Cognitive and clinical correlates of early-stage psychosis: Associations with functioning and the feasibility of a cognitive training intervention

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Abstract

Schizophrenia is associated with a broad range of adverse outcomes - including suicidality and self-harm and impairments in cognitive performance and functioning - that are already present during early stages, including in the clinical high-risk for psychosis (CHR-P) state and first-episode psychosis (FEP). This thesis sought to target several key gaps in existing research literature which limit our current understanding of early-stage psychosis. To this end, the overarching aim of this thesis was to investigate cognitive and clinical correlates of early-stage psychosis including associations with functioning and the feasibility of a computerised cognitive training intervention.

This thesis presents four studies which provide insights with regard to early detection and intervention in the early stages of psychosis. Chapter 2 investigates the prevalence of suicidality and non-suicidal self-harm among community-recruited CHR-P and FEP participants as well as factors associated with current suicidal ideation in the CHR-P group. Meanwhile, Chapters 3 and 4 harness machine learning methods to study cognition in a sample of CHR-P participants primarily recruited from the community. Specifically, Chapter 3 leverages supervised machine learning methods to examine the relationship between cognitive impairment and functioning while Chapter 4 employs unsupervised machine learning methods to examine cognitive heterogeneity and its association with both clinical and functional outcome. Finally, Chapter 5 investigates whether neuroplasticity-based computerised cognitive training can improve cognition and enhance gamma-band activity in a small sample of CHR-P and FEP participants.

Overall, these studies indicate that a considerable proportion of CHR-P and FEP participants experience adverse outcomes, emphasising the need for novel early detection and intervention strategies in the community. Findings are discussed in relation to the feasibility of digital detection and intervention strategies; the need for more tailored and personalised approaches to treatment; the need to develop more accurate models for effective clinical decision-making; and the importance of including psychiatric controls as a reference point. In sum, this thesis builds upon the existing literature and provides insights which have implications for both research and clinical practice.

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Author's Declaration

"I declare that, except where explicit reference is made to the contribution of others, that 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."

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Abbreviations

^{1}H-MRS	Proton magnetic resonance spectroscopy
ACES	Adverse Childhood Experiences Scale
AD	Average distance
ADM	Average distance between means
AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APA	American Psychiatric Association
APN	Average proportion of non-overlap
APS	Attenuated psychotic symptoms
ARC	Activity-regulated cytoskeleton-associated protein
AUC	Area under the curve
AVAQ	Audio-Visual Abnormalities Questionnaire
BAC	Balanced accuracy
BACS	Brief Assessment of Cognition in Schizophrenia
BDI	Beck Depression Inventory
BDNF	Brain-derived neurotrophic factor
BLIPS	Brief limited intermittent psychotic symptoms
BSABS	Bonn Scale for the Assessment of Basic Symptoms
CAARMS	Comprehensive Assessment of At-Risk Mental States
CHR-N	Clinical high-risk-negative
CHR-P	Clinical high-risk for psychosis
CI	Confidence interval
CNB	Penn Computerized Neurocognitive Battery
CNS	Central nervous system
CNV	Copy number variation
COGDIS	Cognitive disturbances
COPER	Cognitive-perceptive basic symptoms
DICS	Dynamic imaging of coherent sources
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalography
EMA	Ecological momentary assessment
EPV	Events per variable
FDR	False discovery rate
FEP	First-episode psychosis
FFT	Fast Fourier transform
FOM	Figure of merit
GABA	Gamma-aminobutyric acid
GAD	Glutamic acid decarboxylase
GAF	Global Assessment of Functioning
GAT	GABA transporter
GF	Global Functioning
GFO	Good functional outcome
GNB	Gaussian naive bayes
GRD	Genetic risk and deterioration syndrome
GRFD	Genetic risk and functional deterioration
GWAS	Genome-wide association study
HC	Healthy control
HPA	Hypothalamic-pituitary-adrenal
ICA	Independent component analysis
ICD	International Statistical Classification of Diseases
IL	Interleukin

IQR	Interquartile range
KMO	Kaiser–Meyer–Olkin
LASSO-LARS	L1-regularised least angle regression
LDA	Linear discriminant analysis
LR	Logistic regression
MEG	Magnetoencephalography
MINI	Mini-International Neuropsychiatric Interview
MNI	Montreal Neurological Institute
MPRAGE	Magnetisation-prepared rapid gradient-echo
MRC	Medical Research Council
MRI	Magnetic resonance imaging
NART	National Adult Reading Test
NMDA	N-methyl-D-aspartate
OR	Odds ratio
PAM	Psychosis Attachment Measure (Chapter 2)
PAM	Partitioning around medoids (Chapter 4)
PANSS	Positive and Negative Syndrome Scale
PAS	Premorbid Adjustment Scale
PCA	Perceptual and Cognitive Anomalies (Chapter 2)
PCA	Principal component analysis (Chapter 4)
PET	Positron emission tomography
PFO	Poor functional outcome
PQ	Prodromal Questionnaire
RCT	Randomised controlled trial
RFC	Random forest classification
ROC	Receiver operating characteristic
RT	Response time
SCID	Structured Clinical Interview for DSM-IV
SIPS	Structured Interview for Prodromal Symptoms
SKL	Scikit-learn
SNc	Substantia nigra pars compacta
SNP	Single nucleotide polymorphism
SNV	Single nucleotide variant
SOPS	Scale of Prodromal Symptoms
SOS	Significant Others Scale
SPECT	Single-photon emission computed tomography
SPI-A	Schizophrenia Proneness Instrument, Adult version
SPI-CY	Schizophrenia Proneness Instrument, Child and Youth version
SQUID	Superconducting quantum interference device
SVM	Support vector machines
TFR	Time-frequency representation
TNF	Tumour necrosis factor
UHR	Ultra-high risk
VIF	Variance inflation factor
VTA	Ventral tegmental area
WAIS	Weschler Adult Intelligence Scale
WHO	World Health Organisation
YouR	Youth Mental Health Risk and Resilience

Previous Publications and Copyright

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KH conceptualised and wrote the chapter. PU reviewed and edited the chapter.

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Authors PU, RG, JG, AG, SL and MS designed the study and wrote the protocol. Authors PU, KH and OK contributed to the conceptualisation of the manuscript. Author KH undertook the statistical analysis, reviewed the literature and wrote the first and subsequent drafts of the manuscript. Author PU contributed to the interpretation of the results and reviewed and edited all drafts of the manuscript. All authors contributed to and have approved the final manuscript.

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Chapter 1 Introduction

1.1 Schizophrenia: A brief overview

Schizophrenia, arguably the most severe and persistent manifestation of psychosis, involves a loss of contact with reality and distortions in thinking, speech, perception, emotion and behaviour (Tandon et al., 2009). It is a debilitating psychiatric disorder associated with both long-term disability and premature death. Indeed, schizophrenia ranks among the top 15 leading causes of disability globally (Vos et al., 2017). Patients are also estimated to die 14.5 years earlier, on average, than the general population which has been partly attributed to the high rates of health-damaging behaviours, such as tobacco smoking, and the high risk of suicide among people with schizophrenia as well as the adverse effects of antipsychotic medication (Hjorthøj et al., 2017).

The lifetime prevalence of schizophrenia is approximately 1% (Nuevo et al., 2012) with a median incidence of 21.7 cases per 100,000 person-years (Jongsma et al., 2019). Typically emerging in late adolescence or early adulthood, the peak age of onset is 20.5 years (Solmi et al., 2022). Sex differences have also been reported, with males having a higher incidence of schizophrenia and earlier age of onset than females (McGrath et al., 2004; van der Werf et al., 2014). Overall, schizophrenia imposes a significant economic burden on patients, their families and society as a whole. In England alone, the total societal cost is estimated at £11.8 billion per year (Andrew et al., 2012).

1.2 Historical perspectives

Although the term schizophrenia was introduced over 110 years ago, descriptions of psychotic symptoms such as delusions, hallucinations and bizarre behaviour have been documented since antiquity (Jeste et al., 1985). However, it was the influential work of both German physician Emile Kraepelin and Swiss psychiatrist Eugen Bleuler that provided the diagnostic foundation for schizophrenia. In the late 19th century, Kraepelin developed his famous system of *Zählkarten*, or “patient cards”, in order to record, and continually revise, the diagnosis and illness course for every new psychiatric patient (Engstrom, 2003). Based on his long-term observations of clinical cases, Kraepelin (1899/1902) delineated two

major forms of psychosis – dementia praecox (now termed schizophrenia) and manic-depressive insanity (now termed bipolar disorder) – a distinction known as the Kraepelinian dichotomy (Rybakowski, 2019). He described dementia praecox as a disorder of intellectual functioning marked by a deteriorating course and poor prognosis. The adjective praecox – meaning "early" – was used to differentiate this disorder from dementia of the elderly, described by his colleague Alois Alzheimer (Collin et al., 2016). Conversely, manic-depressive insanity was described as a disorder of mood or affect with an episodic course, featuring distinct periods of remission and relapse, and a favourable prognosis.

Bleuler (1911/1950), however, objected to the term dementia praecox, arguing that symptom onset could also occur later in life and that deterioration was not inevitable; some patients could experience remission. Therefore, Bleuler proposed the term "schizophrenia", derived from the Greek words "*skhizo*" (to split) and "*phren*" (mind), to replace dementia praecox (Collin et al., 2016). With this new term, he referred to the fragmentation of mental processes, rather than a split in personality or identity. More precisely, Bleuler spoke of a "group of schizophrenias", thus emphasising the heterogeneity in clinical presentation.

The concept of schizophrenia was considerably broadened by Bleuler using two different dichotomies: fundamental/accessory symptoms and primary/secondary symptoms (Moskowitz & Heim, 2011). Fundamental symptoms were unique to schizophrenia and present in all patients whereas accessory symptoms could occur in a variety of different disorders. Primary symptoms were a direct expression of the underlying biological process whereas secondary symptoms reflected adaptations or reactions to the primary disturbance. According to Bleuler, hallucinations and delusions were both accessory and secondary, whereas loosening of associations – that is, loosening of the associative threads connecting all aspects of mental activity – was both fundamental and primary. Therefore, it was clear that Bleuler regarded loosening of associations to be the most important symptom of schizophrenia (McNally, 2016).

On the other hand, Jaspers (1913/1963) placed emphasis on the "ununderstandable" nature of schizophrenia wherein psychotic symptoms were deemed difficult to understand and empathise with. Influenced by this

phenomenological approach, Schneider (1950/1959) produced a list of first-rank symptoms to aid in the diagnosis of schizophrenia. This list comprised a small set of delusions and hallucinations that were relatively easy to identify and define, including audible thoughts, voices arguing, thought withdrawal, thought insertion, thought broadcasting and delusional perception (Mellor, 1970).

1.3 Positive and negative symptoms

The distinction between positive and negative symptoms was introduced by Reynolds (1861) in the context of epilepsy. Positive symptoms, such as spasms and convulsions, were described as an excess of vital properties whereas negative symptoms, such as paralysis and loss of sensation, were described as a negation of vital properties. Hughlings Jackson (1958) subsequently elaborated on this distinction in his hierarchical model of the nervous system. In this model, negative symptoms resulted from a loss of higher inhibitory control and, in turn, positive symptoms manifested from the disinhibition of lower-level processes. Thus, negative symptoms represented a reduction or loss of normal function whereas positive symptoms reflected an exaggeration of normal function.

Positive and negative terminology was first applied to schizophrenia symptoms by Snezhnevsky (1968). Researchers rapidly embraced this distinction in order to better understand and explain the clinical heterogeneity of schizophrenia (Andreasen et al., 1990; Crow, 1980, 1985; Strauss et al., 1974). Crow (1980), for example, proposed that schizophrenia could be classified into two syndromes on the basis of positive and negative symptoms: Type I and Type II. Type I schizophrenia was characterised by positive symptoms, including hallucinations and delusions, a good response to antipsychotic medication and a favourable prognosis whereas Type II schizophrenia was characterised by negative symptoms, including affective flattening and poverty of speech, a poor response to antipsychotic medication and a poor prognosis. Specific pathological processes were also presumed to underlie these two syndromes. While Type I schizophrenia was linked to increased dopamine receptors, Type II schizophrenia was associated with cell loss and structural brain changes. This two-syndrome concept was later amended by replacing the mutually exclusive “types” with a positive and a negative dimension, thereby acknowledging that both syndromes can coexist in the same individual (Crow, 1985).

1.4 Diagnostic systems and the schizophrenia spectrum

Schizophrenia is diagnosed using two main systems: the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM-5; American Psychiatric Association [APA], 2013) and the *International Statistical Classification of Diseases* (11th ed.; ICD-11; World Health Organisation [WHO], 2019). These systems have incorporated the perspectives of Kraepelin, Bleuler and Schneider, although the emphasis placed on each perspective has changed over time (Tandon et al., 2013). When diagnosing schizophrenia, one major difference between the DSM-5 and ICD-11 relates to the symptom duration criterion. The DSM-5 requires a symptom duration of at least 6 months, in line with Kraepelin's emphasis on chronicity, whereas the ICD-11 requires a symptom duration of at least 1 month, in keeping with Bleuler's more optimistic outlook. The influence of Kraepelinian chronicity on DSM-5 is further evidenced by the functional impairment criterion, whereby impairments in social and/or occupational functioning are required for diagnosis in the DSM-5, but not in the ICD-11.

In the DSM-IV (4th ed.; APA, 1994) and ICD-10 (10th ed.; WHO, 2016), the presence of one first-rank symptom was symptomatically sufficient for a schizophrenia diagnosis. However, due to issues with diagnostic accuracy, these symptoms were eliminated from the DSM-5 and de-emphasised in the ICD-11 (Moscarelli, 2020). Currently, at least two characteristic symptoms are required for a diagnosis of schizophrenia, at least one of which should be a positive symptom (i.e. hallucinations, delusions or disorganised speech/thinking). In the DSM-5 and ICD-11, there is also a shift from a categorical approach towards a more dimensional approach when diagnosing schizophrenia and related psychotic disorders (Biedermann & Fleischhacker, 2016). Indeed, schizophrenia is considered part of the so-called schizophrenia spectrum – a heterogeneous group of psychotic disorders that differ in terms of type, duration and complexity of psychopathology (Heckers et al., 2013). In DSM-5, for example, differential diagnoses include schizoaffective disorder and schizophreniform disorder. For a diagnosis of schizophreniform disorder, symptoms of schizophrenia must be present for more than 1 month but less than 6 months whereas for a diagnosis of schizoaffective disorder, symptoms of schizophrenia must co-occur with prominent and enduring mood symptoms, yet also be present for at least 2 weeks in the absence of mood symptoms (Bhati, 2013).

1.5 Natural history of schizophrenia

The natural history of schizophrenia is presumed to evolve through four sequential phases: premorbid, prodromal, psychotic and stable (Tandon et al., 2009). The premorbid phase is characterised by subtle impairments in cognitive, motor and social functioning. Such impairments are poor predictors of full-blown psychosis due to their nonspecific nature and high occurrence in the general population (Rapoport et al., 2005). The prodromal phase is characterised by transient and/or attenuated (subthreshold) positive symptoms, basic symptoms and a marked decline in functioning. The duration of the prodrome can vary from months to years, with an average duration of approximately 5.6 years (Klosterkötter et al., 2001). The psychotic phase marks the formal onset of psychosis and is characterised by florid positive symptoms. Notably, about 30% of first-episode psychosis (FEP) cases do not pass through an identifiable prodromal phase (Shah et al., 2017). Finally, the stable phase is characterised by less prominent positive symptoms and increasingly prominent negative symptoms and cognitive deficits. Positive symptoms are variable, fluctuating over time, whereas negative symptoms and cognitive deficits tend to be more stable and persistent (Harvey et al., 2006). Across the course of schizophrenia, variable degrees of recovery are possible.

1.6 Genetic and environmental risk factors

According to the multiple-hit model, the cumulative and interactive effects of genetic susceptibility and environmental insults during critical periods of neurodevelopment lead to the development of schizophrenia (J. Davis et al., 2016).

1.6.1 Genetic risk factors

1.6.1.1 Twin, family and adoption studies

Twin, family and adoption studies have highlighted the heritable nature of schizophrenia. Indeed, the lifetime risk of developing schizophrenia increases as the genetic relatedness to a person with schizophrenia increases. With respect to the general population, Chou et al. (2017) estimated the prevalence of schizophrenia to be 37.86-fold higher in individuals with an affected twin, 6.3-

fold higher in individuals with an affected first-degree relative and 2.4-fold higher in those with an affected second-degree relative.

The concordance rate of schizophrenia, or the probability that the twin of an affected individual will also develop the disorder, is considerably higher in monozygotic twins compared to dizygotic twins. Specifically, Cardno and Gottesman (2000) found concordance rates between 41% and 65% in monozygotic twins and between 0% and 28% in dizygotic twins. Twin studies have also elucidated the heritability of schizophrenia, which refers to the proportion of phenotypic variance attributable to genetic factors. Heritability estimates for schizophrenia are around 80-85% (T. D. Cannon et al., 1998; Cardno & Gottesman, 2000; Sullivan et al., 2003), further emphasising the substantial genetic component in susceptibility to schizophrenia. More recently, using the Danish Twin Register, Hilker et al. (2018) reported a concordance rate of 33% in monozygotic twins and 7% in dizygotic twins. In addition, the heritability of schizophrenia and, more generally, schizophrenia spectrum disorders was estimated to be 79% and 73%, respectively.

