory deficits in schizophrenia: a selective review of functional magnetic resonance imaging (FMRI) studies. *Behavioral Sciences, 3*(3), 330-347.

Kribakaran, S., Danese, A., Bromis, K., Kempton, M. J., & Gee, D. G. (2020). Meta-analysis of structural magnetic resonance imaging studies in pediatric posttraumatic stress disorder and comparison with related conditions. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 5*(1), 23-34.

Lalousis, P. A., Schmaal, L., Wood, S. J., Reniers, R. L., Barnes, N. M., Chisholm, K., . . . Hwang, G. (2022). Neurobiologically based stratification of recent-onset depression and psychosis: identification of two distinct transdiagnostic phenotypes. *Biological psychiatry, 92*(7), 552-562.

Larosa, A., & Wong, T. P. (2022). The hippocampus in stress susceptibility and resilience: Reviewing molecular and functional markers. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 119*, 110601.

Lau, A., & Tymianski, M. (2010). Glutamate receptors, neurotoxicity and neurodegeneration. *Pflügers Archiv-European Journal of Physiology, 460*, 525-542.

Ledoux, A.-A., Phillips, J. L., Labelle, A., Smith, A., Bohbot, V. D., & Boyer, P. (2013). Decreased fMRI activity in the hippocampus of patients with schizophrenia compared to healthy control participants, tested on a wayfinding task in a virtual town. *Psychiatry Research: Neuroimaging, 211*(1), 47-56.

Lee, M. D., & Wagenmakers, E.-J. (2013). Bayesian cognitive modeling: A practical course.

Levi, P. T., Chopra, S., Pang, J. C., Holmes, A., Gajwani, M., Sassenberg, T. A., . . . Fornito, A. (2023). The effect of using group-averaged or individualized brain parcellations when investigating connectome dysfunction in psychosis. *Network Neuroscience, 7*(4), 1228-1247.

Li, J., Kong, R., Liégeois, R., Orban, C., Tan, Y., Sun, N., . . . Yeo, B. T. (2019). Global signal regression strengthens association between resting-state functional connectivity and behavior. *Neuroimage, 196*, 126-141.

Li, R. R., Lyu, H. L., Liu, F., Lian, N., Wu, R. R., Zhao, J. P., & Guo, W. B. (2018). Altered functional connectivity strength and its correlations with cognitive function in subjects with ultra-high risk for psychosis at rest. *CNS Neuroscience & Therapeutics, 24*(12), 1140-1148.

Li, S., Hu, N., Zhang, W., Tao, B., Dai, J., Gong, Y., . . . Lui, S. (2019). Dysconnectivity of multiple brain networks in schizophrenia: a meta-analysis of resting-state functional connectivity. *Frontiers in Psychiatry, 10*, 482.

Lieberman, J., Girgis, R., Brucato, G., Moore, H., Provenzano, F., Kegeles, L., . . . Corcoran, C. (2018). Hippocampal dysfunction in the pathophysiology of schizophrenia: a selective review and hypothesis for early detection and intervention. *Molecular psychiatry, 23*(8), 1764-1772.

Lieberman, J. A. (1999). Is schizophrenia a neurodegenerative disorder? A clinical and neurobiological perspective. *Biological psychiatry, 46*(6), 729-739.

Lin, A., Wood, S., Nelson, B., Brewer, W., Spiliotacopoulos, D., Bruxner, A., . . . Yung, A. (2011). Neurocognitive predictors of functional outcome two to 13 years after identification as ultra-high risk for psychosis. *Schizophrenia research, 132*(1), 1-7.

Lipska, B. K., Aultman, J. M., Verma, A., Weinberger, D. R., & Moghaddam, B. (2002). Neonatal damage of the ventral hippocampus impairs working memory in the rat. *Neuropsychopharmacology, 27*(1), 47-54.

Lisman, J. E., Coyle, J. T., Green, R. W., Javitt, D. C., Benes, F. M., Heckers, S., & Grace, A. A. (2008). Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends in neurosciences, 31*(5), 234-242.

Lizano, P., Lutz, O., Ling, G., Lee, A. M., Eum, S., Bishop, J. R., . . . Pearlson, G. (2019). Association of choroid plexus enlargement with cognitive, inflammatory, and structural phenotypes across the psychosis spectrum. *American Journal of Psychiatry, 176*(7), 564-572.

Lizano, P., Lutz, O., Ling, G., Lee, A. M., Eum, S., Bishop, J. R., & Keshavan, M. (2019). Association of choroid plexus enlargement with cognitive, inflammatory, and structural phenotypes across the psychosis spectrum. *American Journal of Psychiatry, 176*(7), 564-572.

Lodge, D. J., & Grace, A. A. (2006). The hippocampus modulates dopamine neuron responsivity by regulating the intensity of phasic neuron activation. *Neuropsychopharmacology, 31*(7), 1356-1361.
Logothetis, N. K., & Wandell, B. A. (2004). Interpreting the BOLD signal. *Annu. Rev. Physiol., 66*, 735-769.
Lord, L.-D., Allen, P., Expert, P., Howes, O., Broome, M., Lambiotte, R., . . . Turkheimer, F. E. (2012). Functional brain networks before the onset of psychosis: a prospective fMRI study with graph theoretical analysis. *NeuroImage: Clinical, 1*(1), 91-98.
Lord, L.-D., Allen, P., Expert, P., Howes, O., Lambiotte, R., McGuire, P., . . . Turkheimer, F. E. (2011). Characterization of the anterior cingulate's role in the at-risk mental state using graph theory. *Neuroimage, 56*(3), 1531-1539.
Lu, C., Jin, D., Palmer, N., Fox, K., Kohane, I. S., Smoller, J. W., & Yu, K.-H. (2022). Large-scale real-world data analysis identifies comorbidity patterns in schizophrenia. *Translational psychiatry, 12*(1), 154.
Lun, M. P., Monuki, E. S., & Lehtinen, M. K. (2015). Development and functions of the choroid plexus--cerebrospinal fluid system. *Nature Reviews Neuroscience, 16*(8), 445-457.
Makowski, C., Lewis, J. D., Khundrakpam, B., Tardif, C. L., Palaniyappan, L., Joober, R., . . . Chakravarty, M. M. (2020). Altered hippocampal centrality and dynamic anatomical covariance of intracortical microstructure in first episode psychosis. *Hippocampus, 30*(10), 1058-1072.
Maller, J. J., Welton, T., Middione, M., Callaghan, F. M., Rosenfeld, J. V., & Grieve, S. M. (2019). Revealing the hippocampal connectome through super-resolution 1150-direction diffusion MRI. *Scientific reports, 9*(1), 2418.
Matéos, M., Hacein-Bey, L., Hanafi, R., Mathys, L., Amad, A., Pruvo, J.-P., & Krystal, S. (2023). Advanced imaging in first episode psychosis: a systematic review. *Journal of Neuroradiology, 50*(5), 464-469.
McHugo, M., Armstrong, K., Roeske, M. J., Woodward, N. D., Blackford, J. U., & Heckers, S. (2020). Hippocampal volume in early psychosis: a 2-year longitudinal study. *Translational psychiatry, 10*(1), 306.
McHugo, M., Talati, P., Armstrong, K., Vandekar, S. N., Blackford, J. U., Woodward, N. D., & Heckers, S. (2019). Hyperactivity and reduced activation of anterior hippocampus in early psychosis. *American Journal of Psychiatry, 176*(12), 1030-1038.
Mehta, N. H., Suss, R. A., Dyke, J. P., Theise, N. D., Chiang, G. C., Strauss, S., . . . Babaria, V. (2022). Quantifying cerebrospinal fluid dynamics: A review of human neuroimaging contributions to CSF physiology and neurodegenerative disease. *Neurobiology of Disease*, 105776.
Miklowitz, D. J. (1994). Family risk indicators in schizophrenia. *Schizophrenia bulletin, 20*(1), 137-149.

Misiak, B., Bartoli, F., Carra, G., Stańczykiewicz, B., Gładka, A., Frydecka, D., & Miller, B. J. (2021). Immune-inflammatory markers and psychosis risk: A systematic review and meta-analysis. *Psychoneuroendocrinology, 127*, 10520.

Moghaddam, B., & Javitt, D. (2012). From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. *Neuropsychopharmacology, 37*(1), 4-15.

Montagrin, A., Saiote, C., & Schiller, D. (2018). The social hippocampus. *Hippocampus, 28*(9), 672-679.

Morey, R. D., Rouder, J. N., Jamil, T., & Morey, M. R. D. (2015). Package 'bayesfactor'. *URLh http://cran/r-projectorg/web/packages/BayesFactor/BayesFactor pdf i (accessed 1006 15)*.

Murphy, K., Birn, R. M., Handwerker, D. A., Jones, T. B., & Bandettini, P. A. (2009). The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? *Neuroimage, 44*(3), 893-905.

Nakahara, S., Matsumoto, M., & van Erp, T. G. (2018). Hippocampal subregion abnormalities in schizophrenia: A systematic review of structural and physiological imaging studies. *Neuropsychopharmacology reports, 38*(4), 156-166.