Notably, twins share a similar environment from conception onwards and environmental similarity tends to be higher for monozygotic twins than dizygotic twins which could partly explain the difference in concordance rates (Ingraham & Kety, 2000). Compared to twin and family studies, adoption studies are better able to disentangle genetic influences from environmental factors. Such studies have reported a greater prevalence of schizophrenia in adopted-away children of mothers with schizophrenia than in adopted-away children of control mothers (Heston, 1966; Tienari et al., 2000). Furthermore, Tienari et al. (2004) found that adopted-away children of mothers with a schizophrenia spectrum disorder were significantly more likely to develop a schizophrenia spectrum disorder themselves if they were reared in a dysfunctional, as opposed to healthy, adoptive family, providing support for a gene-environment interaction effect.

1.6.1.2 Molecular genetics

As a result of extensive collaborations and advances in molecular genetics technology, researchers have made considerable progress in elucidating the genetic architecture of schizophrenia over the last decade. This effort has

identified both common genetic variants and rare genetic variants with minor allele frequencies of ≥ 5% and < 1%, respectively (Vorstman et al., 2018).

Genome-wide association studies (GWASs) investigate millions of common genetic variants, often in the form of single nucleotide polymorphisms (SNPs), simultaneously (Legge et al., 2021). A landmark GWAS identified 128 SNPs, spanning 108 independent loci, that met genome-wide significance for an association with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Genes identified within the implicated loci were involved in dopamine synthesis, glutamatergic neurotransmission, synaptic plasticity, neuronal calcium signalling and immunity. More recently, the largest GWAS of schizophrenia to date identified 342 SNPs, spanning 287 independent loci, that met genome-wide significance for an association with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2022). After fine-mapping of the loci, 120 genes were prioritised which were linked to fundamental processes including synaptic organisation and transmission. The SNP-based heritability, or the proportion of phenotypic variance attributable to genome-wide SNPs, was estimated at 24%. Currently, heritability estimates from GWAS are substantially lower than estimates from twin, family and adoption studies, perhaps implying undiscovered genetic variants or overestimated heritability (Owen & Williams, 2021).

Individually, common genetic variants are associated with small increases in risk, with odds ratios (ORs) generally < 1.2. In comparison, rare genetic variants, such as copy number variations (CNVs), are associated with substantial increases in risk, with ORs between 2 and 60 (Rees et al., 2014). CNVs are structural genomic variants, consisting primarily of duplications and deletions, ranging from 1 kilobase (kb) to several megabases (Mb) in size. The largest genome-wide analysis of CNVs in schizophrenia (CNV and Schizophrenia Working Groups of the Psychiatric Genomics Consortium, 2017) identified eight CNVs – six deletions and two duplications – that were significantly associated with the disorder. Any one of these eight CNVs was carried by 1.42% of cases and 0.15% of controls.

Whole exome sequencing studies are able to detect other rare genetic variants including single nucleotide variants (SNVs) and small insertion/deletion (indel) mutations (Rees et al., 2015). Whole exome sequencing targets protein coding

regions, which account for approximately 1% of the human genome, and enables the identification of genetic variation at single-base resolution (Gilissen et al., 2011). Using this approach, Purcell et al. (2014) reported a high polygenic burden of rare, disruptive SNVs and indels in schizophrenia cases versus controls, distributed across many genes. These rare genetic variants were particularly enriched in gene sets associated with voltage-gated calcium channels and the postsynaptic ARC (activity-regulated cytoskeleton-associated protein) complex, which are known to regulate synaptic plasticity (Nanou & Catterall, 2018; Shepherd & Bear, 2011). More recently, in one of the largest exome sequencing studies of a complex trait to date, Singh et al. (2022) identified 10 genes in which rare genetic variants conferred a substantial risk for schizophrenia. Two of these genes, *GRIN2A* and *GRIA3*, code for glutamate receptor subunits, providing support for dysregulated glutamatergic signalling in schizophrenia.

1.6.2 Prenatal and perinatal environmental risk factors

1.6.2.1 Prenatal maternal stress

Prenatal exposure to maternal stress increases the risk of developing schizophrenia. Various maternal stressors have been implicated including bereavement, war and natural disasters. Indeed, Khashan et al. (2008) found that children whose mothers lost a close relative during pregnancy had a nearly 2-fold increased risk of schizophrenia, but only if this bereavement occurred in the first trimester. Meanwhile, Malaspina et al. (2008) found that the incidence of schizophrenia was more than doubled for offspring whose mothers had been in the second month of gestation during the Arab-Israeli war of June 1967. In addition, Guo et al. (2019) recently found that individuals with prenatal exposure to the Great Tangshan Earthquake of 1976 in China had a greater risk of schizophrenia relative to unexposed individuals (OR = 3.38). Specifically, prenatal exposure during the first trimester, but not the second or third trimester, was associated with an increased risk of schizophrenia (OR = 7.45).

These findings suggest that the first trimester of pregnancy is a critical window for heightened vulnerability to maternal stress. Several mechanisms have been proposed including dysregulation of the hypothalamic-pituitary-adrenal (HPA)

axis – a hormonal response system that releases glucocorticoids (stress hormones) into the circulation in response to stress (Paquin et al., 2021).

1.6.2.2 Obstetric complications

Obstetric complications are among the most enduring and best replicated environmental risk factors for schizophrenia. In a comprehensive meta-analysis of population-based studies, three groups of obstetric complications were significantly associated with schizophrenia: complications of pregnancy; abnormal foetal growth and development; and complications of delivery (M. Cannon, Jones, et al., 2002). Interestingly, these findings also extend across the broad psychosis spectrum. A recent meta-analysis (C. Davies et al., 2020) identified several obstetric complications that were significantly associated with the development of psychosis including polyhydramnios (i.e. excess accumulation of amniotic fluid; OR = 3.05), congenital malformations (OR = 2.35), premature rupture of membranes (OR = 2.29), premature birth (OR = 1.35) and maternal hypertension (OR = 1.40).

Hypoxia is one candidate mechanism that might link obstetric complications to the later development of schizophrenia. Research suggests that perinatal hypoxia increases risk for schizophrenia through brain cell oxygen deprivation while prenatal hypoxia increases risk via placental responses, which are partly influenced by genetics (Paquin et al., 2021).

1.6.2.3 Infections

Prenatal exposure to maternal infections, caused by viruses, bacteria or protozoa, may increase risk for schizophrenia (Brown, 2011). Indeed, exposure to influenza during the first trimester is associated with a 7-fold elevated risk of schizophrenia (Brown et al., 2004) while prenatal exposure to rubella is associated with a 5.2-fold increased risk of schizophrenia spectrum disorders (Brown et al., 2000). In addition, immunoglobulin G antibodies against *Toxoplasma gondii* are found to be significantly elevated in neonates who later develop schizophrenia (Blomström et al., 2012; Mortensen et al., 2007). More generally, maternal bacterial infection during pregnancy has been found to increase the risk of psychotic disorders in offspring (OR = 1.8), with stronger

effects for males than females (OR = 2.6 vs. 1.0) and for multisystemic, as opposed to localised, infections (OR = 2.9 vs. 1.6; Y. H. Lee et al., 2020).

Immune responses are suggested to mediate the relationship between prenatal exposure to maternal infection and risk of schizophrenia. Elevated maternal serum concentrations of three proinflammatory cytokines - interleukin-6 (IL-6), IL-1ß and tumour necrosis factor-α (TNF-α) – specifically during the first half of pregnancy, have been associated with the risk of psychosis in offspring (Allswede et al., 2020). These cytokines play a key role in the initial response to infection as well as the initiation and maintenance of inflammatory responses.

1.6.2.4 Nutrition

According to studies of two major famines, the Dutch Hunger Winter of 1944–1945 (Susser et al., 1996; Susser & Lin, 1992) and the Great Chinese Famine of 1959–1961 (St Clair et al., 2005), prenatal exposure to severe famine is associated with a 2-fold increased risk of schizophrenia. The Dutch famine studies, in particular, highlighted periconception (8 weeks before to 4 weeks after conception) as the most critical period of exposure (Susser & St Clair, 2013). Several micronutrient deficiencies, including folate, vitamin D and iron deficiencies, have been proposed to underlie this effect (McGrath et al., 2011).

1.6.2.5 Season and place of birth

People born during winter/spring or in urban areas are also slightly more likely to develop schizophrenia. Indeed, Cheng et al. (2013) found that the winter-spring birth excess in schizophrenia was 5.3% when compared with the general population. This so-called seasonality effect is relatively robust in the northern hemisphere (G. Davies et al., 2003; Torrey et al., 1997) while findings from the southern hemisphere are less consistent (McGrath & Welham, 1999).

Furthermore, people born in densely populated urban areas have approximately double the risk of developing schizophrenia compared to those born in rural areas (Mortensen et al., 1999; Pedersen & Mortensen, 2001b). In one Danish register-based cohort study (Pedersen & Mortensen, 2001a), individuals born in the capital city (Copenhagen) or the capital suburbs had a relative risk of schizophrenia of 2.24 and 1.71, respectively, compared to those born in rural

areas. Similarly, Plana-Ripoll et al. (2021) recently found that individuals born in the most remote areas of Denmark experienced 38% lower rates of schizophrenia than those born in the most urban areas.

Prenatal exposure to infection (Brown, 2011) and vitamin D deficiency (Cui et al., 2021) have been implicated as candidate mechanisms. Indeed, densely populated urban areas and the colder, winter months are both associated with increased spread of infection and reduced exposure to sunlight (Brown, 2011).

1.6.3 Later environmental risk factors

1.6.3.1 Cannabis use

Heavy cannabis users have an approximately 4-fold increase in odds of schizophrenia and psychosis-related outcomes compared with non-users (Manrique-Garcia et al., 2012; Marconi et al., 2016). Escalation of cannabis use in the 5 years prior to psychosis onset (e.g. increasing from no use to daily use) is associated with an increased rate of psychosis onset while daily cannabis use approximately doubles the rate of onset (Kelley et al., 2016). Notably, in the past two decades, the proportion of schizophrenia cases associated with cannabis addiction has increased 3- to 4-fold, primarily due to the increasing use and potency of cannabis (Hjorthøj et al., 2021). In fact, Di Forti et al. (2019) have estimated that, if high-potency cannabis were no longer available, 12.2% of FEP cases could be prevented across 11, predominantly European, sites, rising to 30.3% in London and 50.3% in Amsterdam.

Exogenous cannabinoids are thought to disrupt the regulatory role of the endogenous cannabinoid system and therefore, the maturational refinement of cortical neuronal networks (Gilman et al., 2018). Depending on the dose, frequency and duration of use, exact time window of exposure and pre-existing genetic and environmental vulnerability factors, this could ultimately lead to the development of schizophrenia and related psychoses.

1.6.3.2 Adverse childhood experiences

Adverse childhood experiences increase the odds of subsequent schizophrenia (OR = 3.60; Matheson et al., 2013) as well as psychosis more generally (OR =

2.78; Varese et al., 2012). Indeed, Varese et al. (2012) found significant associations between various types of childhood adversity (sexual, physical and emotional abuse, neglect and bullying) and psychosis, indicating that psychosis risk is increased by exposure to adverse childhood experiences in general, rather than to a specific type of adversity. Assuming causality, Varese et al. (2012) estimated that the number of individuals with psychosis would be reduced by 33% if the childhood aversities under study were entirely removed from the population. Furthermore, Matheson et al. (2013) found that the rates of childhood adversity in schizophrenia did not significantly differ from the rates of childhood adversity in other psychiatric disorders including depression and personality disorders, suggesting that adverse childhood experiences represent a common, as opposed to specific, risk factor.

Various biological and psychological mechanisms have been proposed to mediate the relationship between adverse childhood experiences and psychosis including HPA axis dysregulation, decreased levels of brain-derived neurotrophic factor (BDNF), increased levels of inflammatory markers, insecure attachment styles, dissociation, affective dysregulation and negative cognitive schemas (Misiak et al., 2017; Williams et al., 2018).

1.6.3.3 Migration

First- and second-generation migrants are at increased risk of schizophrenia and related disorders although the level of risk varies by ethnicity and setting (Bourque et al., 2011; Cantor-Graae & Selten, 2005; Selten et al., 2020). In Australia, O'Donoghue et al. (2021) found that migrants from Sub-Saharan Africa and North Africa were at least 3 times more likely to be diagnosed with FEP than Australian-born young people. Meanwhile, in the East of England, Kirkbride et al. (2017) found that people of black Caribbean and black African origin were 4 to 5 times more likely to be diagnosed with FEP than the white British population.

Possible explanations centre on psychosocial factors, including socioeconomic disadvantage, discrimination and social isolation while vitamin D deficiency has also been put forward as a contributing factor (Stilo & Murray, 2019). In particular, the social defeat hypothesis posits that social defeat, or the negative experience of being excluded from the majority group, increases the risk of

schizophrenia via effects on the mesolimbic dopamine system (Selten et al., 2013; Selten & Cantor-Graae, 2005).

1.7 Pathophysiological hypotheses

A number of different hypotheses have been proposed to explain the pathophysiology of schizophrenia, including neurochemical and neurodevelopmental hypotheses.

1.7.1 The dopamine hypothesis

Dopamine, a key neurotransmitter in the central nervous system (CNS), modulates essential physiological functions including voluntary movement, reward, cognition and goal-oriented behaviours (Ledonne & Mercuri, 2017). Dopamine-induced effects are mediated by five G-protein-coupled (metabotropic) receptors which are grouped into two major families: D1-like receptors (D1 and D5) and D2-like receptors (D2, D3 and D4). In the ventral midbrain, dopaminergic pathways mainly originate from dopaminergic cell bodies in the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc). Dopaminergic projections from the VTA target the ventral striatum, namely the nucleus accumbens, via the mesolimbic pathway; as well as the prefrontal cortex via the mesocortical pathway (Trutti et al., 2019). Meanwhile, dopaminergic projections from the SNc project to the dorsal striatum via the nigrostriatal pathway.

The dopamine hypothesis of schizophrenia was first formulated by van Rossum (1966) who proposed a state of excess dopaminergic stimulation in patients based on the observation that antipsychotics, such as chlorpromazine, may block dopamine receptors. This hypothesis was substantiated when the clinical potency of antipsychotics was incontrovertibly associated with dopamine D2 receptor blockade (Creese et al., 1976; Seeman & Lee, 1975) and studies confirmed the psychotogenic effects of dopamine agonists (Lieberman et al., 1987). However, the original dopamine hypothesis was later reformulated based on several new lines of evidence (K. L. Davis et al., 1991). For example, the antipsychotic clozapine was shown to have superior efficacy in patients with treatment-refractory schizophrenia, despite having relatively low affinity for

dopamine D2 receptors. In addition, although antipsychotics could effectively alleviate positive symptoms, they were only minimally effective in treating negative symptoms and cognitive impairments. According to the revised dopamine hypothesis, hyperactivity of dopamine D2 receptor neurotransmission in the mesolimbic pathway leads to positive symptoms while hypofunctionality of dopamine D1 receptor neurotransmission in the mesocortical pathway leads to negative symptoms and cognitive impairments (Toda & Abi-Dargham, 2007).

The development of positron emission tomography (PET) and single-photon emission computed tomography (SPECT) has enabled researchers to investigate the dopamine system in vivo. Meta-analyses of available studies have provided compelling evidence for presynaptic dopaminergic dysfunction in schizophrenia with reports of increased dopamine synthesis and release capacity compared to controls within dorsal (predominantly associative) striatum (McCutcheon et al., 2018). Interestingly, elevated dopamine synthesis capacity has also been found in individuals experiencing psychosis in the context of bipolar disorder (Jauhar et al., 2017) and temporal lobe epilepsy (Reith et al., 1994). Therefore, presynaptic dopamine dysfunction may be transdiagnostic, underlying psychosis irrespective of diagnosis, rather than specific to schizophrenia.

1.7.2 The glutamate hypothesis

Glutamate, the major excitatory neurotransmitter in the CNS, is involved in a plethora of important functions including neurotoxicity, neuronal development, synaptic plasticity, learning and memory (Riedel et al., 2003). Unlike dopamine neurons, which are restricted to particular anatomical pathways, glutamate neurons are widespread throughout the brain (McCutcheon et al., 2020). Glutamate-induced effects are mediated by metabotropic and ionotropic glutamate receptors. The ionotropic glutamate receptors, in particular, are named after their selective agonists: NMDA (N-methyl-D-aspartate), AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainite (Howes et al., 2015).

According to the glutamate hypothesis, dysregulation of the glutamatergic system, specifically NMDA receptor hypofunction, contributes to the pathophysiology of schizophrenia (Kantrowitz & Javitt, 2010). Indeed,

converging lines of evidence suggest that NMDA receptor antagonists, such as phencyclidine and ketamine, can induce manifestations similar to the positive, negative and cognitive symptoms of schizophrenia when administered to healthy participants (K. Beck et al., 2020; Javitt & Zukin, 1991; Krystal et al., 1994; Malhotra et al., 1996) and exacerbate a similarly wide variety of symptoms when administered to schizophrenia patients (K. Beck et al., 2020; Malhotra et al., 1997).

Proton magnetic resonance spectroscopy (^{1}H-MRS) is frequently used to measure in vivo concentrations of glutamate and glutamine. Glutamine is taken to be a marker of glutamatergic neurotransmission as it is generated after the uptake of synaptic glutamate by astrocytes (McCutcheon et al., 2020). Notably, a meta-analysis of ^{1}H-MRS studies (Merritt et al., 2016) found significantly elevated levels of glutamine in the thalamus as well as Glx (the sum of glutamate and glutamine) in the basal ganglia and medial temporal lobe in individuals with FEP or chronic schizophrenia.

1.7.3 The GABA hypothesis

Gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the CNS, is produced from glutamate by glutamic acid decarboxylase (GAD; de Jonge et al., 2017). Specifically, GABA-induced effects are mediated by ionotropic $GABA_A$ receptors and metabotropic $GABA_B$ receptors. In tandem with glutamate, GABA modulates the excitatory/inhibitory (E/I) balance necessary for the proper function of neuronal networks in the brain (Wu & Sun, 2015). Dysfunctional GABAergic inhibition and the subsequent E/I imbalance in the cerebral cortex has been implicated in the pathophysiology of schizophrenia (Nakazawa et al., 2012).

In support of this, one of the most consistent findings from post-mortem studies in schizophrenia is a reduction in mRNA and protein levels of GAD67 - an enzyme responsible for the majority of cortical GABA synthesis (de Jonge et al., 2017). There is also evidence of a reduction in mRNA levels of GAT-1 – a GABA membrane transporter that removes GABA from the extracellular space. Interestingly, these deficits in GABA synthesis and reuptake appear to be relatively specific to the parvalbumin-containing subgroup of GABA interneurons

in dorsolateral prefrontal cortex (Hashimoto et al., 2003; Lewis et al., 2005; Volk et al., 2001) which are also found to express lower levels of parvalbumin mRNA in schizophrenia (Hashimoto et al., 2003). Notably, these fast-spiking interneurons are known to play a pivotal role in the generation of gamma oscillations, a type of high-frequency neuronal oscillation associated with attention and other cognitive processes (Uhlhaas & Singer, 2010).

In contrast, a meta-analysis of ^{1}H-MRS studies (Egerton et al., 2017) found no evidence for significantly altered GABA concentrations in schizophrenia and FEP samples compared to controls. Nevertheless, relative to controls, FEP patients reportedly have lower cerebrospinal fluid concentrations of GABA (Orhan et al., 2018) and decreased GABA levels in the midcingulate cortex (Nakahara et al., 2021) – a region which is activated during cognitive tasks (Bush et al., 2003).

1.7.4 Glutamate, GABA and dopamine: A revised hypothesis

A combination of the glutamate, GABA and dopamine hypotheses may provide the best explanation of schizophrenia symptomatology (Howes et al., 2015). Indeed, dopamine dysregulation may be secondary to altered glutamatergic and GABAergic neurotransmission (Ebenezer, 2015). According to this hypothesis, glutamate released in the prefrontal cortex acts at hypofunctional NMDA receptors situated on parvalbumin-containing GABA interneurons. As a result, there is decreased GABA release on the dendrites of glutamatergic pyramidal neurons in the prefrontal cortex. This disinhibition of the pyramidal neurons leads to increased glutamate release in the VTA which, consequently, affects dopamine release in the mesolimbic and mesocortical dopamine pathways. Specifically, this increased glutamate release stimulates dopamine release in the nucleus accumbens and also stimulates GABAergic interneurons to release GABA, thereby reducing dopamine release in the prefrontal cortex.

1.7.5 The neurodevelopmental hypothesis

According to the neurodevelopmental hypothesis of schizophrenia, a disruption in brain development in early life, resulting from genetic and environmental factors, interacts with later maturational processes to produce the full manifestation of the disorder (Murray & Lewis, 1987; Weinberger, 1987).

Consistent with this hypothesis, children later diagnosed with schizophreniform disorder have been shown to exhibit significant impairments in emotional, interpersonal, neuromotor, receptive language and cognitive development from as young as 3 years of age, with the latter three domains showing particular specificity to the disorder (M. Cannon, Caspi, et al., 2002). Indeed, for every 1-point decrease in premorbid IQ, the risk for schizophrenia increases by 3.7% (Khandaker et al., 2011). The neurodevelopmental hypothesis is further supported by the presence of white matter alterations, similar to those found in schizophrenia, in the early and subclinical stages of schizophrenia (Carletti et al., 2012; Gasparotti et al., 2009). Interestingly, this finding also extends to infants at genetic risk of schizophrenia who reportedly show abnormal white matter development within the first 2 years of life (Ahn et al., 2019).

1.8 The clinical high-risk for psychosis state

The clinical high-risk for psychosis (CHR-P) state was conceptualised around 25 years ago to describe individuals presenting with potentially prodromal symptoms (Fusar-Poli et al., 2013; Yung et al., 1996). CHR-P individuals comprise a clinically heterogenous group, displaying varying levels of attenuated positive symptoms, negative symptoms, affective disturbances, quality of life, impaired functioning and impaired cognition (Salazar de Pablo, Besana, et al., 2021; Velthorst et al., 2019).

For researchers, the CHR-P state offers a temporal window into the “near-psychotic” state, without the confounding effects of illness chronicity and prolonged exposure to antipsychotic medication. At present, the attenuated psychosis syndrome has been included as a condition for further study in the DSM-5 (APA, 2013). The proposed criteria set is not yet intended for clinical use due to various concerns including the substantial number of false positives, the potentially harmful use of antipsychotics in individuals who would not transition to psychosis and the risk of stigmatisation (Zachar et al., 2020).

Currently, there are two complementary sets of CHR-P criteria: the ultra-high risk (UHR) criteria and the basic symptom criteria. Specifically, the UHR criteria were developed to detect imminent risk of psychosis (i.e. within the next 12 months) whereas the basic symptom criteria were developed to detect psychosis

risk as early as possible in the development of the disorder (Schultze-Lutter et al., 2015).

1.8.1 Ultra-high risk criteria

The UHR criteria were originally conceived by Yung et al. (1996). The Comprehensive Assessment of At-Risk Mental States (CAARMS) interview, developed by Yung et al. (2005), is organised into seven domains with corresponding subscales. These are positive symptoms, cognitive change, emotional disturbance, negative symptoms, behavioural change, motor/physical changes and general psychopathology. Only scores from the positive symptom domain are used to evaluate UHR criteria.

In order to meet UHR criteria, individuals must meet one of two impaired functioning criteria, experiencing either: (1) a 30% or greater drop in functioning from a premorbid level for at least 1 month in the past 12 months; or (2) chronically low functioning for the past 12 months or longer. In addition, individuals must also meet criteria for at least one of the following groups:

- Genetic risk and functional deterioration (GRFD) group – Individuals with a schizotypal personality disorder or a first-degree relative with psychosis.
- Attenuated psychotic symptoms (APS) group - Individuals who have experienced subthreshold (intensity or frequency) positive symptoms in the past year.
- Brief limited intermittent psychotic symptoms (BLIPS) group - Individuals who have experienced full threshold positive symptoms in the past year that have not lasted longer than 7 days and have spontaneously resolved without antipsychotic treatment.

Miller et al. (2003) subsequently developed the Structured Interview for Prodromal Symptoms (SIPS) and the associated Scale of Prodromal Symptoms (SOPS). Across interview measures, the majority of UHR individuals are included at intake because of APS (85%), with BLIPS (10%) and GRFD (5%) representing a smaller proportion of cases (Fusar-Poli, Cappucciati, et al., 2016). These groups also have different levels of risk. At 24 months, transition risk is estimated at 39% in the BLIPS group, 19% in the APS group and 3% in the GRFD group.

1.8.2 Basic symptom criteria

Basic symptoms are subtle, subclinical disturbances in mental processes, including thinking, speech, perception and attention, that are subjectively experienced with full and immediate insight (Schultze-Lutter, 2009; Schultze-Lutter, Ruhrmann, et al., 2012). They are regarded as the most direct and immediate psychopathological expression of the neurobiological processes underlying psychosis and the earliest self-experienced signs of a developing psychosis – hence the term "basic".

Initially, basic symptoms were assessed using the Bonn Scale for the Assessment of Basic Symptoms (BSABS; G. Gross et al., 1987). More recently, shorter versions of this scale have been developed, namely the Schizophrenia Proneness Instrument, Adult version (SPI-A; Schultze-Lutter et al., 2007) and the Schizophrenia Proneness Instrument, Child and Youth version (SPI-CY; Schultze-Lutter, Marshall, et al., 2012). The BSABS only assesses the current state of an individual and is simply rated according to symptom presence or absence whereas the SPI-A and the SPI-CY assess basic symptoms on a frequency-based severity scale according to maximum occurrence in the preceding 3 months. Specifically, the SPI-A and the SPI-CY assess two partially overlapping basic symptom criteria: the cognitive disturbances (COGDIS) and the cognitive-perceptive basic symptoms (COPER) criteria (Table 1).

Table 1 - COGDIS and COPER criteria

COGDIS Criteria	COPER Criteria
Inability to divide attention	Thought interference[a]
Disturbance of expressive speech	Thought blockages[a]
Disturbances of abstract thinking	Disturbance of receptive speech[a]
Disturbance of receptive speech[a]	Thought pressure[a]
Thought interference[a]	Unstable ideas of reference[a]
Thought blockages[a]	Thought perseveration
Captivation of attention by details of the visual field	Decreased ability to discriminate between ideas and perception, fantasy and true memories
Thought pressure[a]	Derealisation
Unstable ideas of reference[a]	Visual perception disturbances
	Acoustic perception disturbances

[a] Indicates basic symptoms included within both COPER and COGDIS criteria

To meet COGDIS criteria, participants must report at least two of nine basic symptoms – five of which are also included in the COPER criteria – with a frequency of at least "several times in a month or weekly" (i.e. a frequency-based severity score between 3 and 6) within the past 3 months. To meet COPER criteria, participants must report at least one of 10 basic symptoms as having first occurrence more than 12 months ago and a frequency of at least "several times in a month or weekly" within the past 3 months.

Individuals meeting both UHR (APS and/or BLIPS) and COGDIS criteria at baseline have a significantly higher risk of transition and a shorter time to transition than those meeting either criteria alone (Schultze-Lutter et al., 2014). At 3 years follow-up and beyond, COGDIS samples also have significantly higher conversion rates than samples established by UHR criteria (Schultze-Lutter et al., 2015). Thus, COGDIS is one of three criteria recommended by the European Psychiatric Association for CHR-P assessment, alongside APS and BLIPS UHR criteria.

1.8.3 Risk of transition to psychosis

The risk of transition from a CHR-P state to the first onset of psychosis has declined from 29.1% at 2 years (Fusar-Poli et al., 2012) to 22% at 2 years (Fusar-Poli, Cappucciati, et al., 2016). Several explanations have been proposed to account for declining transition rates including insufficient follow-up durations and the use of community-recruited, as opposed to help-seeking, samples (Fusar-Poli et al., 2020; Fusar-Poli, Schultze-Lutter, et al., 2016). In a recent meta-analysis of observational studies (Salazar de Pablo, Radua, et al., 2021), 25% of CHR-P individuals transitioned to psychosis within 3 years of follow-up. Furthermore, transition risk continued to increase in the long-term, reaching 35% within 10 years of follow-up.

To date, transition to psychosis has been the primary outcome of interest in CHR-P studies. Recently, however, there has been a growing interest in the long-term outcomes of CHR-P individuals who do not transition. In a meta-analysis of remission rates, Simon et al. (2013) found that only 46% of non-transitioned CHR-P individuals experienced remission from a CHR-P state over an average follow-up period of 2 years. A far smaller proportion of individuals appear to recovery both clinically and functionally. Indeed, only 29.8% of non-transitioned UHR

individuals achieve both symptom remission and functional recovery at 2 years (Schlosser et al., 2012) – a figure that drops to just 20.8% at 6 years (Rutigliano et al., 2016). The prevalence of non-psychotic comorbid mental disorders is also high with 68.1% of non-transitioned UHR individuals fulfilling criteria for at least one Axis I diagnosis over an average follow-up period of 7 years (Lin et al., 2015). Mood disorders appear to comprise the most common diagnosis (48.7%), followed by anxiety disorders (34.5%) and substance use disorders (29.2%). Overall, these findings indicate that CHR-P individuals experience several negative outcomes beyond transition to psychosis.

1.9 Suicidality and self-harm

Suicidality and self-harm are highly prevalent in schizophrenia, especially in the early phases of the disorder (Nordentoft et al., 2004). Suicide, the act of intentionally ending one's own life, is a major public health concern worldwide (O'Connor & Nock, 2014). As a whole, suicidality encompasses suicidal ideation, suicide plan, suicide attempt and completed suicide. Suicidal ideation refers to thoughts about ending one's own life; suicide plan is defined as a plan of how to end one's own life; and suicide attempt refers to the engagement in potentially self-injurious behaviour, with at least some intention to end one's own life. In the general population, the lifetime prevalence of suicidal ideation, suicide plan and suicide attempt has been estimated at 9.2%, 3.1% and 2.7%, respectively (Nock et al., 2008). In Scotland, O'Connor et al. (2018) found that 11.3% of young people had a lifetime history of suicide attempts. In addition, 16.2% had a lifetime history of non-suicidal self-harm, which refers to the deliberate injury of one's own body, but without the intention to die.

1.9.1 Evidence from schizophrenia samples

Worldwide, the lifetime prevalence and point prevalence of suicidal ideation have been estimated at 34.5% and 29.9%, respectively, among people with schizophrenia (Bai et al., 2021). In a meta-analysis of epidemiological surveys (Bai et al., 2021), male gender was positively associated with both lifetime and point prevalence of suicidal ideation. In addition, the point prevalence was particularly high in in-patient settings (38.4%) and high-income countries (36.4%)

while the lifetime prevalence was positively associated with survey year and negatively associated with mean age.

People with schizophrenia who report suicidal ideation also have a 5.8-fold higher risk of future suicide than those without suicidal ideation (Hubers et al., 2018). Specifically, the lifetime risk of completed suicide has been estimated at 5% in schizophrenia populations (Hor & Taylor, 2010; Palmer et al., 2005). Again, males appear to have a greater risk than females (Cassidy et al., 2018) which may be partly attributable to the higher levels of stigmatisation, unemployment, alcohol and substance use and impulsivity and aggression experienced by male schizophrenia patients (Bai et al., 2021). Other risk factors for suicide in patients with schizophrenia include history of attempted suicide, younger age, higher IQ, poor adherence to treatment and hopelessness (Cassidy et al., 2018).

Suicide plans and suicide attempts are also common in people living with schizophrenia whereby, worldwide, the lifetime prevalence of suicide plan has been estimated at 44.3% (Bai et al., 2021) while the lifetime prevalence of suicide attempts has been estimated at 26.8% (Lu et al., 2019). According to a meta-analysis of observational studies (Lu et al., 2019), suicide attempts are especially common in high-income countries and regions and in individuals with an earlier age of onset. Other risk factors for suicide attempts in patients with schizophrenia include family history of psychiatric illness, family history of suicide, history of depression and history of alcohol, drug and tobacco use (Cassidy et al., 2018). Male gender, on the other hand, has been identified as a protective factor for suicide attempts, consistent with the "gender paradox" of suicidal behaviour whereby men are less likely to attempt suicide but more likely to use lethal suicide methods. Individuals with schizophrenia are also at high risk for self-harm. Indeed, Mork et al. (2013) reported a lifetime prevalence of approximately 30% for one or more episodes of non-suicidal self-harm. The median number of episodes was six with women significantly more likely to report at least one episode compared to males (43% vs. 20%).

1.9.2 Evidence from first-episode psychosis samples

The risk of suicide is particularly high within the first year after initial hospitalisation for a schizophrenia spectrum disorder, especially in younger age

groups, being almost twice as high as in the later phases of the illness (Nordentoft et al., 2004). In a 10-year follow-up study, Dutta et al. (2010) found that the mortality risk for suicide in FEP samples was approximately 12 times more than would be expected in the general population of England and Wales. As before, the rate of suicide was greatest in the first year after presentation. However, suicide risk also persisted late into the follow-up period with a median time to suicide of 5.6 years.

Over variable follow-up periods, the prevalence of suicide attempts in FEP samples is estimated between 5.28% and 21.6% while the prevalence of completed suicide is estimated between 1% and 4.3% (Sicotte et al., 2021). The strongest risk factors for suicide-related behaviours (attempts and suicides) include depressive symptoms, suicidal ideation/intent, negative life events and non-suicidal self-harm (Fedyszyn et al., 2012). FEP patients who do not use antipsychotic medication also have a 37-fold increased risk of suicide compared to patients who do use antipsychotic medication (Tiihonen et al., 2006).

In addition, prior to the first contact with services, between 7.3% and 33% of FEP individuals have a history of at least one suicide attempt (Sicotte et al., 2021). Interestingly, Melle et al. (2006) found that the rate of severe suicidality in the month preceding first treatment contact was significantly higher among FEP individuals from communities without an early detection programme (suicide attempts and suicide plans: 17%; suicide attempts only: 10%) relative to those from communities with an early detection programme (suicide attempts and suicide plans: 4%; suicide attempts only: 1%). Thus, by lowering the threshold for first treatment contact, early detection programmes can facilitate earlier treatment and lead to reduced rates of serious suicidality at the point of first contact. During the initial 3 years of treatment, suicide risk is also significantly higher among FEP individuals who receive standard psychiatric care compared to those who receive specialised early intervention (Chen et al., 2011; Harris et al., 2008).

Furthermore, between 30.6% and 56.5% of FEP individuals report suicidal ideation at service entry, dropping to between 15.6% and 27% during follow-up (Sicotte et al., 2021). Greater depression and positive symptoms at baseline have been associated with an increased odds of suicidal ideation among FEP

individuals while poorer clinical insight and greater working memory have been associated with a decreased odds of suicidal ideation (Bornheimer et al., 2021). A meta-analysis by Challis et al. (2013) also found that the pooled proportion of FEP individuals with self-harm – broadly defined as suicide attempts, deliberate self-harm, self-injury and self-directed aggression – was 18.4% before treatment and 11.4% after treatment in follow-up periods ranging from 1 to 7 years. In particular, depressed mood and substance use were associated with self-harm both before and after treatment. Using a similar definition of self-harm, Moe et al. (2022) recently found that 11.1% of individuals had at least one self-harm event during follow-up in a large population-based sample of FEP patients. Notably, they also found that the risk of self-harm was highest in the first 3 months following FEP diagnosis.