Networkx. Networkx Documentation.

Niendam, T. A., Bearden, C. E., Johnson, J. K., McKinley, M., Loewy, R., O'Brien, M., . . . Cannon, T. D. (2006). Neurocognitive performance and functional disability in the psychosis prodrome. *Schizophrenia research, 84*(1), 100-111.

O'Neill, A., Mechelli, A., & Bhattacharyya, S. (2019). Dysconnectivity of large-scale functional networks in early psychosis: a meta-analysis. *Schizophrenia bulletin, 45*(3), 579-590.

Ohtani, T., Del Re, E., Levitt, J. J., Niznikiewicz, M., Konishi, J., Asami, T., . . . Shenton, M. E. (2018). Progressive symptom-associated prefrontal volume loss occurs in first-episode schizophrenia but not in affective psychosis. *Brain Structure and Function, 223*, 2879-2892.

Pardoe, H. R., Hiess, R. K., & Kuzniecky, R. (2016). Motion and morphometry in clinical and nonclinical populations. *Neuroimage, 135*, 177-185.

Parkes, L., Fulcher, B., Yücel, M., & Fornito, A. (2018). An evaluation of the efficacy, reliability, and sensitivity of motion correction strategies for resting-state functional MRI. *Neuroimage, 171*, 415-436.

Pessoa, L. (2017). A network model of the emotional brain. *Trends in cognitive sciences, 21*(5), 357-371.

Peters, S. K., Dunlop, K., & Downar, J. (2016). Cortico-striatal-thalamic loop circuits of the salience network: a central pathway in psychiatric disease and treatment. *Frontiers in systems neuroscience, 10*, 104.

Platt, S. R. (2007). The role of glutamate in central nervous system health and disease–a review. *The Veterinary Journal, 173*(2), 278-286.

Power, J. D., Plitt, M., Laumann, T. O., & Martin, A. (2017). Sources and implications of whole-brain fMRI signals in humans. *Neuroimage, 146*, 609-625.
Provenzano, F. A., Guo, J., Wall, M. M., Feng, X., Sigmon, H. C., Brucato, G., . . . Lieberman, J. A. (2020). Hippocampal pathology in clinical high-risk patients and the onset of schizophrenia. *Biological psychiatry, 87*(3), 234-242.
Pruim, R. H., Mennes, M., van Rooij, D., Llera, A., Buitelaar, J. K., & Beckmann, C. F. (2015). ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. *Neuroimage, 112*, 267-277.
Raedler, T., Bymaster, F., Tandon, R., Copolov, D., & Dean, B. (2007). Towards a muscarinic hypothesis of schizophrenia. *Molecular psychiatry, 12*(3), 232-246.
Rajput, D., Wang, W.-J., & Chen, C.-C. (2023). Evaluation of a decided sample size in machine learning applications. *BMC bioinformatics, 24*(1), 48.
Rikandi, E., Mäntylä, T., Lindgren, M., Kieseppä, T., Suvisaari, J., & Raij, T. T. (2022). Functional network connectivity and topology during naturalistic stimulus is altered in first-episode psychosis. *Schizophrenia research, 241*, 83-91.
Rosenberg, S. D., Lu, W., Mueser, K. T., Jankowski, M. K., & Cournos, F. (2007). Correlates of adverse childhood events among adults with schizophrenia spectrum disorders. *Psychiatric services, 58*(2), 245-253.
Rowland, L. M., Astur, R. S., Jung, R. E., Bustillo, J. R., Lauriello, J., & Yeo, R. A. (2005). Selective cognitive impairments associated with NMDA receptor blockade in humans. *Neuropsychopharmacology, 30*(3), 633-639.
Saad, Z. S., Gotts, S. J., Murphy, K., Chen, G., Jo, H. J., Martin, A., & Cox, R. W. (2012). Trouble at rest: how correlation patterns and group differences become distorted after global signal regression. *Brain connectivity, 2*(1), 25-32.
Sabaroedin, K., Tiego, J., & Fornito, A. (2023). Circuit-based approaches to understanding corticostriatothalamic dysfunction across the psychosis continuum. *Biological Psychiatry, 93*(2), 113-124.
Samudra, N., Ivleva, E. I., Hubbard, N. A., Rypma, B., Sweeney, J. A., Clementz, B. A., . . . Tamminga, C. A. (2015). Alterations in hippocampal connectivity across the psychosis dimension. *Psychiatry Research: Neuroimaging, 233*(2), 148-157.
Sasabayashi, D., Yoshimura, R., Takahashi, T., Takayanagi, Y., Nishiyama, S., Higuchi, Y., . . . Nakamura, M. (2021). Reduced hippocampal subfield volume in schizophrenia and clinical high-risk state for psychosis. *Frontiers in Psychiatry, 12*, 642048.
Schaefer, J., Giangrande, E., Weinberger, D. R., & Dickinson, D. (2013). The global cognitive impairment in schizophrenia: consistent over decades and around the world. *Schizophrenia research, 150*(1), 42-50.

Schnack, H. G., & Kahn, R. S. (2016). Detecting neuroimaging biomarkers for psychiatric disorders: sample size matters. *Frontiers in Psychiatry, 7*, 180068.
Schultze-Lutter, F., Addington, J., Ruhrmann, S., & Klosterkötter, J. (2007). Schizophrenia proneness instrument, adult version (SPI-A). *Rome: Giovanni Fioriti*.
Schultze-Lutter, F., Klosterkötter, J., & Ruhrmann, S. (2014). Improving the clinical prediction of psychosis by combining ultra-high risk criteria and cognitive basic symptoms. *Schizophrenia research, 154*(1-3), 100-106.
Seeman, P., & Lee, T. (1975). Antipsychotic drugs: direct correlation between clinical potency and presynaptic action on dopamine neurons. *Science, 188*(4194), 1217-1219.
Senay, O., Seethaler, M., Makris, N., Yeterian, E., Rushmore, J., Cho, K. I. K., . . . Szczepankiewicz, F. (2023). A preliminary choroid plexus volumetric study in individuals with psychosis. *Human Brain Mapping, 44*(6), 2465-2478.
Sheffield, J. M., & Barch, D. M. (2016). Cognition and resting-state functional connectivity in schizophrenia. *Neuroscience & biobehavioral reviews, 61*, 108-120.
Shohamy, D., & Turk-Browne, N. B. (2013). Mechanisms for widespread hippocampal involvement in cognition. *Journal of Experimental Psychology: General, 142*(4), 1159.
Smeland, O. B., Wang, Y., Frei, O., Li, W., Hibar, D. P., Franke, B., . . . Chen, C.-H. (2018). Genetic overlap between schizophrenia and volumes of hippocampus, putamen, and intracranial volume indicates shared molecular genetic mechanisms. *Schizophrenia bulletin, 44*(4), 854-864.
Soldevila-Matías, P., Albajes-Eizagirre, A., Radua, J., García-Martí, G., Rubio, J. M., Tordesillas-Gutierrez, D., . . . Oliver, D. (2022). Precuneus and insular hypoactivation during cognitive processing in first-episode psychosis: Systematic review and meta-analysis of fMRI studies. *Revista de psiquiatria y salud mental, 15*(2), 101-116.
Solmi, M., Seitidis, G., Mavridis, D., Correll, C. U., Dragioti, E., Guimond, S., . . . Fornaro, M. (2023). Incidence, prevalence, and global burden of schizophrenia-data, with critical appraisal, from the Global Burden of Disease (GBD) 2019. *Molecular psychiatry*, 1-9.
Solmi, M., Soardo, L., Kaur, S., Azis, M., Cabras, A., Censori, M., . . . Fusar-Poli, P. (2023). Meta-analytic prevalence of comorbid mental disorders in individuals at clinical high risk of psychosis: the case for transdiagnostic assessment. *Molecular psychiatry, 28*(6), 2291-2300.
Steen, R. G., Mull, C., McClure, R., Hamer, R. M., & Lieberman, J. A. (2006). Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. *The British Journal of Psychiatry, 188*(6), 510-518.
Strazielle, N., & Ghersi-Egea, J.-F. (2000). Choroid plexus in the central nervous system: biology and physiopathology. *Journal of neuropathology & experimental neurology, 59*(7), 561-574.

Su, T.-W., Hsu, T.-W., Lin, Y.-C., & Lin, C.-P. (2015). Schizophrenia symptoms and brain network efficiency: A resting-state fMRI study. *Psychiatry Research: Neuroimaging, 234*(2), 208-218.
Sun, N., Liu, M., Liu, P., Zhang, A., Yang, C., Liu, Z., . . . Zhang, K. (2023). Abnormal cortical-striatal-thalamic-cortical circuit centered on the thalamus in MDD patients with somatic symptoms: Evidence from the REST-meta-MDD project. *Journal of affective disorders, 323*, 71-84.
Svancer, P., & Spaniel, F. (2021). Brain ventricular volume changes in schizophrenia. A narrative review. *Neuroscience Letters, 759*, 136065.
Tadayon, E., Moret, B., Sprugnoli, G., Monti, L., Pascual-Leone, A., Santarnecchi, E., & Initiative, A. s. D. N. (2020). Improving choroid plexus segmentation in the healthy and diseased brain: relevance for tau-PET imaging in dementia. *Journal of Alzheimer's Disease, 74*(4), 1057-1068.
Tamminga, C. A., Clementz, B. A., Pearlson, G., Keshavan, M., Gershon, E. S., Ivleva, E. I., & Gibbons, R. (2021). Biotyping in psychosis: using multiple computational approaches with one data set. *Neuropsychopharmacology, 46*(1), 143-155.
Tandon, R., Gaebel, W., Barch, D. M., Bustillo, J., Gur, R. E., Heckers, S., . . . Tsuang, M. (2013). Definition and description of schizophrenia in the DSM-5. *Schizophrenia research, 150*(1), 3-10.
Thakkar, K. N., McCleery, A., Minor, K. S., Lee, J., Humpston, C. S., Chopik, W. J., . . . Park, S. (2023). Moving from risk to resilience in psychosis research. *Nature Reviews Psychology, 2*(9), 537-555.
Tu, P.-C., Lee, Y.-C., Chen, Y.-S., Li, C.-T., & Su, T.-P. (2013). Schizophrenia and the brain's control network: aberrant within- and between-network connectivity of the frontoparietal network in schizophrenia. *Schizophrenia research, 147*(2-3), 339-347.
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., . . . Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage, 15*(1), 273-289.
Uhlhaas, P. J., Gajwani, R., Gross, J., Gumley, A. I., Lawrie, S. M., & Schwannauer, M. (2017). The youth mental health risk and resilience study (YouR-Study). *BMC psychiatry, 17*, 1-8.
Vallone, D., Picetti, R., & Borrelli, E. (2000). Structure and function of dopamine receptors. *Neuroscience & biobehavioral reviews, 24*(1), 125-132.
van den Heuvel, M. P., de Lange, S. C., Zalesky, A., Seguin, C., Yeo, B. T., & Schmidt, R. (2017). Proportional thresholding in resting-state fMRI functional connectivity networks and consequences for patient-control connectome studies: Issues and recommendations. *Neuroimage, 152*, 437-449.
Van Den Heuvel, M. P., & Fornito, A. (2014). Brain networks in schizophrenia. *Neuropsychology review, 24*, 32-48.

Van Dijk, K. R., Sabuncu, M. R., & Buckner, R. L. (2012). The influence of head motion on intrinsic functional connectivity MRI. *Neuroimage, 59*(1), 431-438.
van Doorn, J., van den Bergh, D., Böhm, U., Dablander, F., Derks, K., Draws, T., . . . Haaf, J. M. (2021). The JASP guidelines for conducting and reporting a Bayesian analysis. *Psychonomic Bulletin & Review, 28*, 813-826.
Van Erp, T. G., Greve, D. N., Rasmussen, J., Turner, J., Calhoun, V. D., Young, S., . . . Glover, G. H. (2014). A multi-scanner study of subcortical brain volume abnormalities in schizophrenia. *Psychiatry Research: Neuroimaging, 222*(1-2), 10-16.
Van Erp, T. G., Hibar, D. P., Rasmussen, J. M., Glahn, D. C., Pearlson, G. D., Andreassen, O. A., . . . Dale, A. M. (2016). Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Molecular psychiatry, 21*(4), 547-553.
van Erp, T. G., Hibar, D. P., Rasmussen, J. M., Glahn, D. C., Pearlson, G. D., Andreassen, O. A., & Turner, J. A. (2016). Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Molecular Psychiatry, 21*(4), 547-553.
Van Erp, T. G., Walton, E., Hibar, D. P., Schmaal, L., Jiang, W., Glahn, D. C., & Fatouros-Bergman, H. (2018). Cortical brain abnormalities in 4474 individuals with schizophrenia and 5098 control subjects via the enhancing neuro imaging genetics through meta analysis (ENIGMA) consortium. *Biological psychiatry, 84*(9), 644-654.
van Haren, N. E., Schnack, H. G., Koevoets, M. G., Cahn, W., Pol, H. E. H., & Kahn, R. S. (2016). Trajectories of subcortical volume change in schizophrenia: a 5-year follow-up. *Schizophrenia research, 173*(3), 140-145.
Vargas, T., Dean, D. J., Osborne, K. J., Gupta, T., Ristanovic, I., Ozturk, S., . . . Mittal, V. A. (2018). Hippocampal subregions across the psychosis spectrum. *Schizophrenia bulletin, 44*(5), 1091-1099.
Velakoulis, D., Wood, S. J., Wong, M. T., McGorry, P. D., Yung, A., Phillips, L., . . . Desmond, P. (2006). Hippocampal and amygdala volumes according to psychosis stage and diagnosis: A magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra–high-risk individuals. *Archives of general psychiatry, 63*(2), 139-149.
Videbech, P., & Ravnkilde, B. (2004). Hippocampal volume and depression: a meta-analysis of MRI studies. *American Journal of Psychiatry, 161*(11), 1957-1966.
Vieira, S., Gong, Q.-y., Pinaya, W. H., Scarpazza, C., Tognin, S., Crespo-Facorro, B., . . . Scheepers, F. E. (2020). Using machine learning and structural neuroimaging to detect first episode psychosis: reconsidering the evidence. *Schizophrenia bulletin, 46*(1), 17-26.
Vieira, S., Gong, Q., Scarpazza, C., Lui, S., Huang, X., Crespo-Facorro, B., . . . Scheepers, F. (2021). Neuroanatomical abnormalities in first-episode psychosis across independent samples: a multi-centre mega-analysis. *Psychological medicine, 51*(2), 340-350.

Vieira, S., Pinaya, W. H., & Mechelli, A. (2017). Using deep learning to investigate the neuroimaging correlates of psychiatric and neurological disorders: Methods and applications. *Neuroscience & biobehavioral reviews, 74*, 58-75.

Vissink, C. E., Winter-van Rossum, I., Cannon, T. D., Fusar-Poli, P., Kahn, R. S., & Bossong, M. G. (2022). Structural brain volumes of individuals at clinical high risk for psychosis: a meta-analysis. *Biological Psychiatry Global Open Science, 2*(2), 147-152.

Vita, A., De Peri, L., Deste, G., & Sacchetti, E. (2012). Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies. *Translational psychiatry, 2*(11), e190-e190.

Wainer, J., & Cawley, G. (2021). Nested cross-validation when selecting classifiers is overzealous for most practical applications. *Expert Systems with Applications, 182*, 115222.

Walter, A., Suenderhauf, C., Harrisberger, F., Lenz, C., Smieskova, R., Chung, Y., . . . Bendfeldt, K. (2016). Hippocampal volume in subjects at clinical high-risk for psychosis: A systematic review and meta-analysis. *Neuroscience & biobehavioral reviews, 71*, 680-690.

Waszczuk, K., Rek-Owodziń, K., Tyburski, E., Mak, M., Misiak, B., & Samochowiec, J. (2021). Disturbances in white matter integrity in the ultra-high-risk psychosis state—a systematic review. *Journal of Clinical Medicine, 10*(11), 2515.

Williams, M. R., Macdonald, C., & Turkheimer, F. E. (2023). Histological examination of choroid plexus epithelia changes in schizophrenia. *Brain, Behavior, and Immunity, 111*, 292-297.

Wilson, S., Bair, J., Thomas, K. M., & Iacono, W. G. (2017). Problematic alcohol use and reduced hippocampal volume: a meta-analytic review. *Psychological medicine, 47*(13), 2288-2301.

Winton-Brown, T. T., Fusar-Poli, P., Ungless, M. A., & Howes, O. D. (2014). Dopaminergic basis of salience dysregulation in psychosis. *Trends in neurosciences, 37*(2), 85-94.

Wood, S. J., Kennedy, D., Phillips, L. J., Seal, M. L., Yücel, M., Nelson, B., . . . Velakoulis, D. (2010). Hippocampal pathology in individuals at ultra-high risk for psychosis: a multi-modal magnetic resonance study. *Neuroimage, 52*(1), 62-68.

Wood, S. J., Velakoulis, D., Smith, D. J., Bond, D., Stuart, G. W., McGorry, P. D., . . . Desmond, P. (2001). A longitudinal study of hippocampal volume in first episode psychosis and chronic schizophrenia. *Schizophrenia research, 52*(1-2), 37-46.

Wyatt, R. J. (1991). Neuroleptics and the natural course of schizophrenia. *Schizophrenia bulletin, 17*(2), 325-351.

Xiong, Y., Hong, H., Liu, C., & Zhang, Y. Q. (2023). Social isolation and the brain: effects and mechanisms. *Molecular psychiatry, 28*(1), 191-201.

Yan, C.-G., Craddock, R. C., He, Y., & Milham, M. P. (2013). Addressing head motion dependencies for small-world topologies in functional connectomics. *Frontiers in human neuroscience, 7*, 910.