1.9.3 Evidence from clinical high-risk for psychosis samples

High rates of suicidality and self-harm are also evident in CHR-P samples. A meta-analysis by Taylor et al. (2015) demonstrated a high prevalence of recent (2-week) suicidal ideation (66%), lifetime self-harm (49%) and lifetime suicide attempts (18%) in the UHR population. Furthermore, using data from small UHR samples, Hutton et al. (2011) found that 11.8% of individuals had current suicide plans at baseline while Welsh and Tiffin (2014) found that 30% had attempted suicide and 53.33% had engaged in self-harm within the past 6 months.

In a retrospective study of schizophrenia patients, Andriopoulos et al. (2011) also found that the prevalence of suicidal ideation (26%) and suicide attempts (7.5%) in the prodromal phase were 3.8-fold and 8-fold greater, respectively, than in a matched control sample. However, the retrospective design may have led to inaccurate reporting and/or recall bias. Indeed, using a cross-sectional design, Hui et al. (2013) later found that 72% of UHR individuals had recent (2-week) suicidal ideation in comparison to 9.1% of healthy controls (HCs).

Moreover, there is evidence, albeit limited, for significantly greater levels of suicidality in CHR-P samples when compared to other clinical groups, including FEP individuals and help-seeking youth who do not meet CHR-P criteria. Indeed, Pelizza et al. (2020) have shown that recent (2-week) suicidal ideation is significantly more frequent (and severe) in UHR individuals (60%) compared to

both FEP individuals (36.9%) and non-UHR help-seeking individuals (33.3%). The proportion of individuals reporting at least one previous suicide attempt was also significantly greater in the UHR group (14.5%) compared to the FEP group (5.7%). Similarly, Granö et al. (2013) found that the odds of recent (2-week) suicidal ideation were increased 3.6-fold in CHR-P participants relative to help-seeking adolescents who did not meet CHR-P criteria. However, Preti et al. (2009) were unable to detect any significant differences in suicidality and self-harm between UHR and FEP individuals.

Various risk factors for suicidality and self-harm have been identified in CHR-P samples. Indeed, comorbid diagnoses of anxiety or depression, depression symptoms, social anxiety and internalised stigma are associated with higher suicidality and self-harm scores among UHR participants (Fusar-Poli et al., 2014; Pyle et al., 2015). Exposure to childhood adversities and trauma may also increase the risk of suicidality in CHR-P individuals via two independent pathways (Schmidt et al., 2017). In the first pathway, dysfunctional beliefs, a lack of positive coping strategies and depressiveness are proposed to mediate this relationship while, in the second, albeit weaker, pathway, cognitive basic symptoms are proposed to mediate this relationship independently.

Furthermore, several studies have focused on risk factors for current suicidal ideation. In correlational analyses, the severity of suicidal ideation appears to be positively associated with negative symptoms and depression severity and negatively associated with global functioning and quality of life in UHR samples (Gill et al., 2015; Pelizza et al., 2020). Andriopoulos et al. (2011) also identified depressive mood (OR = 52.9), marked impairment in role (occupational) functioning (OR = 13.6) and smoking (OR = 14.5) as independent predictors of suicidal ideation during the prodromal phase. Indeed, depression severity reportedly explains 26.9% of the variance in recent (2-week) suicidal ideation among UHR individuals (Pelizza et al., 2019). Furthermore, Bang et al. (2017) found that the intensity of recent (past month) suicidal ideation was significantly associated with suspiciousness/persecutory ideas in a UHR sample, independent of depressive symptom severity (adjusted R^2 = .19).

Interestingly, both baseline suicidal ideation (Grivel et al., 2018) and baseline suicidality and self-harm in general (Demjaha et al., 2012) appear to be

unrelated to the rate of transition to psychosis in UHR samples, yet baseline suicidal ideation is significantly associated with suicidal behaviour at follow-up (Grivel et al., 2018). Therefore, early identification of suicide risk in CHR-P populations is crucial since a heightened risk of suicide may be more urgent than the risk of psychosis transition (Bang et al., 2017; Pelizza et al., 2020).

1.10 Cognitive impairments

Cognitive impairment is a central feature of schizophrenia, encompassing a wide variety of neurocognitive and social cognitive domains (M. F. Green et al., 2019). Specifically, neurocognition refers to a wide range of mental abilities in domains such as processing speed, learning and memory, attention/vigilance, working memory and reasoning and problem solving. On the other hand, social cognition refers to the mental operations that are required to perceive, interpret and process social information and includes domains such as emotion processing, social perception, attributional bias/style and theory of mind. Several meta-analyses have also highlighted widespread cognitive impairments among FEP (Mesholam-Gately et al., 2009) and CHR-P (Catalan, Salazar de Pablo, et al., 2021) individuals. Across the lifespan of schizophrenia, there is evidence of premorbid generalised cognitive impairment that worsens throughout development and stabilises by the onset of psychosis, in line with the neurodevelopmental hypothesis of schizophrenia (Sheffield et al., 2018).

Importantly, considerable cognitive heterogeneity has been identified within schizophrenia spectrum disorder (Carruthers et al., 2019), FEP (Oomen et al., 2021) and CHR-P (Velthorst et al., 2019) samples. Data-driven approaches, such as cluster analysis, provide an opportunity to characterise this within-group variability by delineating homogeneous cognitive subgroups which may have significance for prognosis and treatment planning (Lewandowski et al., 2014).

1.10.1 Evidence from schizophrenia samples

Clinically significant neurocognitive impairment, defined as performance of at least one standard deviation below the population mean in two or more neurocognitive domains, is evident in 84% of individuals with schizophrenia (Reichenberg et al., 2009). Indeed, meta-analyses have revealed moderate to

severe impairments in individuals with schizophrenia relative to HCs across all neurocognitive domains, suggestive of a generalised cognitive impairment (Fioravanti et al., 2012; Heinrichs & Zakzanis, 1998; Schaefer et al., 2013). Notably, effect sizes tend to be somewhat larger in the domains of processing speed and memory and slightly smaller in the domains of spatial reasoning and language and vocabulary. Interestingly, effect sizes also tend to be larger in studies with a greater proportion of male patients, indicating that males may have more severe cognitive impairments (Schaefer et al., 2013).

In terms of social cognition, Savla et al. (2013) similarly found that, compared to controls, individuals with schizophrenia have reduced performance on all domains of social cognition, with large effects for social perception, emotion perception/processing and theory of mind. Greater impairments in emotion processing were found to be associated with longer duration of illness while greater impairments in social and emotion perception were found to be associated with inpatient status.

Importantly, cognitive heterogeneity is substantial within schizophrenia spectrum disorder samples. According to a recent systematic review (Carruthers et al., 2019), three distinct cognitive subgroups reliably emerge in these samples: relatively intact, intermediate and globally impaired. However, the study with the largest sample to date identified two cognitive subgroups: cognitively impaired and cognitively spared (M. J. Green et al., 2013). Specifically, the cognitively impaired subgroup, comprising 47.6% of the sample, were impaired across all cognitive measures while the cognitively spared subgroup, comprising 52.4% of the sample, performed relatively well on all cognitive measures. Interestingly, the cognitively impaired subgroup were more likely to be unemployed and had poorer global functioning and greater negative symptom severity compared to the cognitively spared subgroup.

Cognitive subgroups have also been identified in cross-diagnostic samples, comprising individuals with schizophrenia spectrum disorders alongside individuals diagnosed with mood disorders (J. Lee et al., 2017; R. S. C. Lee et al., 2015; Lewandowski et al., 2014, 2018; Van Rheenen et al., 2017). A systematic review (M. J. Green et al., 2019) found that such cross-diagnostic studies typically converge in identifying four cognitive subgroups, differentiating

two separate subgroups with intermediate impairment. Notably, the cross-diagnostic clustering approach appears to be superior to independent diagnostic clustering in reducing cognitive heterogeneity (Van Rheenen et al., 2017).

1.10.2 Evidence from first-episode psychosis samples

Cognitive impairments in FEP samples are similar in pattern and magnitude to those observed in chronic schizophrenia samples (Sheffield et al., 2018). In one meta-analysis (Mesholam-Gately et al., 2009), FEP individuals had medium to large impairments across all 10 cognitive domains assessed relative to HCs. The largest impairments were evident for immediate verbal memory (*d* = -1.20) and processing speed (*d* = -0.96) while the smallest impairment was evident for motor skills (*d* = -0.64).

Another meta-analysis (Fatouros-Bergman et al., 2014) examined neurocognitive impairments in antipsychotic-naïve FEP participants. They similarly found medium to large impairments in all neurocognitive domains relative to HCs, with the largest impairments in verbal memory (*d* = -1.03), working memory (*d* = -0.97) and processing speed (*d* = -1.03), supporting the existence of significant neurocognitive impairment that is independent of antipsychotic use. As regards social cognition, FEP individuals show more consistent impairments in emotion processing (particularly, fear and sadness recognition) and theory of mind, compared to social perception and attributional style (Healey et al., 2016). The meta-analysis by Mesholam-Gately et al. (2009) yielded a medium effect size (*d* = -0.77) for social cognition across 5 studies. However, the range of effect sizes within and across studies was highly variable (*d* = -0.23 to -1.94).

Certainly, cognitive heterogeneity is substantial in FEP samples. Using cluster analysis, the majority of studies have identified three cognitive subgroups with approximately 28% to 54% of FEP individuals assigned to a relatively intact subgroup, 36% to 53% to a moderately impaired subgroup and 9% to 27% to a severely impaired subgroup (Oomen et al., 2021; Sauvé et al., 2018; Tan et al., 2021; Uren et al., 2017). Reser et al. (2015), on the other hand, reported two separate intermediate subgroups – one characterised by visual memory impairments and the other by attentional and working memory impairments – resulting in four cognitive subgroups overall. Meanwhile, Amoretti et al. (2021)

and Wenzel et al. (2021) did not identify any intermediate subgroups and instead, converged on a two-cluster solution in which 43.9% and 62% of FEP individuals, respectively, were assigned to the cognitively spared subgroup.

Interestingly, the most common finding across studies, irrespective of the cluster solution, is for greater negative symptom severity in the cognitively impaired, versus cognitively spared, subgroup (Amoretti et al., 2021; Oomen et al., 2021; Reser et al., 2015; Sauvé et al., 2018; Uren et al., 2017; Wenzel et al., 2021), with some evidence for greater positive symptom severity (Oomen et al., 2021; Sauvé et al., 2018; Uren et al., 2017). Relative to the spared subgroup, FEP individuals in the impaired subgroup also appear to have poorer functioning at baseline (Amoretti et al., 2021; Oomen et al., 2021; Uren et al., 2017; Wenzel et al., 2021) as well as reduced premorbid functioning throughout childhood, early adolescence and late adolescence in the domain of scholastic performance (Tan et al., 2021). Meanwhile, FEP individuals in the spared subgroup are found to have greater premorbid IQ than those in the impaired subgroup, suggesting that high premorbid IQ may act as a buffer against later cognitive impairment (Reser et al., 2015; Tan et al., 2021; Uren et al., 2017; Wenzel et al., 2021). Importantly, clinical and functional outcomes are especially poor for cognitively impaired FEP individuals with greater negative symptom severity (Oomen et al., 2021; Uren et al., 2017) and poorer functioning also evident in impaired, relative to spared, subgroups at follow-up (Uren et al., 2017).

1.10.3 Evidence from clinical high-risk for psychosis samples

Meta-analyses have reported small to medium cognitive impairments in CHR-P samples that are intermediate in magnitude between HCs and those with FEP or established/multi-episode schizophrenia (Catalan, Salazar de Pablo, et al., 2021; Giuliano et al., 2012; Hauser et al., 2017). In the largest meta-analysis characterising cognitive functioning in CHR-P individuals to date (Catalan, Salazar de Pablo, et al., 2021), significant impairments were found across all 15 cognitive domains assessed relative to HCs. The most impaired domains were olfaction and verbal learning while the least impaired domains were social cognition and motor functioning. Notably, CHR-P individuals had better general intelligence, verbal learning and executive functioning, but not processing speed or premorbid IQ, when compared to FEP individuals.

Moreover, a smaller meta-analysis by Zheng et al. (2018) found that CHR-P individuals had large impairments in overall cognition, processing speed and attention/vigilance and medium impairments in working memory, reasoning and problem solving and visual and verbal learning, compared to HCs. Overall, the largest effect size was evident for processing speed (*d* = -1.21). Interestingly, slowed processing speed is proposed to underlie impairment in an array of neurocognitive domains and therefore to account for the generalised neurocognitive impairment among UHR (Randers et al., 2021) and FEP (Andersen et al., 2013; Rodríguez-Sánchez et al., 2007) individuals. Conversely, Zheng et al. (2018) were unable to detect significant differences in social cognition (*d* = -0.33) between CHR-P individuals and HCs, contrasting with findings from larger meta-analyses (Catalan, Salazar de Pablo, et al., 2021; T. Y. Lee et al., 2015). Indeed, significant impairments have been identified in all domains of social cognition among CHR-P individuals relative to HCs, with a large impairment in attributional bias, medium impairments in emotion processing and theory of mind and a small impairment in social perception (T. Y. Lee et al., 2015).

Interestingly, UHR individuals reportedly have poorer visual form perception and perceptual thinking (Ilonen et al., 2010) as well as visuospatial performance (Lindgren et al., 2010) when compared to non-UHR help-seeking individuals, indicating that reduced visuospatial ability may be specific to the UHR state. However, Carrión et al. (2018) did not detect any significant differences between non-transitioned UHR individuals and non-UHR help-seeking individuals, with overall neurocognitive performance in both groups at around -0.4 standard deviations below HCs. Indeed, a recent meta-analysis (Millman et al., 2022) found that neurocognitive impairment among non-transitioned CHR-P individuals was typically indistinguishable from clinical comparators, especially in the domains of working memory, verbal memory and fluency. Thus, neurocognitive impairments may not be specific to the UHR state and instead, may reflect a transdiagnostic vulnerability to psychopathology.

To date, one study has used cluster analysis to partition UHR individuals based on neurocognitive performance. Velthorst et al. (2019) derived four cognitive subgroups in a sample comprising UHR individuals, unaffected first-degree relatives of psychosis patients and HCs. Considerable cognitive heterogeneity

was evident with 14.5% of UHR participants labelled as significantly impaired, 29.5% as mildly impaired, 42.8% as normal and 13.2% as high normal, with the latter two subgroups reflecting average and above average performance, respectively, relative to HCs. The significantly impaired subgroup, which also contained 6.1% of first-degree relatives and 5.5% of HCs, distinguished itself from the other subgroups by larger deviations from HCs on processing speed and declarative memory. Interestingly, the significantly impaired subgroup also had a transition rate of 58%, a 40% chance of developing a schizophrenia spectrum disorder and significantly worse functioning at baseline and 12 months.

1.11 Clinical and functional outcomes and their relationship with cognition

Cognitive performance is shown to be significantly associated with functional outcomes and, to a lesser extent, clinical outcomes, in schizophrenia (Lepage et al., 2014), FEP (Lindgren et al., 2020) and CHR-P (Carrión et al., 2013) samples. Functional outcomes encompass quality of life, employment, independent living, social relationships and engagement in daily activities whereas clinical outcomes tend to focus more on psychopathology, for example, persistence or remission of symptoms (Lepage et al., 2014). Notably, remission and recovery rates remain low. According to a recent meta-analysis (Catalan, Richter, et al., 2021), 54% of FEP individuals are in symptomatic remission around 4 years after the onset of psychosis while 32% meet criteria for recovery, defined as symptomatic remission and significant functional improvement, after 5.5 years.

1.11.1 Evidence from schizophrenia samples

According to a recent study, 31% of individuals with a schizophrenia spectrum disorder have good functioning at baseline while 44% and 36% have good functional outcome 3 years and 6 years later, respectively (de Nijs et al., 2021). In general, both neurocognitive and social cognitive domains demonstrate small to medium relationships with functional outcomes in schizophrenia spectrum disorder samples (Fett et al., 2011; Halverson et al., 2019). However, social cognition appears to have a stronger involvement with functional outcomes than neurocognition. In one meta-analysis, Fett et al. (2011) found that social cognition accounted for 16% of the variance in community functioning while

neurocognition accounted for 6%. Similarly, a later meta-analysis by Halverson et al. (2019) found that social cognition could explain more unique variance in functional outcomes than neurocognition (7.3% vs. 4.4%).

Social cognition is also proposed to act as a mediator between neurocognition and functional outcome, with around 25% of the variance in functional outcome being explained by such mediation models in schizophrenia spectrum disorder samples (Schmidt et al., 2011). However, a significant proportion of the variance in functional outcome is not explained by neurocognitive or social cognitive performance, indicating that other factors are involved. Indeed, negative symptoms (Ventura et al., 2009), defeatist beliefs (Grant & Beck, 2009), intrinsic motivation (Nakagami et al., 2008) and metacognition (Lysaker et al., 2010) have also been proposed to mediate the relationship between neurocognition and functioning among those diagnosed with a schizophrenia spectrum disorder.