Yao, L., Lui, S., Liao, Y., Du, M.-Y., Hu, N., Thomas, J. A., & Gong, Q.-Y. (2013). White matter deficits in first episode schizophrenia: an activation likelihood estimation meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 45*, 100-106.

Yao, N., Winkler, A. M., Barrett, J., Book, G. A., Beetham, T., Horseman, R., . . . Mathias, S. (2017). Inferring pathobiology from structural MRI in schizophrenia and bipolar disorder: modeling head motion and neuroanatomical specificity. *Human brain mapping, 38*(8), 3757-3770.

Young, J., Kempton, M. J., & McGuire, P. (2016). Using machine learning to predict outcomes in psychosis. *The Lancet Psychiatry, 3*(10), 908-909.

Yung, A., Phillips, L., Yuen, H., & McGorry, P. (2006). Comprehensive assessment of at risk mental state. *Parkville Victoria: The PACE Clinic, ORYGEN Research Centre, University of Melbourne, Department of Psychiatry*.

Zarif, H., Nicolas, S., Guyot, M., Hosseiny, S., Lazzari, A., Canali, M. M., & Petit-Paitel, A. (2018). CD8+ T cells are essential for the effects of enriched environment on hippocampus-dependent behavior, hippocampal neurogenesis and synaptic plasticity. *Brain, Behavior, and Immunity, 69*, 235-254.

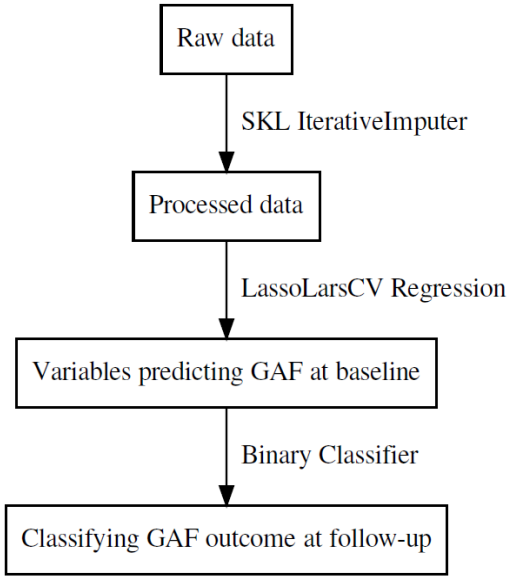
Zhang, T., Xu, L., Tang, X., Wei, Y., Hu, Q., Hu, Y., . . . Li, C. (2020). Real-world effectiveness of antipsychotic treatment in psychosis prevention in a 3-year cohort of 517 individuals at clinical high risk from the SHARP (ShangHai At Risk for Psychosis). *Australian & New Zealand Journal of Psychiatry, 54*(7), 696-706.

Zhao, L., Taso, M., Dai, W., Press, D. Z., & Alsop, D. C. (2020). Non-invasive measurement of choroid plexus apparent blood flow with arterial spin labeling. *Fluids and Barriers of the CNS, 17*, 1-11.

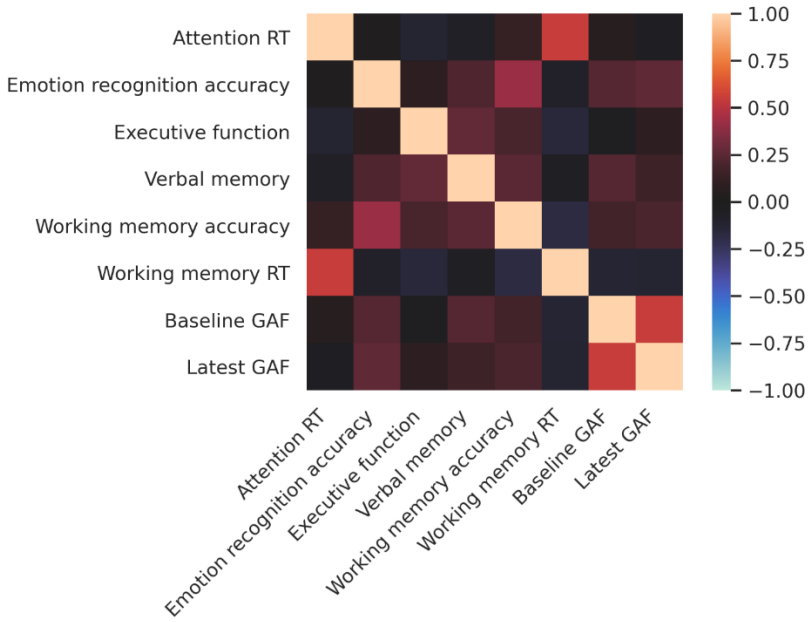
Zhou, Y. F., Huang, J. C., Zhang, P., Fan, F. M., Chen, S., Fan, H. Z., . . . Hong, L. E. (2020). Choroid Plexus Enlargement and Allostatic Load in Schizophrenia. *Schizophr Bull, 46*(3), 722-731. doi:10.1093/schbul/sbz100

Zikidi, K., Gajwani, R., Gross, J., Gumley, A. I., Lawrie, S. M., Schwannauer, M., . . . Uhlhaas, P. J. (2020). Grey-matter abnormalities in clinical high-risk participants for psychosis. *Schizophrenia research, 226*, 120-128.

Appendix 1: Supplementary Materials for Chapter 1

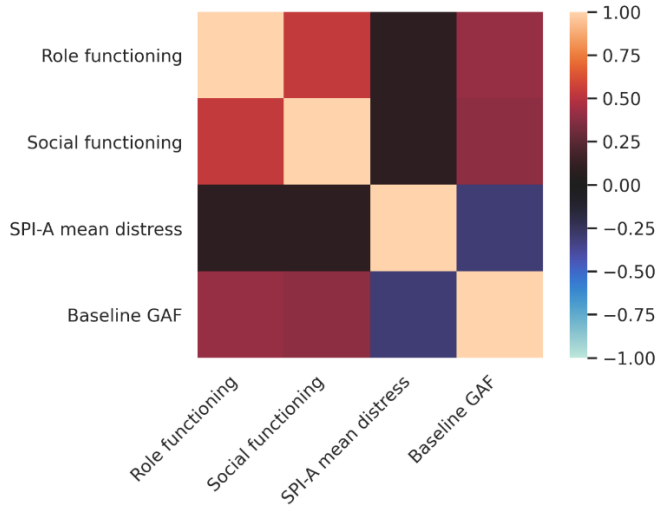


Supplementary Figure 1: Flowchart showing the sequence of analyses used. Data was first prepared for regression, variables associated with GAF scores at baseline were identified, and GAF outcomes were classified using those variables.

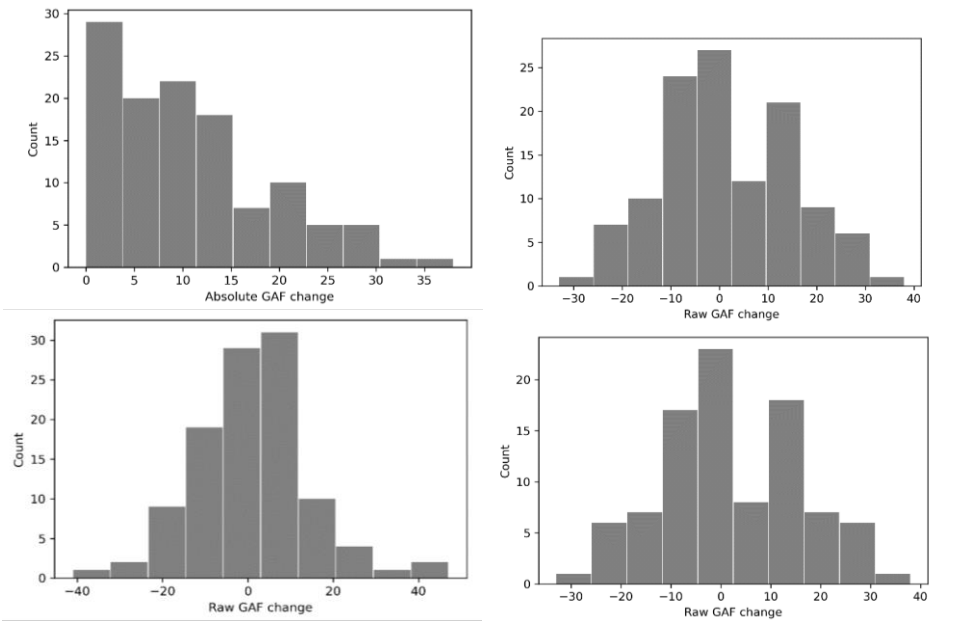


Supplementary Figure 2: Correlation matrix showing the relationship between nonzero predictors and baseline GAF scores for the cognitive LASSO-LARS regression model for the CHR-P group (N = 146). The

latest GAF score is added to this figure for visualisation purposes only and has not been entered in the regression model.



Supplementary Figure 3: Correlation matrix showing the relationship between nonzero predictors and baseline GAF scores for the combined LASSO-LARS regression model for the CHR-N group (N = 47).



Supplementary Figure 4: GAF score changes in the CHR-P group: (A) absolute change in GAF scores between baseline and 6-12 month follow-up (N = 146); (B) raw change in GAF scores between baseline and 6-12 month follow-up (N = 146); (C) raw change in GAF scores

between baseline and 6-month follow-up (N = 108); (D) raw change in GAF scores between baseline and 12-month follow-up (N = 94).

Supplementary Table 1. Demographic, clinical, functioning and cognitive characteristics across sites for CHR-P participants (N = 146)

Variable	Glasgow (N = 109)	Edinburgh (N = 37)	*p*-value
Age (years), mean (SD)	20.79 (3.95)	23.46 (4.39)	< .001
Gender, female n (%)	78 (71.6)	26 (70.3)	.881
Education (years), mean (SD)	14.51 (2.73)	16.95 (3.39)	< .001
CAARMS severity, median (range)	24 (0-74)	34 (12-72)	.006
CAARMS mean distress, median (range)	25 (0-86)	39 (0-85)	.005
SPI-A severity, median (range)	6 (0-74)	7 (0-39)	.987
SPI-A mean distress, median (range)	3 (0-28)	4 (0-12)	.339
CHR-P criteria subgroup, n (%)			
CAARMS	33 (30.3)	12 (32.4)	.806
SPI-A	33 (30.3)	4 (10.8)	.019
CAARMS/SPI-A	43 (39.4)	21 (56.8)	.067
ACES total, median (range)	2 (0-8)	2 (0-6)	.991
Comorbidity, n (%)			
Anxiety disorder	80 (73.4)	24 (64.9)	.322
Mood disorder	75 (68.8)	22 (59.5)	.298
Alcohol abuse/dependence	31 (28.4)	15 (40.5)	.171
Drug abuse/dependence	19 (17.4)	5 (13.5)	.579
Eating disorder	5 (4.6)	6 (16.2)	.021
Medication, n (%)			

Antipsychotic	3 (2.8)	1 (2.7)	.987
Mood stabiliser	2 (1.8)	2 (5.4)	.250
Antidepressant	32 (29.4)	21 (56.8)	.003
Anti-anxiety	4 (3.7)	6 (16.2)	.009
GAF, median (range)	58 (21-95)	58 (40-80)	.715
Poor baseline functioning, n (%)	79 (72.5)	27 (73.0)	.953
PFO, n (%)	51 (46.8)	19 (51.4)	.840
Social functioning, median (range)	8 (3-10)	8 (6-9)	.474
Role functioning, median (range)	8 (3-9)	8 (4-9)	.711
PAS average, median (range)	1.26 (0-3.43)	1.14 (0.29-2.50)	.984
BACS, mean (SD)			
Verbal memory	-0.47 (1.14)	0.50 (1.12)	< .001
Motor speed	-0.60 (1.22)	-1.05 (1.14)	.017
Attention & processing speed	-0.45 (1.12)	-0.57 (1.21)	.452
Verbal fluency	-0.15 (1.17)	0.09 (1.41)	.187
Executive function	-0.11 (1.38)	0.31 (1.16)	.093
Working memory	-0.29 (1.35)	0.53 (1.42)	.001
Composite score	-0.75 (1.61)	-0.10 (1.91)	.051
CNB, mean (SD)			
Emotion recognition accuracy	-0.16 (1.13)	-0.19 (1.12)	.763
Emotion recognition RT	0.12 (1.19)	1.97 (1.77)	< .001
Attention accuracy	-0.72 (2.58)	-0.69 (2.68)	.943
Attention RT	-0.05 (0.88)	-0.27 (0.84)	.142
Working memory accuracy	-0.33 (1.67)	-0.62 (1.76)	.298
Working memory RT	-0.04 (0.81)	-0.06 (0.86)	.941

Note. CHR-P, clinical high-risk for psychosis; CAARMS, Comprehensive Assessment of At-Risk Mental States; SPI-A, Schizophrenia Proneness Instrument, Adult version; ACES, Adverse Childhood Experience Scale; GAF, Global Assessment of Functioning; PFO, poor functional outcome; PAS,

Premorbid Adjustment Scale; BACS, Brief Assessment of Cognition in Schizophrenia; CNB, Penn Computerized Neurocognitive Battery; RT, response time

Supplementary Table 2: Permutation feature importance scores for nonzero variables for the CHR-P (N= 146) and CHR-N (N = 47) LASSO-LARS baseline models

Variable	Permutation feature importance score		
	CHR-P combined model	CHR-P cognitive model	CHR-N combined model
Social functioning	0.18		0.04
PAS average	0.04		
Role functioning	0.04		0.10
Working memory RT	0.01	0.04	
SPI-A mean distress	0.01		0.05
ACES total	0.02		
Motor speed	< 0.01		
Verbal memory	< 0.01	0.08	
Emotion recognition accuracy	< 0.01	0.05	
Total CAARMS severity	0.05		
SPI-A severity	0.01		
CAARMS mean distress	0.01		

Attention RT	0.02
Executive function	0.01
Working memory RT	0.04

Note. CHR-P, clinical high-risk for psychosis; CHR-N, clinical high-risk-negative; CAARMS, Comprehensive Assessment of At-Risk Mental States; SPI-A, Schizophrenia Proneness Instrument, Adult version; ACES, Adverse Childhood Experience Scale; GAF, Global Assessment of Functioning; PAS, Premorbid Adjustment Scale; RT, response time. Here, importance (i) for variable j is calculated using the R2 score for the fitted model, and new R2 scores ($S_{k,j}$) obtained after randomly shuffling variable column j for k iterations in the following manner:

$$i_j = s - \frac{1}{K}\sum_{k=1}^{K} s_{k,j}$$

Supplementary Table 3: Nonzero coefficients and variable significance for the combined LASSO-LARS model for the CHR-P group (N = 146).

Variable	**Coefficient (cv.glmnet)**	**Coefficient (selectiveInference)**	***p*-value (selectiveInference)**
Verbal memory	0.20	0.57	.464
SPI-A mean distress	-0.18	-0.27	.370
Executive function	0	0	-
ACES total	-0.49	-0.76	.116
Motor speed	-0.15	1.18	.116
Verbal fluency	0	0	-
Attention & processing speed	0	0	-
BACS composite score	0	0	-
CAARMS mean distress	-0.02	-0.05	.416
Emotion recognition RT	0	0	-

Working memory accuracy	0	0	-
PAS average	-2.08	-2.79	.071
Emotion recognition accuracy	0.06	0.52	.539
Total CAARMS severity	-0.10	-0.09	.256
SPI-A severity	-0.05	-0.08	.493
Role functioning	1.22	1.42	.119
Social functioning	2.97	2.96	.002
Working memory	0	0	-
Working memory RT	-0.83	-2.19	.051
Attention RT	0	0	-

Note. CHR-P, clinical high-risk for psychosis; CHR-N, clinical high-risk-negative; CAARMS, Comprehensive Assessment of At-Risk Mental States; SPI-A, Schizophrenia Proneness Instrument, Adult version; ACES, Adverse Childhood Experience Scale; GAF, Global Assessment of Functioning; PAS, Premorbid Adjustment Scale; RT, response time. Coefficients were calculated using the R packages glmnet and selectiveInference, whereby the former is a different implementation of the algorithm used in the main text. The second set of coefficients and *p*-values were obtained using the package selectiveInference, which implements a procedure proposed by Lockhart et al. (2014). Due to implementation differences, the coefficients obtained through the two different functions differ slightly from each other; and both differ from those obtained using Python because random state settings do not transfer between platforms.

Appendix 2: Supplementary Materials for Chapter 2

Supplementary Table 1: Subcortical volumes and linear model analyses

Subcortical Volumes (mean mm, SD)				
	HC	CHR-N	CHR-P	FEP
Amygdala	1286 (219.2)	1275 (203.3)	1272 (197.1)	1246 (186.4)
Caudate	3822 (415.2)	3767 (434.7)	3750 (412)	3823 (475.1)
Hippocampus	4069 (328.5)	4108 (366.9)	3908 (428.7)	3892 (416.8)
Nucleus Accumbens	533.9 (87.72)	514.4 (84.79)	533 (77.47)	540.1 (96.8)
Pallidum	1801 (194.8)	1762 (143.7)	1763 (178.9)	1852 (181.8)
Putamen	5380 (521.7)	5197 (467.6)	5205 (552.3)	5440 (590.7)
Thalamus	8144 (699.1)	8062 (617)	7979 (744.7)	8169 (737.3)
Subcortex Linear Models, hemispheres averaged (t, p)				
Amygdala	16.71 (< 0.001)	0.17 (0.863)	-0.08 (0.939)	-1.9 (0.059)
Caudate	30.8 (< 0.001)	-0.24 (0.813)	-1.48 (0.140)	-1.04 (0.300)
Hippocampus	29.36 (< 0.001)	1.22 (0.225)	-2.38 (0.018)	-3.75 (<0.001)
Nucleus Accumbens	17.54 (< 0.001)	-0.73 (0.46)	0.28 (0.78)	-0.64 (0.53)
Pallidum	35.05 (< 0.001)	-0.49 (0.624)	-1.28 (0.202)	-0.09 (0.930)
Putamen	33.67 (< 0.001)	-1.36 (0.176)	-2.4 (0.017)	-0.78 (0.433)
Thalamus	44.36 (< 0.001)	0.41 (0.682)	-1.43 (0.153)	-2.25 (0.025)
Subcortex Linear Models, left hemispere (t, p)				
	HC [intercept]	CHR-N	CHR-P	FEP