In terms of clinical outcomes, schizophrenia patients with greater neurocognitive ability appear to have a higher likelihood of achieving remission (Helldin et al., 2006). Johansson et al. (2020) recently investigated whether specific neurocognitive domains, assessed at baseline, were related to remission status over 5 consecutive years in patients with schizophrenia spectrum disorders. Overall, patients in the non-remission group had significantly poorer working memory, executive function and premorbid IQ than the group in stable remission with minimal symptoms. Interestingly, however, only premorbid IQ emerged as a significant predictor of remission status.

1.11.2 Evidence from first-episode psychosis samples

FEP individuals also display relatively poor long-term functioning. According to one study (Klærke et al., 2019), 41% of FEP patients have functional remission at 4 to 18 years follow-up (mean = 9.6 years). In a recent meta-analysis (Cowman et al., 2021), all cognitive domains under study were found to have a significant positive association with psychosocial functioning among individuals with early psychosis both cross-sectionally and longitudinally (r = 0.21 to 0.43), with the strongest associations observed for general cognitive ability and social cognition. Importantly, these associations remained significant even after accounting for symptom severity, duration of untreated psychosis and illness duration.

In terms of general cognitive ability, Leeson et al. (2009) found that poorer premorbid IQ and current IQ predicted poorer social functioning at 4-year follow-up among FEP individuals, after accounting for symptom scores. The amount of variance explained by IQ was relatively small, however, corresponding to 8% for premorbid IQ and 12% for current IQ. Focusing on social cognition, Horan et al. (2012) found that higher social cognition scores at baseline were associated with significantly better work functioning, independent living and social functioning at 12 months. The association between social cognition scores and work functioning remained significant even after accounting for clinical symptoms while associations with independent living and social functioning were diminished. More recently, Griffiths et al. (2021) found that poor social knowledge at baseline predicted poor social outcome at 12-month follow-up, explaining 6.4% of the variance, while poor verbal learning and memory at baseline predicted poor role outcome at 12-month follow-up, explaining 7.6% of the variance. However, these associations were no longer significant after accounting for negative symptoms. Indeed, negative symptoms emerged as the only significant predictor of poor role and social outcomes, explaining 20.2% and 15.9% of the variance, respectively.

These results concur with Lindgren et al. (2020) who evaluated both clinical and functional outcomes. In this study, impaired neurocognition at baseline was associated with poorer 1-year outcomes in terms of social and occupational level, occupational status and maintaining of life goals. Regarding specific domains, processing speed was associated with remission, occupational status and maintaining of life goals at follow-up while social cognition was associated with occupational status at follow-up and the need for hospital treatment in the first year after psychosis onset. Again, although most of these associations were retained when accounting for positive and affective symptoms, cognition no longer predicted outcomes at follow-up when accounting for negative symptoms. Other neurocognitive domains have also been associated with clinical outcomes in FEP samples. For example, Torgalsbøen et al. (2014) found that attention/vigilance scores at baseline significantly predicted remission status at 6-month follow-up while Hui et al. (2019) found that individuals with better short-term verbal memory at baseline were more likely to be relapse-free over 10 years.

1.11.3 Evidence from clinical high-risk for psychosis samples

Significant functional impairments are already present before the onset of psychosis. Indeed, 65.4% of UHR participants have poor social functioning while 66.9% have poor role functioning at baseline (Carrión et al., 2011). Furthermore, non-transitioned UHR individuals show persistent functional impairments at follow-up 3 to 5 years later with 40.3% of individuals displaying poor social outcomes and 45.5% displaying poor role outcomes (Carrión et al., 2013).

Reduced cognitive performance at baseline is consistently linked to impairments in functioning, although there is significant heterogeneity regarding the specific domains involved. Indeed, baseline impairments in global neurocognition (Carrión et al., 2011; Meyer et al., 2014), verbal learning and memory (Carrión et al., 2013; Hedges et al., 2022; Lin et al., 2011; Niendam et al., 2006), processing speed (Bolt et al., 2019; Carrión et al., 2011; Lin et al., 2011) and emotion recognition (Glenthøj et al., 2016, 2019; Modinos et al., 2019) have been associated with poor social and/or role functioning at both baseline and follow-up in UHR samples. Interestingly, although Glenthøj et al. (2019) found that emotion recognition latency was associated with four measures of functioning at baseline, this relationship was only maintained with one measure after controlling for processing speed.

Moreover, Carrión et al. (2011) found that global neurocognition scores accounted for 8% and 5% of the variance in social and role functioning, respectively, among UHR individuals at baseline. Specifically, processing speed was found to be a significant predictor of functioning at baseline, independent of positive symptoms, accounting for 10% and 7% of the variance in social and role functioning, respectively. Recently, Bolt et al. (2019) similarly found that impairments in processing speed at baseline were predictive of role functioning at follow-up in a UHR sample, uniquely explaining 3.4% of the variance, while impairments in verbal fluency at baseline were predictive of social functioning at follow-up, uniquely explaining 3.6% of the variance.

While these findings emphasise the importance of cognition for explaining psychosocial functioning, the amount of variance accounted for is relatively low, suggesting that other factors are involved. In a UHR sample, Carrión et al. (2013)

found that reduced processing speed, impaired social functioning and greater disorganised symptoms at baseline predicted poor social outcome at follow-up, accounting for 39% of the variance. Meanwhile, reduced verbal memory, motor disturbances and impaired role functioning at baseline predicted poor role outcome at follow-up, accounting for 32% of the variance. Importantly, this latter finding was independent of transition to psychosis and overall, social and role prediction models demonstrated high discriminative abilities with areas under the curve (AUCs) of 0.82 and 0.77, respectively. Similarly, Glenthøj, Kristensen, et al. (2020) found that reduced processing speed, impaired social functioning and greater negative symptoms at baseline predicted poor social outcome at 12-month follow-up among UHR individuals, explaining 52% of the variance. In contrast, impaired role functioning at baseline was the only predictor of poor role outcome at follow-up, explaining 25.2% of the variance. Nevertheless, this indicates that impaired functioning at baseline is a strong contributor to persistent functional impairments and concurs with evidence of a robust association between poor premorbid functioning and poor functional outcome among CHR-P individuals (Salokangas et al., 2014, 2021).

Relevant clinical outcomes include persistence of UHR status and transition to psychosis. Recently, a large meta-analysis (Catalan, Salazar de Pablo, et al., 2021) found that baseline impairments in verbal learning, visual memory, processing speed, attention/vigilance and general intelligence were associated with the longitudinal risk of psychosis onset, with small to medium effect sizes. In contrast, social cognition was not associated with transition to psychosis in an earlier meta-analysis (van Donkersgoed et al., 2015). In addition, impairments in immediate verbal memory have been found to predict non-remission from the UHR state at 2-year follow-up (Hedges et al., 2022; Simon et al., 2012). However, according to Glenthøj et al. (2021), neither neurocognitive nor social cognitive domains could predict remission from the UHR state at 12-month follow-up.

1.12 Cognitive training

Cognitive impairment has emerged as a promising intervention target in schizophrenia. In particular, there has been a growing interest in neuroplasticity-based computerised cognitive training. This approach aims to

improve higher-level cognitive functions, such as attention and working memory, through repetitive and intensive training (i.e. drill and practice training) of more basic cognitive processes, via progressively more challenging exercises (Reddy et al., 2014; Vinogradov et al., 2012). Interestingly, computerised cognitive training programmes that employ drill and practice training can effectively improve cognitive impairments in schizophrenia (Prikken et al., 2019). However, there is currently only preliminary evidence for their effectiveness in FEP (Fisher et al., 2015; Loewy et al., 2022) and CHR-P (Glenthøj et al., 2017) samples. Notably, drill and practice training differs from drill and strategy coaching which involves an explicit focus on teaching cognitive strategies, such as mnemonics, that can be applied to everyday life (Wykes et al., 2011).

Importantly, neural oscillations are a fundamental mechanism for enabling the synchronisation of neural activity within and between cortical areas during normal brain functioning and therefore, for enabling cognitive and perceptual processes (Uhlhaas et al., 2008). Specifically, neural oscillations are rhythmic patterns of neural activity in the CNS that occur at low and high frequencies, denoted as delta (0–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–30 Hz) and gamma (30–200 Hz). In particular, task-induced gamma-oscillations are shown to be impaired in chronic schizophrenia, FEP and CHR-P samples, relative to HCs (Grent-'t-Jong et al., 2016, 2020). However, while computerised cognitive training has been shown to enhance task-related gamma-band activity in schizophrenia (Dale et al., 2016, 2020; Popov et al., 2012), the impact on oscillatory activity in FEP and CHR-P participants is currently unknown. Notably, these studies employed magnetoencephalography (MEG) – a non-invasive neuroimaging technique with high temporal and good spatial resolution that allows researchers to track brain activity by measuring the magnetic fields generated by neurons in the brain (J. Gross, 2019).

1.12.1 Evidence from schizophrenia samples

Computerised cognitive training has been the focus of recent meta-analyses in schizophrenia spectrum disorder samples. For example, Kambeitz-Ilankovic et al. (2019) found that computerised cognitive training was associated with small to moderate improvements in cognition, functioning and clinical symptoms. Interestingly, computerised cognitive training was significantly more effective in

improving verbal memory and working memory when supplemented with therapeutic support in the form of strategy provision, employment programmes and metacognitive training. Meanwhile, Prikken et al. (2019) focused solely on studies utilising computerised drill and practice methods. Patients receiving cognitive training were found to have significant improvements in attention, working memory, positive symptoms and depressive symptoms relative to patients assigned to a control condition that did not target cognitive functioning.

A small number of studies have also reported increased task-related gamma-band activity after computerised cognitive training (Dale et al., 2016, 2020; Popov et al., 2012). Popov et al. (2012) randomly assigned schizophrenia inpatients to 20 hours of computerised auditory training over 4 weeks or to a broader computerised cognitive training programme of similar duration and intensity. They found increased gamma-band activity (60-80 Hz) in a centro-parietal cluster in response to auditory stimuli, but only after auditory training. Similarly, Dale et al. (2016, 2020) randomly assigned schizophrenia patients to 50 hours of computerised auditory training or 50 hours of computer games over 10 weeks. After training, patients in the auditory training condition showed increased high gamma-band activity (63-117 Hz): (1) within left dorsolateral prefrontal cortex and left inferior frontal gyrus immediately after stimulus presentation and later in bilateral temporal cortices during an auditory discrimination task (Dale et al., 2016); and (2) within left middle frontal and left middle-superior temporal cortices during stimulus encoding as part of an auditory working memory task (Dale et al., 2020). Interestingly, Dale et al. (2020) also found that patients in the computer games control condition had increased high gamma-band activity within regions of the right hemisphere during stimulus encoding, thus highlighting intervention-specific patterns of neuroplasticity during auditory encoding.

To date, studies of cognitive training in schizophrenia have largely focused on auditory processing. In contrast, fewer studies have examined methods for targeting visual processing impairments (Demmin et al., 2019). Recently, Scoriels et al. (2020) randomly assigned individuals with schizophrenia or schizoaffective disorder to 40 hours of auditory or visual computerised training. Participants in the visual training group showed significant improvements in

global cognition, attention and reasoning and problem solving pre- to post-training while those in the auditory training group showed significant improvements in reasoning and problem solving only. Furthermore, participants in the visual training group displayed significant decreases in positive, negative and general symptoms pre- to post-training whereas only positive symptoms were found to decrease in the auditory training group. Overall, visual and auditory training appear to be differentially effective in targeting cognitive impairment and symptomatology in schizophrenia.

1.12.2 Evidence from first-episode psychosis samples

Few studies have examined the impact of computerised cognitive training self-delivered by participants at home, without therapist support, in the early course of psychosis. In one such study, Fisher et al. (2015) randomly assigned 86 individuals with recent-onset schizophrenia to 40 hours of computerised auditory training or 40 hours of computer games over 8 weeks. Individuals in the auditory training condition demonstrated significant improvements in global cognition, verbal memory and problem solving relative to those in the computer games control condition. In addition, both groups showed a small but significant decrease in symptoms. However, there were no significant differences for functional outcome measures.

These findings have recently been updated to incorporate the final sample (N = 147) and to investigate durable effects 6 months post-training (Loewy et al., 2022). In the updated sample, individuals in the auditory training condition demonstrated significant improvements in global cognition and problem solving relative to those in the computer games control condition from pre- to post-training and also from pre-training to 6-month follow-up. Notably, individuals in the auditory training condition also demonstrated significant improvements in working memory relative to controls from pre- to post-training while the previous improvement in verbal memory was no longer significant, most likely due to differences in the sample sizes and analyses used. As before, functioning showed no improvement. However, individuals in the auditory training condition did show significantly greater improvement than the control group in positive symptoms from pre-training to 6-month follow-up. Therefore, computerised

cognitive training, completed independently and remotely, appears to improve both cognition and symptoms.

Several studies have also explored the neurobiological effects of cognitive training in recent-onset schizophrenia. In a subset of individuals from the Fisher et al. (2015) study, improvements in global cognition were significantly correlated with increases in left thalamic volume (Ramsay et al., 2018) and thalamo-temporal connectivity (Ramsay et al., 2020) in the auditory training group. Furthermore, cognitive enhancement therapy, which involves drill and strategy coaching, has been shown to protect against grey matter loss (Eack et al., 2010) and to enhance resting-state functional connectivity between frontal and temporal brain regions (Eack et al., 2016) among individuals in the early course of a schizophrenia spectrum disorder, with most of these neuroplastic changes also related to improvements in neurocognition and/or social cognition. However, the extent to which these effects were mediated by the computerised cognitive training element or by other elements of the intervention, such as the group-based social skills training, is unclear.

1.12.3 Evidence from clinical high-risk for psychosis samples

A recent systematic review examining six studies on computerised cognitive training in the CHR-P population provided preliminary evidence for the effectiveness of cognitive training on cognition and functional outcome (Glenthøj et al., 2017). Five of these studies delivered computerised cognitive training via drill and practice methods, with training either delivered in a group-based training format (Choi et al., 2017; Rauchensteiner et al., 2011) or completed independently at the participant's home or in the research facility (Hooker et al., 2014; Loewy et al., 2016; Piskulic et al., 2015).

Piskulic et al. (2015) and Loewy et al. (2016) both randomised UHR participants to either 40 hours of computerised auditory training or 40 hours of computer games. Specifically, Loewy et al. (2016) found that individuals in the auditory training group had a significant improvement in verbal memory compared to those in the computer games control group (d = 0.61) pre- to post-training whereas Piskulic et al. (2015) did not detect any significant between-group differences in cognitive performance. In terms of adherence, the average

training duration was closer to 20 hours across both groups in both studies and attrition rates were high with 38% (Loewy et al., 2016) to 48% (Piskulic et al., 2015) of individuals in the auditory training group discontinuing the intervention.

On the other hand, Choi et al. (2017) achieved better participant engagement with an attrition rate of 10% in the group exposed to computerised cognitive training. Specifically, Choi et al. (2017) randomised UHR individuals to either 30 hours of processing speed training or 30 hours of arcade-style games over 2 months. Processing speed training incorporated pupillometry-based neurofeedback where task difficulty is adjusted in real-time based on each participant's pupil response. Overall, individuals in the processing speed training group had faster motoric and non-motoric processing speed at post-training and 2-month follow-up and better social adjustment at follow-up compared to those in the active control group, with medium to large effect sizes. Furthermore, improvements in motoric processing speed between pre-training and follow-up were correlated with improvements in social adjustment and social anxiety.

Two small uncontrolled pilot studies have also been conducted in addition to the aforementioned randomised controlled trials (RCTs). Rauchensteiner et al. (2011) examined the differential effects of computerised cognitive training in CHR-P individuals (n = 10) as compared to patients with schizophrenia (n = 16). Specifically, participants were asked to complete 10 hours of cognitive training within 4 weeks. They found that the CHR-P group had significant improvements in attention and long-term verbal memory from pre- to post-training. In addition, the CHR-P group had significantly greater improvements in long-term verbal memory when compared to the group of patients with schizophrenia. Meanwhile, Hooker et al. (2014) examined the feasibility and potential benefits of a 40-hour computerised cognitive training programme over 8 weeks in a single group of UHR participants (N = 14). Participants had significant improvements in processing speed pre- to post-training (d = 0.63) and, notably, improvements in processing speed were also associated with gains in role functioning.

Overall, these studies suggest that computerised cognitive training may have efficacy for improving cognition in the domains of verbal memory, attention and processing speed in the CHR-P population. Importantly, however, the

neurobiological effects of computerised cognitive training in the CHR-P population are largely unknown.

1.13 Aims of this thesis

Clearly, the early stages of psychosis (i.e. CHR-P and FEP stages) are associated with a broad range of negative outcomes including suicidality and self-harm and impairments in cognitive performance and functioning. Thus, current findings emphasise the need for more effective early detection and intervention strategies.

Chapters 2 to 4 of this thesis will leverage data from the Youth Mental Health Risk and Resilience (YouR) study (Uhlhaas et al., 2017) in order to investigate suicidality and non-suicidal self-harm, cognitive impairment, cognitive heterogeneity and functioning in more representative samples of CHR-P and FEP individuals (i.e. samples primarily recruited from the general population). While it is not recommended to directly screen individuals in the community using CHR-P assessment tools, this can become viable if individuals undergo adequate risk enrichment beforehand via, for example, screening questionnaires (Fusar-Poli et al., 2019). Using such an approach, the YouR-study recently provided the first evidence for the feasibility of a web-based screening platform for detecting CHR-P and FEP individuals at the population level (McDonald et al., 2019).

In addition, Chapter 5 will utilise previous participants of the YouR-study to investigate the feasibility of a digital intervention in the early stages of psychosis. Digital mental health approaches present new opportunities for improving early intervention strategies in an engaging and tailored manner. For example, computerised cognitive training offers several advantages over traditional cognitive training including remotely accessible training; structured, flexible and standardised exercises; automatic adaptation of exercise difficulty based on participants' performance; online monitoring of participants' progress; and the possibility to perform the training with little support, thereby reducing costs (Kambeitz-Ilankovic et al., 2019; Prikken et al., 2019).

Overall, this thesis aims to address several important gaps in our current understanding of early-stage psychosis. Firstly, the majority of studies examining

suicidality and self-harm in the early stages of psychosis have recruited individuals via clinical pathways, thus limiting the generalisability of findings. Therefore, Chapter 2 aims to investigate the prevalence of suicidality and non-suicidal self-harm among community-recruited CHR-P and FEP participants as well as factors associated with current suicidal ideation in the CHR-P group. Furthermore, although previous studies have highlighted substantial impairments in both cognition and functioning in CHR-P samples, the contribution of cognitive impairments to poor functioning remains unclear. Therefore, focusing on CHR-P individuals, Chapter 3 aims to investigate the potential utility of including cognitive variables in models of functioning via machine learning methods. In addition, since little is known about cognitive heterogeneity in the CHR-P state, Chapter 4 aims to investigate whether cognitive subgroups can be identified in the early stages of psychosis using cluster analysis and, if so, whether these subgroups are associated with clinical and functional outcomes in the CHR-P group. Finally, although computerised cognitive training in the early stages of psychosis appears to be effective in improving cognition, the effect on oscillatory brain activity is not yet known. To address this issue, Chapter 5 reports on a pilot study which aims to investigate whether neuroplasticity-based computerised cognitive training can improve cognition and enhance oscillatory brain activity in a small sample of CHR-P and FEP participants.

The assessment materials used in Chapters 2 to 5 are outlined in the Glossary of Measures on pages 201-206.

Chapter 2 Prevalence and predictors of suicidality and non-suicidal self-harm among individuals at clinical high-risk for psychosis: Results from a community-recruited sample

This chapter is an exact copy of the author accepted manuscript of the following publication:

Haining, K., Karagiorgou, O., Gajwani, R., Gross, J., Gumley, A. I., Lawrie, S. M., Schwannauer, M., Schultze-Lutter, F., & Uhlhaas, P. J. (2021). Prevalence and predictors of suicidality and non-suicidal self-harm among individuals at clinical high-risk for psychosis: Results from a community-recruited sample. *Early Intervention in Psychiatry, 15*(5), 1256–1265. https://doi.org/10.1111/eip.13075

The supplementary material for Chapter 2 is presented in Appendix A.

2.1 Abstract

Aim: Suicidal thoughts and behaviours are prevalent in individuals with schizophrenia. However, research examining the prevalence and predictors of suicidality and self-harm in participants at clinical high-risk for psychosis (CHR-P) is limited and mostly focuses on help-seeking participants recruited through clinical pathways. The current study sought to assess the prevalence of suicidality and self-harm and identify predictors of current suicidal ideation in community-recruited CHR-P participants.

Methods: Data were available for 130 CHR-P participants, 15 participants with first-episode psychosis (FEP), 47 participants not fulfilling CHR-P criteria (CHR-Ns) and 53 healthy controls (HCs). Current and lifetime suicidality and self-harm were assessed using the Mini-International Neuropsychiatric Interview (MINI) and the Comprehensive Assessment of At-Risk Mental States (CAARMS). Multivariable logistic regression analysis was used to determine predictors of current suicidal ideation in the CHR-P group.

Results: A considerable proportion of CHR-P participants disclosed current suicidal ideation (34.6%). Overall, FEP individuals were at greatest risk, with considerably high prevalence rates for current suicidal ideation (73.3%), lifetime self-harm behaviour (60.0%) and lifetime suicide attempt (60.0%). In the CHR-P sample, current suicidal ideation was predicted by lifetime suicide attempts, lower CAARMS severity, impaired social functioning and greater comorbidity.

Conclusions: Our findings suggest that suicidality and self-harm are highly prevalent in community-recruited CHR-P and FEP individuals. Accordingly, these results highlight the importance of further research into the determinants of suicidality and self-harm during at-risk and early stages of psychosis, and the implementation of intervention strategies to reduce adverse outcomes in these populations.

2.2 Introduction

Psychotic disorders, such as schizophrenia, are strongly linked to high levels of suicidality. Compared to the general population, individuals with schizophrenia have a 13-fold greater risk of suicide (Too et al., 2019) and approximately 4.9% die by suicide (Palmer, Pankratz, & Bostwick, 2005). Individuals with first-episode psychosis (FEP) comprise a particularly vulnerable group. Indeed, suicide risk is elevated by 60% within the first year of treatment relative to later stages (Nordentoft et al., 2004).

Research examining the prevalence of suicidality and self-harm in individuals at clinical high-risk for psychosis (CHR-P) is more limited albeit emerging (Pelizza et al., 2020; Taylor, Hutton, & Wood, 2015). CHR-P participants are characterised using ultra-high risk (UHR) criteria, which include attenuated psychotic symptoms, brief frank psychosis and functional decline with genetic risk (Yung et al., 2005), as well as basic symptom criteria relying on perceptual and cognitive disturbances self-experienced with full and immediate insight (Schultze-Lutter, 2009; Schultze-Lutter et al., 2012). Over a 2-year period, around 20% of individuals meeting UHR criteria transition to psychosis (Fusar-Poli, Cappucciati, et al., 2016). Moreover, in a UHR sample, approximately 45% of nonconverters experienced either poor social or role outcome (Carrión et al., 2013); impairments previously related to persistence of CHR-P symptoms (Michel, Ruhrmann, Schimmelmann, Klosterkötter, & Schultze-Lutter, 2018).

A recent meta-analysis reported prevalence rates of 66% for current suicidal ideation, 18% for lifetime suicide attempts and 49% for lifetime self-harm behaviour in UHR samples, comparable to those observed in FEP cohorts (Taylor et al., 2015). Furthermore, in a retrospective study of prodromal suicide risk among individuals with schizophrenia, 25.5% had experienced suicidal ideation and 7.5% had attempted suicide (Andriopoulos, Ellul, Skokou, & Beratis, 2011). More recently, Pelizza et al. (2020) found that UHR individuals disclosed more severe suicidal ideation and were more likely to report previous suicide attempts than FEP and non-UHR/FEP samples. Therefore, there is a need to further identify the factors underlying the emergence of suicidality and self-harm in CHR-P populations.

However, relatively little is known about the predictors of suicidality and self-harm in CHP-P individuals. Paranoid thinking, depressive symptoms and impaired role functioning have been found to predict current suicidal ideation (Andriopoulos et al., 2011; Bang et al., 2017; Pelizza et al., 2019), while the presence of personality disorders and history of trauma strongly predict suicide attempts (Zuschlag, Korte, & Hamner, 2018), consistent with findings in established schizophrenia and other psychiatric populations (Aaltonen et al., 2016; Bornheimer, 2016; Fuller-Thomson & Hollister, 2016). Within these latter cohorts, suicidal ideation and previous suicide attempts have been identified as two of the strongest predictors of completed suicide (Fosse, Ryberg, Carlsson, & Hammer, 2017; Lopez-Morinigo et al., 2016) and future suicide attempts (Bertelsen et al., 2007; Horwitz, Czyz, & King, 2015).

To date, the majority of studies investigating suicidality and self-harm in CHR-P populations involve help-seeking participants recruited through clinical pathways by UHR criteria. Accordingly, it is unclear whether the prevalence rates and predictors of suicidality and self-harm identified in these studies generalise to more representative community samples as well as CHR-P individuals recruited using UHR and/or basic symptom criteria. This is an important question given that recruitment pathways have been shown to impact on transition rates in CHR-P samples. Indeed, pretest risk for psychosis, although enriched in help-seeking samples, appears to be lower in community-recruited samples, reducing the likelihood of subsequent transitions (Fusar-Poli, Schultze-Lutter, et al., 2016).

In the current study, we sought to assess the prevalence of suicidality and self-harm in community-recruited CHR-P and FEP participants. We also included participants who did not fulfil CHR-P criteria but were characterised by psychiatric comorbidities (CHR-Ns) as well as a group of healthy controls (HCs). In addition, we aimed to identify predictors of current suicidal ideation in the CHR-P group. Social support, insecure attachment orientations and cognitive ability were also investigated given their relation with suicidality in the general population (Kleiman & Liu, 2013; Kosidou, Dalman, Fredlund, & Magnusson, 2014; Sörberg, Allebeck, Melin, Gunnell, & Hemmingsson, 2013; Zortea, Gray, & O'Connor, 2019).

Given these findings, we hypothesised that (1) CHR-P and FEP participants would show comparably higher levels of suicidality and self-harm than CHR-N and HC participants and (2) a range of clinical, functional and cognitive variables would emerge as significant predictors of current suicidal ideation in CHR-P participants.

2.3 Methods

2.3.1 Participants

Participants were recruited 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. Utilising an online-screening approach (McDonald et al., 2019), potential CHR-P participants from the general population were directed to our website (www.yourstudy.org.uk) via email invitations, posters and flyers over a 4-year period. FEP and CHR-N participants were also recruited using this approach while HCs were obtained from an existing volunteer database. Screening questionnaires comprised (a) the 16-item Prodromal Questionnaire (PQ-16; Ising et al., 2012) and (b) a nine-item scale of Perceptual and Cognitive Anomalies (PCA) for assessing basic symptoms. Participants were invited for clinical interviews if they positively endorsed six or more items on the PQ-16 and/or three or more items on the PCA.

Data were available for 130 CHR-P individuals that were recruited across two sites: Glasgow (n = 94; 72.3%) and Edinburgh (n = 36; 27.7%). We also obtained a community-recruited sample of 15 FEP participants, 47 CHR-N participants and 53 HCs.

2.3.2 Instruments and measures

In order to establish CHR-P criteria, 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, Addington, Ruhrmann, & Klosterkötter, 2007) were

administered by trained research assistants and MSc/PhD level researchers. Participants were recruited into the CHR-P group if they met SPI-A COGDIS/COPER criteria and/or one of the following CAARMS criteria: attenuated psychotic symptoms (APS), genetic risk and functional deterioration (GRFD) or brief limited intermittent psychotic symptoms (BLIPS). FEP criteria were established using the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987) as well as the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 2002).

Current (past month) and lifetime suicidality and self-harm were assessed using the six-item suicidality module of the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) as well as questions contained in the CAARMS suicidality and self-harm subscale. For FEP participants, only the latter assessment of suicidality and self-harm was available.

In addition, with the exception of the FEP group, all participants were assessed with the Global Functioning: Social (GF: Social) and Role (GF: Role) scales (Cornblatt et al., 2007), Premorbid Adjustment Scale (PAS; Cannon-Spoor, Potkin, & Wyatt, 1982), Adverse Childhood Experiences Scale (ACES; Felitti et al., 1998), Psychosis Attachment Measure (PAM; Berry, Wearden, Barrowclough, & Liversidge, 2006), Significant Others Scale (SOS; Power, Champion, & Aris, 1988) and Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004). Psychiatric comorbidity was calculated from the MINI by summing the number of current comorbid Axis I disorders disclosed by participants from a possible total of five (mood disorder, anxiety disorder, drug abuse/dependence, alcohol abuse/dependence, eating disorder).

2.3.3 Statistical methods

Data were analysed using SPSS version 26 with statistical significance set at $p < .05$ (two-tailed). The BACS composite score was calculated by averaging the *z*-scores obtained from the six primary measures and re-standardising this value using the means and standard deviations of sex-specific HCs (Keefe et al., 2004). Overall, 1.2% of the data (48 of 4,030 values) were missing and imputed by Bayesian imputation.

Group differences were analysed using Kruskal-Wallis *H* tests and Pearson's chi-square or Fisher-Freeman-Halton tests followed by appropriate Bonferroni-corrected post hoc tests if required. Collinearity of predictors was defined as any variance inflation factor (VIF) > 2 and tolerance < 0.40. Multivariable logistic regression analysis, using stepwise backward selection (likelihood ratio), was employed to determine predictors of current suicidal ideation in the CHR-P group. This outcome variable was prioritised as it did not violate the events per variable (EPV) rule of 5:1 suggested by Vittinghoff and McCulloch (2007). The overall variance explained by the model was measured by the Nagelkerke pseudo R^2 statistic (R^2N). Diagnostic accuracy of the model was determined using the area under the receiver operating characteristic (ROC) curve (AUC).

2.4 Results

2.4.1 Demographic data

CHR-P individuals were significantly impaired relative to CHR-N and HC participants, displaying greater CAARMS and SPI-A severity, higher comorbidity, lower social and role functioning and greater levels of insecure attachment (Table 2). As expected, FEP participants had significantly higher CAARMS severity compared to all other groups and greater antipsychotic use compared to CHR-P participants. Although significant group differences emerged for age, these effects did not survive Bonferroni-corrected post hoc tests.

A significantly larger proportion of FEP and CHR-P participants received current or past treatment compared to HCs (Table 2). Twenty percent of FEP participants and 16.2% of CHR-P participants were in current treatment while 60.0% of FEP participants and 45.4% of CHR-P participants received past treatment. CHR-N participants (31.9%) were also significantly more likely than HCs (5.7%) to have engaged in past treatment.

In addition, among the CHR-P group, 39 (30.0%) met CAARMS criteria, 32 (24.6%) met SPI-A criteria and 59 (45.4%) met both. Of those meeting CAARMS, 95.9% met APS criteria, 2.0% met GRFD criteria and 2.0% met both APS and GRFD criteria; while, of those meeting SPI-A criteria, 46.2% met COPER criteria, 14.3% met COGDIS criteria and 39.6% met both. Furthermore, the FEP group consisted

of participants with SCID DSM-IV psychotic disorder not otherwise specified (n = 7; 46.7%), schizophrenia (n = 6; 40.0%) and schizoaffective disorder (n = 2; 13.3%).

Table 2 - Demographic, clinical, functional and cognitive characteristics of the total sample (N = 245)

	CHR-P (1) (N = 130)	FEP (2) (N = 15)	CHR-N (3) (N = 47)	HC (4) (N = 53)	*p*	Effect size[a]	Post hoc test[b]
Age (years), mean (SD)	21.64 (4.27)	23.73 (4.79)	22.94 (4.80)	22.42 (3.36)	.044	η^2_p = 0.033	..
Gender, female n (%)	94 (72.3)	10 (66.7)	30 (63.8)	36 (67.9)	.727	*V* = 0.073	..
Education (years), mean (SD)	15.40 (2.95)	15.80 (3.38)	16.45 (3.44)	16.47 (2.85)	.070	η^2_p = 0.029	..
Suicidality and self-harm, n (%)							
Self-harm intention (past month)	37 (28.5)	..	4 (8.5)	0 (0)	<.001	*V* = 0.325	1 > 3,4
Self-harm behaviour (past month)	7 (5.4)	3 (20.0)	0 (0)	0 (0)	.005	*V* = 0.244	2 > 3,4
Self-harm behaviour (lifetime)	37 (28.5)	9 (60.0)	5 (10.6)	2 (3.8)	<.001	*V* = 0.349	2 > 3,4 & 1 > 4
Suicide plan (past month)	12 (9.2)	1 (6.7)	3 (6.4)	1 (1.9)	.332	*V* = 0.114	..
Suicidal ideation (past month)	45 (34.6)	11 (73.3)	9 (19.1)	1 (1.9)	<.001	*V* = 0.397	2 > 1,3,4 & 1,3 > 4
Suicide attempt (past month)	3 (2.3)	1 (6.7)	0 (0)	0 (0)	.201	*V* = 0.134	..
Suicide attempt (lifetime)	38 (29.2)	9 (60.0)	4 (8.5)	0 (0)	<.001	*V* = 0.393	1,2 > 3,4
MINI suicidality risk, n (%)							
Low	28 (21.5)	..	3 (6.4)	1 (1.9)	.001	*V* = 0.255	1 > 4
Moderate	21 (16.2)	..	3 (6.4)	0 (0)	.003	*V* = 0.224	1 > 4
High	21 (16.2)	..	5 (10.6)	0 (0)	.007	*V* = 0.207	1,3 > 4
CAARMS severity, median (range)	29 (0-74)	88 (38-122)	6 (0-24)	0 (0-12)	<.001	η^2_p = 0.408	2 > 1 > 3 > 4
SPI-A severity, median (range)	7 (0-74)	14 (0-109)	0 (0-7)	0 (0-2)	<.001	η^2_p = 0.338	1, 2 > 3,4