Amygdala	13.65 (<0.001)	1.18 (0.239)	0.42 (0.678)	-1.88 (0.061)
Caudate	30.02 (<0.001)	0.16 (0.873)	-1.01 (0.314)	-1.35 (0.179)
Hippocampus	27.15 (<0.001)	0.57 (0.566)	-2.69 (0.008)	-3.69 (<0.001)
Nucleus Accumbens	13.78 (<0.001)	-1.11 (0.27)	-0.28 (0.78)	-0.55 (0.58)
Pallidum	31.35 (<0.001)	-0.36 (0.72)	-0.50 (0.61)	0.38 (0.71)
Putamen	32.78 (<0.001)	-1.81 (0.071)	-2.51 (0.013)	-0.60 (0.549)
Thalamus	44.36 (<0.001)	0.41 (0.682)	-1.43 (0.153)	-2.25 (0.025)

Subcortex Linear Models, right hemisphere (t, p)

	HC [intercept]	CHR-N	CHR-P	FEP
Amygdala	14.99 (<0.001)	-0.98 (0.330)	-0.59 (0.556)	-1.34 (0.182)
Caudate	29.08 (<0.001)	-0.61 (0.541)	-1.83 (0.069)	-0.65 (0.518)
Hippocampus	25.36 (<0.001)	1.60 (0.112)	-1.58 (0.116)	-3.02 (0.003)
Nucleus Accumbens	17.03 (<0.001)	-0.18 (0.86)	0.78 (0.44)	-0.56 (0.25)
Pallidum	33.67 (<0.001)	-0.56 (0.577)	-1.91 (0.057)	-0.57 (0.567)
Putamen	32.61 (<0.001)	-0.82 (0.411)	-2.15 (0.033)	-0.92 (0.356)
Thalamus	43.43 (<0.001)	0.78 (0.438)	-1.00 (0.319)	-1.83 (0.069)

Subcortex Linear Models (additional covariates), left hemispere (t, p)

	HC [intercept] (N=48)	CHR-N (N=35)	CHR-P (N=107)	FEP (N=13)	TBV	Age	Education	Handedness (right/left ratio)
Amygdala	11.57 (<0.001)	-0.19 (0.853)	0.40 (0.690)	-0.77 (0.444)	5.79 (<0.001)	-0.15 (0.883)	1.99 (0.048)	1.52 (0.131)

Caudate	25.16 (<0.001)	-0.16 (0.875)	-0.63 (0.532)	1.49 (0.138)	8.68 (<0.001)	-2.16 (0.032)	0.36 (0.720)	1.10 (0.271)
Hippocampus	20.83 (<0.001)	1.05 (0.294)	-1.82 (0.070)	-1.86 (0.065)	6.40 (<0.001)	1.27 (0.206)	0.67 (0.504)	1.69 (0.092)
Nucleus Accumbens	14.33 (<0.001)	-0.44 (0.658)	0.70 (0.486)	0.95 (0.343)	7.20 (<0.001)	-0.61 (0.542)	1.66 (0.098)	0.55 (0.582)
Pallidum	27.51 (<0.001)	-0.64 (0.525)	-0.15 (0.883)	0.79 (0.432)	12.84 (<0.001)	-0.72 (0.470)	2.24 (0.026)	0.88 (0.382)
Putamen	29.74 (<0.001)	-1.74 (0.083)	-1.62 (0.106)	0.80 (0.424)	12.50 (<0.001)	-1.22 (0.225)	1.37 (0.173)	1.26 (0.208)
Thalamus	38.66 (<0.001)	0.86 (0.390)	-0.49 (0.622)	-0.09 (0.928)	17.31 (<0.001)	0.49 (0.627)	1.75 (0.081)	1.61 (0.110)

Subcortex Linear Models additional covariates), right hemisphere (t, p)

	HC [intercept]	CHR-N	CHR-P	FEP	TBV	Age	Education	Handedness
Amygdala	11.48 (<0.001)	0.51 (0.61)	-0.15 (0.88)	-0.43 (0.67)	4.10 (<0.001)	0.70 (0.49)	0.28 (0.78)	0.06 (0.95)
Caudate	25.68 (<0.001)	-0.51 (0.61)	-1.16 (0.25)	-0.86 (0.39)	9.25 (<0.001)	-1.20 (0.23)	-0.18 (0.86)	0.40 (0.69)
Hippocampus	22.86 (<0.001)	0.57 (0.568)	-2.28 (0.024)	-1.85 (0.066)	6.88 (<0.001)	0.73 (0.463)	0.19 (0.849)	2.23 (0.027)
Nucleus Accumbens	13.55 (<0.001)	-0.78 (0.44)	0.32 (0.75)	0.95 (0.34)	6.70 (<0.001)	0.36 (0.72)	-0.14 (0.88)	1.63 (0.10)
Pallidum	29.52 (<0.001)	-0.19 (0.85)	-0.79 (0.43)	1.54 (0.13)	14.06 (<0.001)	-0.06 (0.95)	1.64 (0.10)	0.69 (0.49)
Putamen	29.49 (<0.001)	-1.15 (0.252)	-1.95 (0.053)	0.66 (0.511)	12.54 (<0.001)	-1.28 (0.204)	1.24 (0.217)	1.09 (0.276)
Thalamus	37.42 (<0.001)	0.86 (0.39)	-0.47 (0.64)	-0.03 (0.98)	15.98 (<0.001)	0.49 (0.63)	1.45 (0.15)	1.65 (0.10)

Note. p-values shown are uncorrected. Sample sizes for the additional covariate analysis are smaller due to missing data.

Supplementary Table 2: Correlations between hippocampal volumes and clinical severity, functioning and cognitive performance

Correlations with hippocampal volume (CHR-P group)				
	Right hippocampus r	p	Left hippocampus r	p
Total CAARMS severity	0.083	0.389	0.082	0.394
CAARMS UTC	0.035	0.716	0.067	0.486
CAARMS NBI	0.031	0.743	-0.006	0.953
CAARMS PA	0.095	0.320	0.019	0.841
CAARMS DS	0.117	0.223	0.191	0.117
Total SPI-A severity	0.120	0.203	0.082	0.394
GAF 0	-0.141	0.140	-0.089	0.345
GAF 6m	-0.118	0.266	0.069	-0.118
GAF 12m	0.088	0.452	0.282	0.013
BACS composite score	-0.022	0.859	0.046	0.703
BACS verbal fluency	-0.022	0.857	0.046	0.704
BACS working memory	-0.035	0.771	-0.034	0.779
BACS ToL	-0.022	0.858	0.046	0.704
BACS motor speed	-0.022	0.858	0.046	0.703

BACS symbol coding	-0.021	0.859	0.046	0.703

BACS, Brief Assessment of Cognition in Schizophrenia; CAARMS, Comprehensive Assessment of At Risk Mental States; HC, healthy controls; CHR-N, clinical risk-negative; CHR-P, clinical high-risk positive; FEP, first-episode psychosis; GAF, global assessment of functioning; SPI-A, Schizophrenia Proneness Instrument, Adult version; SD, standard deviation of the mean; AD, antidepressant; AP, antipsychotic

Note. P-values are shown without correction.