ACES total, median (range)	2 (0-8)	··	1 (0-5)	0 (0-4)	<.001	η^2_p = 0.111	1 > 4
Comorbidity, median (range)	2 (0-5)	··	1 (0-3)	0 (0)	<.001	η^2_p = 0.306	1,3 > 4 & 1 > 3
Psychological treatment, n (%)							
Current	21 (16.2)	3 (20.0)	5 (10.6)	0 (0)	.015	*V* = 0.207	1,2 > 4
Past	59 (45.4)	9 (60.0)	15 (31.9)	3 (5.7)	<.001	*V* = 0.353	1,2,3 > 4
Medication, n (%)							
Antidepressants	46 (35.4)	7 (46.7)	13 (27.7)	0 (0)	<.001	*V* = 0.333	1,2,3 > 4
Mood stabilisers	4 (3.1)	0 (0)	0 (0)	0 (0)	.534	*V* = 0.121	··
Antipsychotics	2 (1.5)	2 (13.3)	0 (0)	0 (0)	.039	*V* = 0.243	2 > 1,4
Anxiolytics	8 (6.2)	2 (13.3)	1 (2.1)	0 (0)	.060	*V* = 0.165	··
Social functioning (current), median (range)	8 (3-10)	··	8 (6-9)	9 (8-10)	<.001	η^2_p = 0.224	4 > 1,3 & 3 > 1
Role functioning (current), median (range)	8 (3-9)	··	8 (5-9)	9 (5-9)	<.001	η^2_p = 0.191	4 > 1,3 & 3 > 1
PAS average, median (range)	1.20 (0-3.43)	··	0.86 (0-3.86)	0.43 (0-1.64)	<.001	η^2_p = 0.183	1,3 > 4
Social support, mean (SD)	5.05 (0.89)	··	5.30 (0.87)	6.02 (0.59)	<.001	η^2_p = 0.168	4 > 1,3
Insecure attachment, mean (SD)	1.75 (0.46)	··	1.41 (0.50)	1.01 (0.46)	<.001	η^2_p = 0.226	1,3 > 4 & 1 > 3
BACS composite score, mean (SD)	-0.39 (1.64)	··	-0.02 (1.38)	0 (1.01)	.140	η^2_p = 0.017	··

Note: CHR-P, clinical high-risk for psychosis; FEP, first episode psychosis; CHR-N, clinical high-risk-negative; HC, healthy control; MINI, Mini-International Neuropsychiatric Interview; CAARMS, Comprehensive Assessment of At-Risk Mental States; SPI-A, Schizophrenia Proneness Instrument, Adult version; ACES, Adverse Childhood Experiences Scale; PAS, Premorbid Adjustment Scale; BACS, Brief Assessment of Cognition in Schizophrenia.
[a] Effect sizes were eta squared (η^2p) for Kruskal-Wallis *H* tests (small effect = 0.01, medium effect = 0.06, large effect = 0.14) and Cramer's *V* for Pearson's chi-square or Fisher-Freeman-Halton tests (small effect = 0.1, medium effect = 0.3, large effect = 0.5).
[b] 1 = CHR-P, 2= FEP, 3 = CHR-N, 4 = HC

2.4.2 Suicidality and self-harm prevalence

Lifetime suicide attempts were significantly more prominent in individuals meeting CHR-P (29.2%) and FEP (60.0%) criteria compared to CHR-N (8.5%) and HC (0%) participants (Table 2; Figure 1). In addition, relative to HCs, CHR-P participants more commonly disclosed current suicidal ideation (34.6%), current self-harm intention (28.5%) and lifetime self-harm behaviour (28.5%) whilst CHR-N participants were more likely to report current suicidal ideation (19.1%). Current self-harm intention was also reported significantly more in CHR-P than in CHR-N individuals (28.5% vs. 8.5%). Overall, 32.4% of CHR-P and 17.0% of CHR-N participants were categorised as currently at moderate- to high-risk of suicide. The FEP group was at greatest risk, with considerably high prevalence rates for current suicidal ideation (73.3%), lifetime self-harm behaviour (60.0%) and lifetime suicide attempt (60.0%).

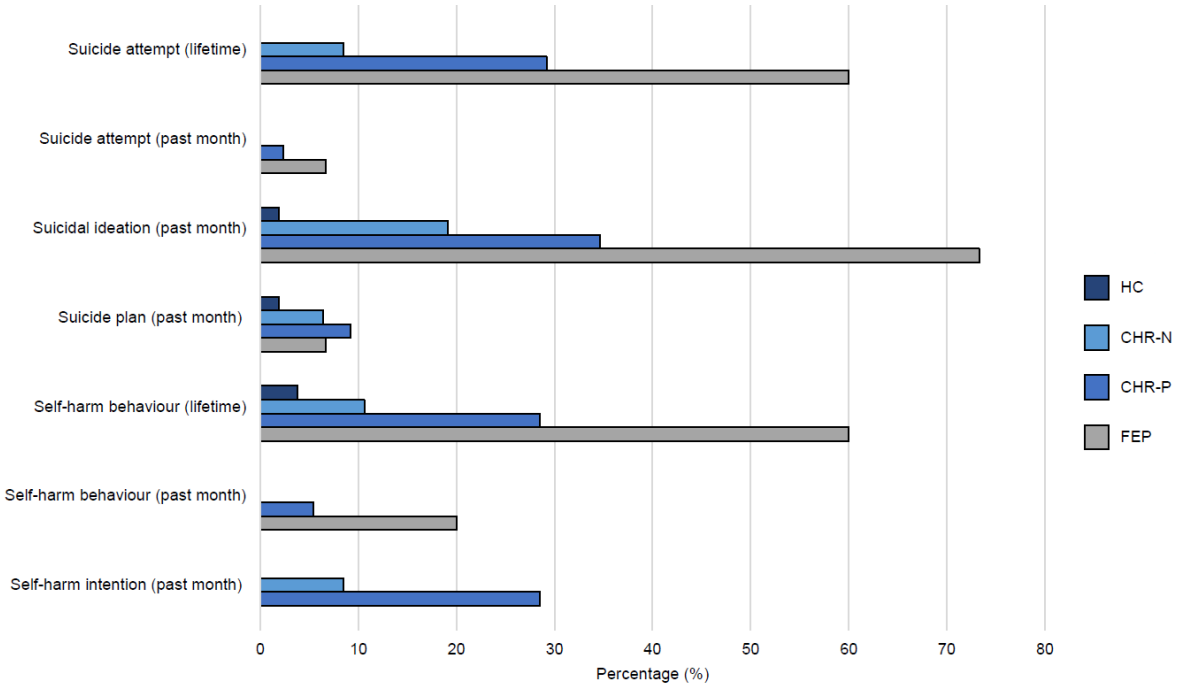

Figure 1 - Suicidality and self-harm profile of the total sample (N = 245)

2.4.3 Impact of recruitment pathway

We further compared our community-recruited CHR-P sample to a smaller group of CHR-P individuals (n = 16) recruited via referrals from clinical services in NHS Greater Glasgow and Clyde and NHS Lothian as well as student counselling

services (Supplementary Table 1). Referred participants had significantly fewer years of education, poorer functioning and lower BACS composite score than community-recruited participants. However, no significant group differences were observed on suicide-related variables.

2.4.4 Predictors of current suicidal ideation in CHR-P participants

Multivariable logistic regression analysis was used to determine predictors of current suicidal ideation in CHR-P individuals. We did not identify any sources of multicollinearity among the potential predictor variables.

Predictors of current suicidal ideation in CHR-P participants included lifetime suicide attempts, lower CAARMS severity, impaired social functioning and premorbid adjustment and greater comorbidity although premorbid adjustment did not contribute significantly to the model (Table 3).

Table 3 - Multivariable logistic regression model for suicidal ideation (past month) in CHR-P participants (N = 130)

Variable	Beta	SE	Wald	*p*	OR (95% CI)	AUC (SE) [95% CI]	R^2_N	Sensitivity	Specificity
Suicide attempt (lifetime)	0.994	0.484	4.221	.040	2.701 (1.047-6.969)				
CAARMS severity	-0.030	0.015	4.110	.043	0.971 (0.943-0.999)				
Social functioning (current)	-0.496	0.216	5.246	.022	0.609 (0.399-0.931)	0.797 (0.039) [0.720-0.874]	0.324	46.7	82.4
Premorbid adjustment	0.577	0.344	2.804	.094	1.780 (0.906-3.495)				
Comorbidity	0.489	0.199	6.030	.014	1.631 (1.104-2.411)				

Note. CHR-P, clinical high-risk for psychosis; CAARMS, Comprehensive Assessment of At-Risk Mental States; Beta, unstandardised regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval; AUC, area under the curve; R^2_N, Nagelkerke pseudo R^2 statistic.

This model explained 32.4% of the variance with an acceptable AUC of 0.797 (p < .001), specificity of 82.4% and sensitivity of 46.7% (Figure 2).

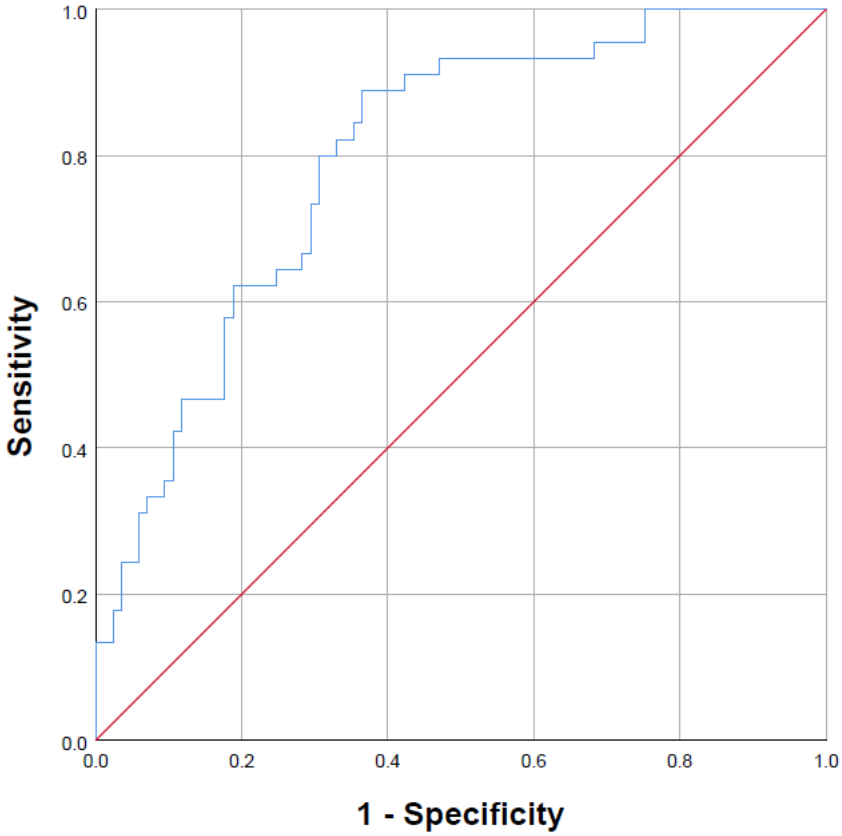

Figure 2 - Receiver-operating characteristic curve for the multivariable logistic regression model predicting suicidal ideation (past month) in CHR-P participants (N = 130)

2.5 Discussion

We examined the prevalence of suicidality and self-harm in CHR-P and FEP samples as well as predictors of current suicidal ideation in CHR-P individuals. Our findings suggest that suicidality and self-harm are highly prevalent in community-recruited CHR-P and FEP groups with the latter at greatest risk. In addition, lifetime suicide attempts, lower CAARMS severity, impaired social functioning and greater comorbidity significantly predicted current suicidal ideation in CHR-P participants.

2.5.1 Suicidality and self-harm prevalence

Our findings highlight significant levels of suicidality and self-harm in CHR-P individuals recruited from the community. Current suicidal ideation was most commonly disclosed with a prevalence rate of 34.6%, comparable to previous estimates of 30% (DeVylder et al., 2012) and 42.9% (Gill et al., 2015) within help-seeking UHR samples. Similarly large proportions of our CHR-P sample reported lifetime suicide attempts (29.2%), lifetime self-harm behaviour (28.5%) and current self-harm intention (28.5%). Interestingly, prevalence estimates for lifetime suicide attempts are generally lower in help-seeking UHR samples, ranging between 8.6% and 18% (Pelizza et al., 2019, 2020; Preti, Meneghelli, Pisano, & Cocchi, 2009; Taylor et al., 2015). One possibility is that clinically-recruited UHR participants, through their established contact with mental health services, have better coping skills in comparison to community-recruited individuals. Overall, the current findings demonstrate that high rates of suicidality and self-harm are not restricted to clinically-recruited UHR samples.

In contrast to previous studies, our results suggest that suicidality and self-harm are more prevalent in FEP as compared to CHR-P participants, especially with regard to current suicidal ideation (Pelizza et al., 2019, 2020; Preti et al., 2009). Our FEP group exhibited prevalence rates for current suicidal ideation (73.3%), lifetime self-harm behaviour (60.0%) and lifetime suicide attempts (60.0%) that were approximately two to 11 times greater than those typically reported in FEP samples (Bertelsen et al., 2007; Challis, Nielssen, Harris, & Large, 2013; Pelizza et al., 2020; Preti et al., 2009), possibly resulting from our focus on community-recruitment. Indeed, given that only 20.0% of FEP participants were in current psychological treatment and 13.3% received antipsychotics, these individuals may not be receiving appropriate clinical attention and support for their heightened psychotic symptoms and associated distress, thereby increasing suicidality risk.

Notably, CHR-N individuals were characterised by relatively modest suicidality and self-harm, potentially attributable to the lower comorbidity and better functioning observed in this group relative to the CHR-P sample. Significantly more CHR-N participants reported current suicidal ideation (19.1%) compared to HCs (1.9%), however; contrasting with the higher prevalence rates of 33.3%

(Pelizza et al., 2020) and 45% (Pelizza et al., 2019) reported in help-seeking samples.

2.5.2 Predictors of current suicidal ideation in CHR-P participants

In the CHR-P group, significant predictors of current suicidal ideation included lifetime suicide attempts, lower CAARMS severity, impaired social functioning and greater comorbidity. The final model explained 32.4% of the variance in current suicidal ideation, in line with previous findings in help-seeking UHR cohorts (Bang et al., 2017; Pelizza et al., 2019).

Our results also concur with prior research in UHR and schizophrenia samples wherein depressive mood, increased psychiatric comorbidity and poor functioning have emerged as predictors of suicidal ideation (Andriopoulos et al., 2011; Bornheimer, 2016; Harvey et al., 2018; Pelizza et al., 2019). Furthermore, these findings are in accordance with the interpersonal theory of suicide (Joiner, 2005; Van Orden et al., 2010) which implicates perceived alienation from, and lack of meaningful connections with, friends, family and others (i.e. thwarted belongingness). The emergence of lower, rather than higher, CAARMS severity as a significant predictor of current suicidal ideation, however, contrasts with previous findings in help-seeking UHR samples (Bang et al., 2017).

Overall, the strongest predictor of current suicidal ideation was lifetime suicide attempts, concurring with previous findings in schizophrenia (Kim et al., 2010). Given that suicidal ideation is also highly predictive of future suicide attempts and completed suicide in both schizophrenia samples and psychiatric patient populations (Bertelsen et al., 2007; Fosse et al., 2017; Horwitz et al., 2015; Lopez-Morinigo et al., 2016), effectively identifying CHR-P individuals with current suicidal ideation is a critical step towards managing risk and reducing suicide deaths.

Contrary to findings from the general population (Kleiman & Liu, 2013; Kosidou et al., 2014; Sörberg et al., 2013; Zortea et al., 2019), social support, insecure attachment orientations and cognitive ability did not emerge as predictors of suicidality, perhaps owing to differing assessment measures. In addition, although characterised by excellent specificity, the prediction model yielded

limited sensitivity. This issue is commonly noted for suicide prediction models which may limit their clinical value (Kessler, Bossarte, Luedtke, Zaslavsky, & Zubizarreta, 2020). In order to optimise model performance, future research should consider employing advanced machine learning methods as well as more comprehensive predictor sets incorporating, for example, biological predictors.

2.5.3 Limitations

The sample size of CHR-P participants with current suicidal ideation was relatively small, limiting the number of variables that could be included in a single model and perhaps reducing the generalisability of the findings.

In addition, information regarding suicidality and self-harm was elicited via self-report questions – a method particularly susceptible to social desirability response bias; or to exaggeration by individuals seeking help. Our methodological approach also involved a single retrospective assessment of suicidality and self-harm (e.g. past month/lifetime). Given that suicidal ideation is known to fluctuate rapidly over just a few hours, this approach may be of limited value (Kleiman et al., 2017). In order to capture fine-grained variation in suicidality and self-harm, future research should turn to time-intensive techniques such as ecological momentary assessment (EMA) which allow data to be collected repeatedly, in real-time and in naturalistic settings (de Beurs, Kirtley, Kerkhof, Portzky, & O'Connor, 2015).

2.6 Conclusions

Our findings emphasise the high prevalence of suicidality and self-harm in community-recruited CHR-P and FEP individuals. Moreover, we demonstrated that lifetime suicide attempts, lower CAARMS severity, impaired social functioning and greater comorbidity were able to significantly predict current suicidal ideation in CHR-P participants, with lifetime suicide attempts comprising the strongest predictor. Therefore, the current findings highlight that CHR-P individuals recruited outside traditional early intervention services represent a vulnerable group that requires novel approaches for detection; and early intervention aimed at suicide prevention. Whether prediction models can be applied to suicidality prevention in CHR-P samples remains, however, an open

question. We expect that, by incorporating larger collaborative datasets, longitudinal study designs, machine learning approaches and real-time measures, model performance will improve, thereby optimising youth mental health.

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Chapter 3 The relationship between cognitive deficits and impaired short-term functional outcome in clinical high-risk for psychosis participants: A machine learning and modelling approach

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The supplementary material for Chapter 3 is presented in Appendix B.

3.1 Abstract

Aim: 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.

Methods: 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-P 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 to predict functional outcome in CHR-P individuals.

Results: 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.

Conclusions: 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.

3.2 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-P 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.

3.3 Methods

3.3.1 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%).

3.3.2 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.

3.3.3 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.

3.3.4 Statistical analysis

3.3.4.1 Pre-processing

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.

3.3.4.2 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.

3.3.4.3 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.

3.3.4.4 Classification analysis

We trained classifiers to categorise CHR-P individuals into GFO/PFO based on the last available follow-up data (6 months [n = 24] or 12 months [n = 94]). 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 (10,000 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.