Supplementary Table 3: Hippocampal shape analysis

Hippocampal shape analysis			
	Peak F	p	Peak coordinates (x, y ,z)*
HC vs CHR-P			
right	25.050	0.070 NS	
left	8.120	0.530 NS	
HC vc CHR-N			
right	8.530	0.290 NS	
left	10.360	0.170 NS	
HC vs FEP			
right	16.140	<0.01	116, 105, 50
left	18.910	<0.001	62, 106, 50
CHR-P vs FEP			
right	10.520	0.230 NS	

left	19.910	0.010 NS	120, 103, 61

Supplementary Table 4: Effects of antidepressant use on subcortical volumes in the CHR-P group

Antidepressant effects on subcortical volumes		
	t	p
AD vs no AD (CHR-P)		
Amydgala		
right	-1.155	0.251
left	-1.455	0.149
Caudate		
right	1.549	0.124
left	1.119	0.266
Hippocampus		
right	0.097	0.923
left	0.638	0.525
Nucleus Accumbens		
right	-0.710	0.479
left	0.525	0.601
Pallidum		
right	-0.342	0.733
left	-0.749	0.455
Putamen		
right	-0.106	0.916

left	-0.189	0.850
Thalamus		
right	-0.943	0.348
left	-0.660	0.510

Supplementary Table 5: Effects of antipsychotic use on subcortical volumes in the FEP group

AP vs no AP (FEP)		
Amydgala		
right	1.334	0.205
left	-0.240	0.814
Caudate		
right	0.486	0.635
left	1.273	0.225
Hippocampus		
right	1.240	0.243
left	0.654	0.524
Nucleus Accumbens		
right	0.157	0.878
left	-0.229	0.820
Pallidum		

right	0.295	0.772
left	0.270	0.792
Putamen		
right	-0.509	-0.620
left	-0.125	0.903
Thalamus		
right	-0.129	0.899
left	-0.314	0.759

Note: Data only available for 15 FEP subjects

Supplementary Table 6: Relationship between GAF scores and hippocampal volumes in the CHR-P group

Relationship between hippocampal volumes and functional outcomes		
	Z (binomial GLM)	p
Baseline GAF	-0.550	0.580
GAF (6m)	0.980	0.330
GAF (12m)	2.510	0.012

Appendix 3: Supplementary Materials for Chapter 3

Supplementary Table 1: Model coefficients and BF01 for all groups for CP volumes obtained using GMM, with original scaling. Mean posterior estimate and BF01 are taken from Bayesian linear models, t and p values are taken from frequentist testing. All models compare HC versus the clinical group listed, with HC at the intercept, and using ventricular volume and age as covariates. BF01 is pertaining to the model including group vs. the null model as described in Methods.

Model	Variable	Posterior (M)	t	p	BF01
CHR-N	(Intercept)	702.01	8.79	<.001	
	Group	-6.48	0.02	0.982	27.83 ±1.21%
	VV	0.038	9.25	<.001	
	VV * Group	-0.001	-0.29	0.769	
	Age	2.64	0.60	0.551	
CHR-P	(Intercept)	684.05	8.79	<.001	
	Group	-15.68	-0.78	0.436	15.29 ±1.2%
	VV	0.04	9.25	<.001	
	VV * Group	-0.0004	-0.04	0.971	
	Age	2.24	0.60	0.551	
FEP	(Intercept)	715.63	8.79	<.001	
	Group	-22.78	0.37	0.715	2.565 ±1.19%
	VV	0.035	9.25	<.001	
	VV * Group	-0.005	-1.55	0.122	
	Age	2.13	0.60	0.551	

SCZ	(Intercept)	747.22	8.79	<.001	
	Group	-6.30	1.44	0.152	3.732 ±1.11%
	VV	0.03	9.25	<.001	
	VV * Group	-0.01	-1.95	0.053	
	Age	1.58	0.60	0.551	

Supplementary Table 2: Model coefficients and BF01 for all groups for CP volumes obtained using Freesurfer. Mean posterior estimate and BF01 are taken from Bayesian linear models, t and p values are taken from frequentist testing. All models compare HC versus the clinical group listed, with HC at the intercept, and using ventricular volume and age as covariates. BF01 is pertaining to the model including group vs. the null model as described in Methods.

Model	Variable	Posterior (M)	t	p	BF01
CHR-N	(Intercept)	449.22	16.05	<0.001	
	Group	-7.72	-0.74	0.463	13.55 ±1.23%
	VV	126.78	9.86	<0.001	
	VV * Group	12.47	1.07	0.288	
	Age	0.88	0.40	0.693	
CHR-P	(Intercept)	434.15	16.05	<0.001	
	Group	-16.74	-2.27	0.024	3.093 ±1.09%
	VV	121.48	9.86	<0.001	
	VV * Group	5.79	0.75	0.452	
	Age	0.89	0.40	0.693	

FEP	(Intercept)	463.78	16.05	<0.001	
	Group	-16.28	-1.63	0.103	3.28 ±1.21%
	VV	97.99	9.86	<0.001	
	VV * Group	-14.56	-1.75	0.081	
	Age	1.72	0.40	0.693	
SCZ	(Intercept)	514.62	16.05	<0.001	
	Group	24.53	1.83	0.069	7.108 ±1.86%
	VV	112.06	9.86	<0.001	
	VV * Group	-1.8	-0.25	0.806	
	Age	0.11	0.40	0.693	

Appendix 4: Supplementary Materials for Chapter 4

Supplementary Information

Supplement I: fmriprep preprocessing

We used the fmriprep package (21 series) with the following command: /opt/conda/bin/fmriprep /data /out participant --use-aroma --skip-bids-validation --bold2t1w-dof 12 --output-spaces MNI152NLin2009cAsym. The following description is automatically provided by fmriprep and is intended to be provided unaltered; please note that it refers to one subject due to the command being run in a loop, but the same processing was applied to the entire dataset. No changes were made to the below text except for formatting adjustments:

Results included in this manuscript come from preprocessing performed using *fMRIPrep* 21.0.2 (Esteban, Markiewicz, et al. (2018); Esteban, Blair, et al. (2018); RRID:SCR_016216), which is based on *Nipype* 1.6.1 (K. Gorgolewski et al. (2011); K. J. Gorgolewski et al. (2018); RRID:SCR_002502).

Preprocessing of B_0 inhomogeneity mappings

A total of 1 fieldmaps were found available within the input BIDS structure for this particular subject. A B_0 nonuniformity map (or *fieldmap*) was estimated from the phase-drift map(s) measure with two consecutive GRE (gradient-recalled echo) acquisitions. The corresponding phase-map(s) were phase-unwrapped with prelude (FSL 6.0.5.1:57b01774).

Anatomical data preprocessing

A total of 1 T1-weighted (T1w) images were found within the input BIDS dataset. The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al. 2010), distributed with ANTs 2.3.3 (Avants et al. 2008, RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a *Nipype* implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was

performed on the brain-extracted T1w using fast (FSL 6.0.5.1:57b01774, RRID:SCR_002823, Zhang, Brady, and Smith 2001). Brain surfaces were reconstructed using recon-all (FreeSurfer 6.0.1, RRID:SCR_001847, Dale, Fischl, and Sereno 1999), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (RRID:SCR_002438, Klein et al. 2017). Volume-based spatial normalization to two standard spaces (MNI152NLin2009cAsym, MNI152NLin6Asym) was performed through nonlinear registration with antsRegistration (ANTs 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The following templates were selected for spatial normalization: *ICBM 152 Nonlinear Asymmetrical template version 2009c* [Fonov et al. (2009), RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym], *FSL's MNI ICBM 152 non-linear 6th Generation Asymmetric Average Brain Stereotaxic Registration Model* [Evans et al. (2012), RRID:SCR_002823; TemplateFlow ID: MNI152NLin6Asym].

Functional data preprocessing

For each of the 1 BOLD runs found per subject (across all tasks and sessions), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using mcflirt (FSL 6.0.5.1:57b01774, Jenkinson et al. 2002). BOLD runs were slice-time corrected to 0.962s (0.5 of slice acquisition range 0s-1.93s) using 3dTshift from AFNI (Cox and Hyde 1997, RRID:SCR_005927). The BOLD time-series (including slice-timing correction when applied) were resampled onto their original, native space by applying the transforms to correct for head-motion. These resampled BOLD time-series will be referred to as *preprocessed BOLD in original space*, or just *preprocessed BOLD*. The BOLD reference was then co-registered to the T1w reference using bbregister (FreeSurfer) which implements boundary-based registration (Greve and Fischl 2009). Co-registration was configured with twelve degrees of freedom to account for distortions remaining in the BOLD reference. Several confounding time-series were calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS and three

region-wise global signals. FD was computed using two formulations following Power (absolute sum of relative motions, Power et al. (2014)) and Jenkinson (relative root mean square displacement between affines, Jenkinson et al. (2002)). FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* (following the definitions by Power et al. 2014). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (*CompCor*, Behzadi et al. 2007). Principal components are estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 2% variable voxels within the brain mask. For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) are generated in anatomical space. The implementation differs from that of Behzadi et al. in that instead of eroding the masks by 2 pixels on BOLD space, the aCompCor masks are subtracted a mask of pixels that likely contain a volume fraction of GM. This mask is obtained by dilating a GM mask extracted from the FreeSurfer's *aseg* segmentation, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks are resampled into BOLD space and binarized by thresholding at 0.99 (as in the original implementation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the *k* components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al. 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardised DVARS were annotated as motion outliers. The BOLD time-series were resampled into standard space, generating a *preprocessed BOLD run in MNI152NLin2009cAsym space*. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Automatic removal of motion artifacts using independent component analysis (ICA-AROMA, Pruim et al. 2015) was performed on the *preprocessed BOLD on MNI*

space time-series after removal of non-steady state volumes and spatial smoothing with an isotropic, Gaussian kernel of 6mm FWHM (full-width half-maximum). Corresponding "non-aggresively" denoised runs were produced after such smoothing. Additionally, the "aggressive" noise-regressors were collected and placed in the corresponding confounds file. All resamplings can be performed with *a single interpolation step* by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using antsApplyTransforms (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos 1964). Non-gridded (surface) resamplings were performed using mri_vol2surf (FreeSurfer).

Many internal operations of *fMRIPrep* use *Nilearn* 0.8.1 (Abraham et al. 2014, RRID:SCR_001362), mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in *fMRIPrep*'s documentation.

Copyright Waiver

The above boilerplate text was automatically generated by fMRIPrep with the express intention that users should copy and paste this text into their manuscripts *unchanged*. It is released under the CC0 license.

Note that the fmriprep pipeline was run exactly as described, but in line with prior applications where ICA-AROMA regressors have been applied to data with less or no smoothing (Aquino et al., 2022), the regressors were applied to images smoothed with a 3mm FWHM Gaussian kernel as a final step. ICA-AROMA was chosen due to its ability to retain most data, unlike e.g. censoring approaches with similar denoising performance (Parkes et al., 2018).

References

Abraham, Alexandre, Fabian Pedregosa, Michael Eickenberg, Philippe Gervais, Andreas Mueller, Jean Kossaifi, Alexandre Gramfort, Bertrand Thirion, and Gael Varoquaux. 2014. "Machine Learning for Neuroimaging with Scikit-Learn." *Frontiers in Neuroinformatics* 8. https://doi.org/10.3389/fninf.2014.00014.

Avants, B. B., C. L. Epstein, M. Grossman, and J. C. Gee. 2008. "Symmetric Diffeomorphic Image Registration with Cross-Correlation: Evaluating Automated Labeling of Elderly and Neurodegenerative Brain." *Medical Image Analysis* 12 (1): 26–41. https://doi.org/10.1016/j.media.2007.06.004.

Behzadi, Yashar, Khaled Restom, Joy Liau, and Thomas T. Liu. 2007. "A Component Based Noise Correction Method (CompCor) for BOLD and Perfusion Based fMRI." *NeuroImage* 37 (1): 90–101. https://doi.org/10.1016/j.neuroimage.2007.04.042.

Cox, Robert W., and James S. Hyde. 1997. "Software Tools for Analysis and Visualization of fMRI Data." *NMR in Biomedicine* 10 (4-5): 171–78. https://doi.org/10.1002/(SICI)1099-1492(199706/08)10:4/5<171::AID-NBM453>3.0.CO;2-L.

Dale, Anders M., Bruce Fischl, and Martin I. Sereno. 1999. "Cortical Surface-Based Analysis: I. Segmentation and Surface Reconstruction." *NeuroImage* 9 (2): 179–94. https://doi.org/10.1006/nimg.1998.0395.

Esteban, Oscar, Ross Blair, Christopher J. Markiewicz, Shoshana L. Berleant, Craig Moodie, Feilong Ma, Ayse Ilkay Isik, et al. 2018. "fMRIPrep." *Software*. https://doi.org/10.5281/zenodo.852659.

Esteban, Oscar, Christopher Markiewicz, Ross W Blair, Craig Moodie, Ayse Ilkay Isik, Asier Erramuzpe Aliaga, James Kent, et al. 2018. "fMRIPrep: A Robust Preprocessing Pipeline for Functional MRI." *Nature Methods*. https://doi.org/10.1038/s41592-018-0235-4.

Evans, AC, AL Janke, DL Collins, and S Baillet. 2012. "Brain Templates and Atlases." *NeuroImage* 62 (2): 911–22. https://doi.org/10.1016/j.neuroimage.2012.01.024.

Fonov, VS, AC Evans, RC McKinstry, CR Almli, and DL Collins. 2009. "Unbiased Nonlinear Average Age-Appropriate Brain Templates from Birth to Adulthood." *NeuroImage* 47, Supplement 1: S102. https://doi.org/10.1016/S1053-8119(09)70884-5.

Gorgolewski, K., C. D. Burns, C. Madison, D. Clark, Y. O. Halchenko, M. L. Waskom, and S. Ghosh. 2011. "Nipype: A Flexible, Lightweight and Extensible Neuroimaging Data Processing Framework in Python." *Frontiers in Neuroinformatics* 5: 13. https://doi.org/10.3389/fninf.2011.00013.

Gorgolewski, Krzysztof J., Oscar Esteban, Christopher J. Markiewicz, Erik Ziegler, David Gage Ellis, Michael Philipp Notter, Dorota Jarecka, et al. 2018. "Nipype." *Software*. https://doi.org/10.5281/zenodo.596855.

Greve, Douglas N, and Bruce Fischl. 2009. "Accurate and Robust Brain Image Alignment Using Boundary-Based Registration." *NeuroImage* 48 (1): 63–72. https://doi.org/10.1016/j.neuroimage.2009.06.060.

Jenkinson, Mark, Peter Bannister, Michael Brady, and Stephen Smith. 2002. "Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images." *NeuroImage* 17 (2): 825–41. https://doi.org/10.1006/nimg.2002.1132.

Klein, Arno, Satrajit S. Ghosh, Forrest S. Bao, Joachim Giard, Yrjö Häme, Eliezer Stavsky, Noah Lee, et al. 2017. "Mindboggling Morphometry of Human Brains." *PLOS Computational Biology* 13 (2): e1005350. https://doi.org/10.1371/journal.pcbi.1005350.

Lanczos, C. 1964. "Evaluation of Noisy Data." *Journal of the Society for Industrial and Applied Mathematics Series B Numerical Analysis* 1 (1): 76–85. https://doi.org/10.1137/0701007.

Power, Jonathan D., Anish Mitra, Timothy O. Laumann, Abraham Z. Snyder, Bradley L. Schlaggar, and Steven E. Petersen. 2014. "Methods to Detect, Characterize, and Remove Motion Artifact in Resting State fMRI." *NeuroImage* 84 (Supplement C): 320–41. https://doi.org/10.1016/j.neuroimage.2013.08.048.

Pruim, Raimon H. R., Maarten Mennes, Daan van Rooij, Alberto Llera, Jan K. Buitelaar, and Christian F. Beckmann. 2015. "ICA-AROMA: A Robust ICA-Based Strategy for Removing Motion Artifacts from fMRI Data." *NeuroImage* 112 (Supplement C): 267–77. https://doi.org/10.1016/j.neuroimage.2015.02.064.

Satterthwaite, Theodore D., Mark A. Elliott, Raphael T. Gerraty, Kosha Ruparel, James Loughead, Monica E. Calkins, Simon B. Eickhoff, et al. 2013. "An improved framework for confound regression and filtering for control of motion artifact in the preprocessing of resting-state functional connectivity data." *NeuroImage* 64 (1): 240–56. https://doi.org/10.1016/j.neuroimage.2012.08.052.

Tustison, N. J., B. B. Avants, P. A. Cook, Y. Zheng, A. Egan, P. A. Yushkevich, and J. C. Gee. 2010. "N4itk: Improved N3 Bias Correction." *IEEE Transactions on Medical Imaging* 29 (6): 1310–20. https://doi.org/10.1109/TMI.2010.2046908.

Zhang, Y., M. Brady, and S. Smith. 2001. "Segmentation of Brain MR Images Through a Hidden Markov Random Field Model and the Expectation-Maximization Algorithm." *IEEE Transactions on Medical Imaging* 20 (1): 45–57. https://doi.org/10.1109/42.906424.

Supplementary Table: Functional connectivity analysis, all results where p < 0.02 (before rounding). Significant results (post-FDR correction) are highlighted with *.

Contrast	**ROI pair**	**t**	**p**	**p (FDR)**
HC vs CHR-P	Hippocampus-R & Frontal-Inf-Tri-L	-3.26	0.0014	0.086
	Hippocampus-R & Amygdala-L	2.89	0.0046	0.14
	Hippocampus-R & Putamen-R	-2.75	0.0067	0.14
	Hippocampus-L & Caudate-R	2.51	0.013	0.21
HC vs FEP	Hippocampus-R & Frontal-Inf-Tri-R	-4.19	0.0001	0.0046 *
	Hippocampus-R & Frontal-Med-Orb-L	-2.60	0.013	0.22
CHR-P vs FEP	Hippocampus-R & Frontal-Inf-Tri-R	-3.71	0.0005	0.023 *
	Hippocampus-R & Thalamus-R	3.47	0.0007	0.023 *
	Hippocampus-R & Frontal-Sup-R	-2.55	0.0129	0.27
HC vs CHR-N	Hippocampus-R & Frontal-Inf-Tri-L	3.45	0.0014	0.054
	Hippocampus-R & Putamen-R	3.34	0.0020	0.054
	Hippocampus-R & Pallidum-L	3.16	0.0026	0.054
CHR-N vs FEP	Hippocampus-R & Frontal-Inf-Tri-R	-3.094	0.003	0.20
	Hippocampus-R & Frontal-Sup-R	-2.509	0.016	0.33
CHR-N vs FEP	Hippocampus-L & Frontal-Sup-Orb-R	2.482	0.016	0.33
	Hippocampus-R & Frontal-Inf-Tri-R	-3.094	0.003	0.20
CHR-N vs CHR-P	Hippocampus-L & Caudate-L	3.06	0.0032	0.18
	Hippocampus-R & Pallidum-L	-2.82	0.0072	0.18
	Hippocampus-L & Caudate-R	-2.72	0.0089	0.18