3.4 Results

3.4.1 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 4). 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 2.

Table 4 - 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 Experiences 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

3.4.2 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 3). 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.

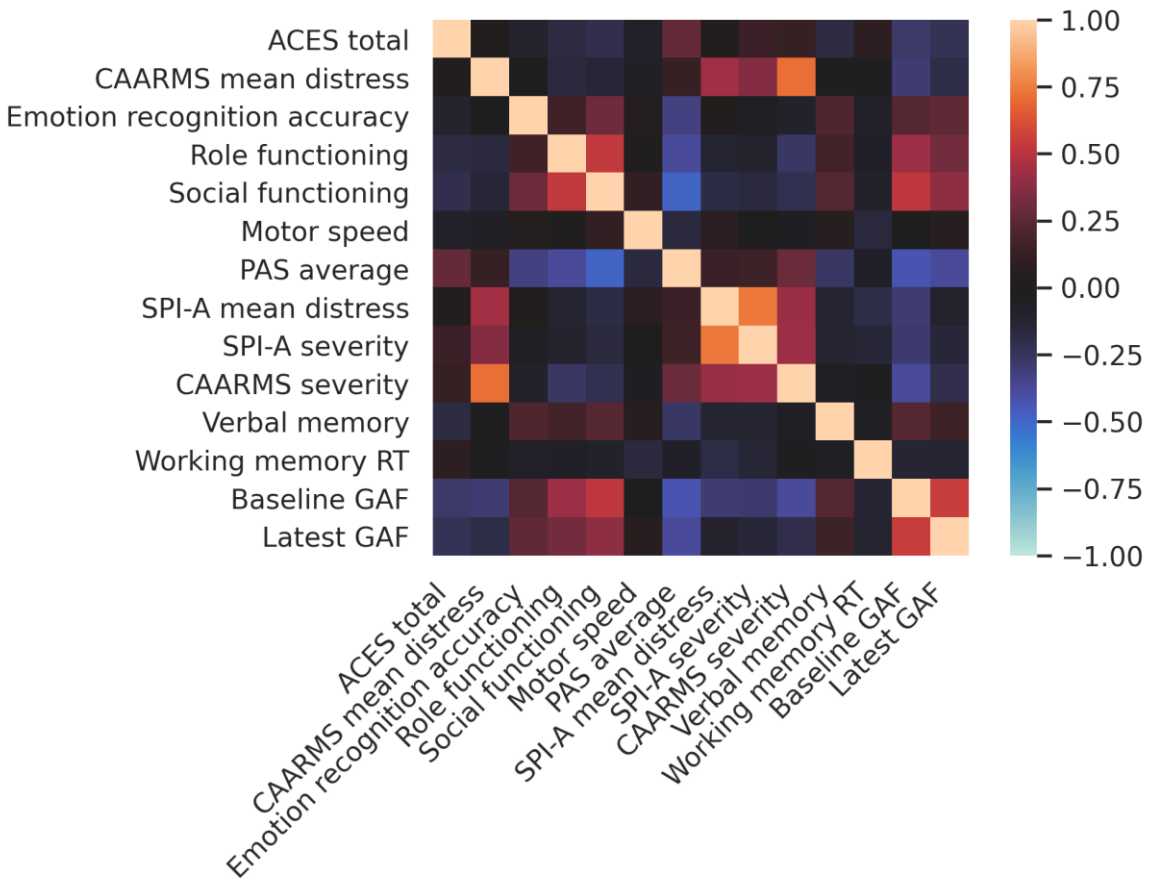

Figure 3 - Correlation matrix showing the relationship between nonzero predictors and baseline GAF scores for the combined LASSO-LARS regression model for the CHR-P group (N = 146). The latest GAF score is added to this figure for visualisation purposes only and has not been entered in the regression model.

Concurring with permutation feature importance scores (Supplementary Table 3), social functioning (β = 2.97) emerged as the strongest predictor in the combined model (Table 5; Supplementary Table 4) whereas verbal memory (β = 1.88) was a particularly strong predictor in the cognitive model (Table 5).

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 5, Supplementary Table 3). The cognitive model for the CHR-N group, however, failed to explain any variance in GAF scores.

Table 5 - Nonzero LASSO-LARS regression coefficients for CHR-P (N = 146) and CHR-N (N = 47) baseline models

Variable	ß coefficient		
	CHR-P combined model	CHR-P cognitive model	CHR-N combined model
Social functioning	2.97		1.12
PAS average	-2.15		
Role functioning	1.24		2.07
Working memory RT	-0.96	-1.88	
SPI-A mean distress	-0.85		-0.63
ACES total	-0.51		
Motor speed	-0.24		
Verbal memory	0.24	1.88	
Emotion recognition accuracy	0.11	1.75	
Total CAARMS severity	-0.10		
SPI-A severity	-0.05		
CAARMS mean distress	-0.02		
Attention RT		1.27	
Executive function		-0.60	
Working memory RT		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 Experiences Scale; GAF, Global Assessment of Functioning; PAS, Premorbid Adjustment Scale; RT, response time

3.4.3 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 3). Permutation tests on AUC scores indicated that all mixed-site classifiers performed significantly above chance (Table 6). The classifiers performed consistently, showing a mean BAC of 0.63 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 6), with a mean AUC of 0.64 and a mean BAC of 0.63 across classifiers. Again, sensitivity was consistently higher than specificity.

Table 6 - Mixed-site and cross-site classifiers in the CHR-P sample (N = 118)

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, Table 7). 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 7 - Classifiers using baseline functioning variables in the CHR-P sample (N = 118)

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.

3.4.4 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).

3.5 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.

3.5.1 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 while cognitive and clinical variables were weaker predictors. 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.

3.5.2 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.

3.5.3 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.

3.6 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.

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Chapter 4 Characterising cognitive heterogeneity in individuals at clinical high-risk for psychosis: A cluster analysis with clinical and functional outcome prediction

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The supplementary material for Chapter 4 is presented in Appendix C.

4.1 Abstract

Aim: Schizophrenia is characterised by cognitive impairments that are already present during early stages, including in the clinical high-risk for psychosis (CHR-P) state and first-episode psychosis (FEP). Moreover, data suggest the presence of distinct cognitive subtypes during early-stage psychosis, with evidence for spared vs. impaired cognitive profiles that may be differentially associated with symptomatic and functional outcomes. Using cluster analysis, we sought to determine whether cognitive subgroups were associated with clinical and functional outcomes in CHR-P individuals.

Methods: Data were available for 146 CHR-P participants of whom 122 completed a 6- and/or 12-month follow-up; 15 FEP participants; 47 participants not fulfilling CHR-P criteria (CHR-Ns); and 53 healthy controls (HCs). We performed hierarchical cluster analysis on principal components derived from neurocognitive and social cognitive measures. Within the CHR-P group, clusters were compared on clinical and functional variables and examined for associations with global functioning, persistent attenuated psychotic symptoms and transition to psychosis.

Results: Two discrete cognitive subgroups emerged across all participants: 45.9% of CHR-P individuals were cognitively impaired compared to 93.3% of FEP, 29.8% of CHR-N and 30.2% of HC participants. Cognitively impaired CHR-P participants also had significantly poorer functioning at baseline and follow-up than their cognitively spared counterparts. Specifically, cluster membership predicted functional but not clinical outcome.

Conclusions: Our findings support the existence of distinct cognitive subgroups in CHR-P individuals that are associated with functional outcomes, with implications for early intervention and the understanding of underlying developmental processes.

4.2 Introduction

Schizophrenia is a debilitating psychiatric disorder characterised by psychotic symptoms, including hallucinations and delusions, as well as impairments in cognition, sensory processing and psychosocial functioning [1, 2]. Cognitive impairments span several domains including processing speed, working memory, executive functions, attention and social cognition [3, 4]. Schizophrenia is preceded, in the majority of cases, by a clinical high-risk for psychosis (CHR-P) state lasting approximately 5-6 years [5]. CHR-P status is determined using ultra-high risk (UHR) criteria, encompassing attenuated psychotic symptoms (APS), brief frank psychosis and functional decline with genetic risk [6], as well as basic symptom criteria that involve self-experienced perceptual and cognitive disturbances [7, 8]. CHR-P individuals are also characterised by widespread cognitive impairments intermediate between healthy controls (HC) and first-episode psychosis (FEP) patients [9, 10]. These impairments, especially in attention, working memory and declarative memory, are more pronounced in CHR-P individuals who later transition to psychosis [11]. However, cognitive performance within the CHR-P state is highly variable with small-to-large effect size impairments (Cohen's *d* = -0.35 to -0.84) in those who transition to psychosis and small-to-medium impairments (*d* = -0.26 to -0.67) in those who do not [9]. Accordingly, novel approaches may be required to identify subtypes of CHR-P participants with different cognitive profiles, with possible implications for the understanding of underlying pathophysiology and accurate prediction of outcomes.

Data-driven approaches, such as cluster analysis, classify individuals according to levels and patterns of performance, rather than pre-determined grouping criteria [12]. Cognitive subgroups have successfully been identified in cross-diagnostic samples, comprising individuals with schizophrenia-spectrum disorders or mood disorders [12–16]. These findings support the existence of a range of cognitive impairments across different syndromes with evidence for two [14], three [13, 16] and four [12, 15] cognitive subgroups.

Furthermore, emerging evidence suggests that cluster analysis can identify phenotypes that relate more closely to specific clinical and functional trajectories than existing diagnostic categories [17]. Indeed, such approaches

have highlighted poorer functioning and greater symptom severity in cognitively impaired vs. cognitively spared subgroups in schizophrenia-spectrum populations [12, 15, 18–21]. Moreover, subgroups with impaired cognition have also been associated with reductions in brain volume [22, 23] and different profiles of treatment response [24].

There is preliminary evidence for similar profiles of cognitive impairment in FEP patients, with little consensus on the number of emergent clusters [25–28]. Wenzel et al. [28] and Reser et al. [25] identified two and four cognitive subgroups in FEP patients, respectively, with high negative symptom severity and low premorbid IQ characteristic of the most cognitively impaired subgroup. Interestingly, Uren et al. [27] and Sauvé et al. [26] both obtained a three-cluster solution and found that 28% and 54% of FEP participants, respectively, aggregated with HCs in the cognitively spared subgroup, supporting the existence of an FEP subgroup with intact cognitive functioning. According to Uren et al. [27], cluster membership was associated with symptom severity and functioning from baseline to 6 months, highlighting the potential utility of cognitive clustering for prognosis and early intervention.

To our knowledge, only one study has used cluster analysis to examine cognitive profiles in CHR-P participants. Velthorst et al. [29] derived four distinct cognitive subgroups, whereby 44% of CHR-P participants were significantly or mildly impaired and 56% displayed average or above average cognitive scores. In addition, cognitive subgroups yielded prognostic information with cluster membership predicting conversion to psychosis over a 30-month follow-up period. However, this study did not examine the predictive utility of cognitive subgroups in relation to global functioning or symptom persistence and did not include any measures of social cognition. Furthermore, it is unclear whether these findings from help-seeking CHR-P participants would generalise to more representative samples recruited outside clinical pathways.

To address these important questions, we sought to identify cognitive clusters in a sample of CHR-P and FEP participants, primarily recruited from the community, alongside individuals who did not fulfil CHR-P criteria but were characterised by affective and substance use disorders (CHR-Ns) and HCs. Specifically, we performed cluster analysis on principal components derived

from both neurocognitive and social cognitive measures. We then examined the distribution of diagnostic groups across clusters and investigated whether cognitive subgroups were associated with clinical and functional variables at baseline and follow-up in the CHR-P group. Given previous findings in CHR-P and FEP samples [25–27, 29], we hypothesised the existence of at least three distinct cognitive profiles. In addition, we expected CHR-P individuals with pronounced cognitive deficits to exhibit the poorest functioning and greatest symptom severity at baseline and follow-up as well as cluster membership to predict clinical and functional outcomes in the CHR-P group.

4.3 Methods

4.3.1 Participants

Participants were recruited through the ongoing Youth Mental Health Risk and Resilience (YouR) study [30] which seeks to identify neurobiological and psychological mechanisms and predictors of psychosis risk. CHR-P participants from the general population were recruited through an online-screening approach (www.your-study.org.uk) [31]. FEP and CHR-N participants were also recruited using this method while HCs were obtained from a volunteer database. A smaller number of CHR-P and FEP individuals were also recruited via referrals from clinical services in NHS Greater Glasgow and Clyde and NHS Lothian as well as student counselling services. Ethical approval was obtained from the West of Scotland Research Ethics Service and the University of Glasgow. All participants provided written informed consent.

Baseline data were available for 146 CHR-P participants, 15 participants with first-episode psychosis (FEP), 47 participants who did not fulfil CHR-P criteria (CHR-Ns) and 53 healthy controls (HCs). Unlike HCs, CHR-N participants met criteria for mood and anxiety disorders as well as substance use. Thus, the inclusion of the CHR-N group allowed us to potentially disentangle the impact of psychiatric comorbidity from the CHR-P state since mood and anxiety disorders are common in this population [32]. Referred participants comprised 11.0% of the CHR-P sample and 46.7% of the FEP sample. One hundred and twenty-two CHR-P participants (83.6%) also completed a follow-up session 6- and/or 12-months later.

Previous publications by our group have reported baseline demographic, clinical, functional and cognitive data from similar or smaller samples [31, 33–35].

4.3.2 Baseline assessments

In order to establish CHR-P criteria, participants received the positive scale of the Comprehensive Assessment of At-Risk Mental States (CAARMS) [6] and the Cognitive Disturbances (COGDIS) and Cognitive-Perceptive Basic Symptoms (COPER) items of the Schizophrenia Proneness Instrument, Adult version (SPI-A) [36].

Participants were recruited into the CHR-P group if they met one or both SPI-A criteria (i.e. COGDIS, COPER) and/or at least one of the following CAARMS criteria: APS, genetic risk and functional deterioration (GRFD), brief limited intermittent psychotic symptoms (BLIPS). FEP criteria were established using the Structured Clinical Interview for DSM-IV (SCID) [37] and the Positive and Negative Syndrome Scale (PANSS) [38].

Cognitive assessments consisted of the Brief Assessment of Cognition in Schizophrenia (BACS) [39] and three tasks from the Penn Computerized Neurocognitive Battery (CNB) [40]: 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 (Supplementary Table 5). Furthermore, with the exception of the FEP group, all participants were assessed with the Mini-International Neuropsychiatric Interview (MINI) [41], Global Assessment of Functioning (GAF) scale from the DSM-IV-TR, Global Functioning: Social (GF: Social) and Role (GF: Role) scales [42], Premorbid Adjustment Scale (PAS) [43] and National Adult Reading Test (NART) [44].

4.3.3 Clinical and functional outcome

CHR-P participants were invited for follow-up interviews at 6- and 12-months. These involved the positive scale of the CAARMS as well as the GAF, GF: Social and GF: Role scales. Based on the most recent GAF score, CHR-P participants were divided into good functional outcome (GAF ≥ 65) and poor functional

outcome (GAF < 65) groups, in line with previous research [45, 46]. CAARMS persistence was operationalised as meeting APS criteria at both baseline and the latest follow-up assessment. Transitions to psychosis, recorded over a 36-month follow-up period, were also defined according to CAARMS criteria and subsequently followed up with the Structured Clinical Interview for DSM-IV (SCID) [37] in order to establish the specific psychosis diagnoses.

4.3.4 Statistical analysis

Data were analysed using R version 4.0.1 [47] with statistical significance set at $p < .05$ (two-tailed). Overall, 0.48% of the data (52 of 10,904 values) were missing and imputed by Bayesian imputation.

In line with Keefe et al. [48], BACS raw scores for each cognitive domain were converted into standardized *z*-scores using the means and standard deviations (SDs) of sex-specific HCs. For consistency, CNB raw accuracy and RT scores were calculated in the same way, albeit without correction for sex. RT *z*-scores were multiplied by −1, to produce speed values where, as for accuracy, higher scores reflect better performance. CNB efficiency scores were then generated for each domain by taking the arithmetic mean of the accuracy and RT *z*-scores. Outliers beyond ±5.0 *z*-scores were curtailed to values of +5.0 or −5.0. NART-derived estimates of premorbid full-scale IQ were obtained using a recently re-standardised calculation [49]. CAARMS severity was calculated by multiplying the global score by the frequency score for each domain and summing these products [50] while SPI-A severity was calculated by summing the frequency scores for each basic symptom.

In the first step, a principal component analysis (PCA) was conducted on 20 cognitive tests with oblique (oblimin) rotation, so as to allow for possible correlations between the factors, using the *psych* [51] and *GPArotation* [52] packages. Data suitability for PCA was assessed with the Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy [53, 54] and Bartlett's test of sphericity [55]. In order to determine the appropriate number of principle components to extract, we used the Kaiser criterion of eigenvalues >1 [56] as well as scree plot inspection [57]. Cronbach's α was used to determine the internal consistency of data.

In the second step, we evaluated the clustering tendency of our data as well as the optimal clustering approach. Clustering tendency of the resulting component scores was assessed using the Hopkins (H) statistic via the *clustertend* package [58]. A value close to 1 indicates uniformly distributed data while highly clustered data yields a value close to 0. In order to identify the optimal clustering algorithm and number of clusters, we used the *clValid* package [59] which simultaneously compares the different clustering solutions in terms of validation measures. We tested for the presence of two to six clusters, implementing three clustering methods: (1) k-means, (2) partitioning around medoids (PAM) and (3) agglomerative hierarchical clustering. Internal validation measures were calculated as connectivity, silhouette width and Dunn index. Stability validation measures comprised the average proportion of non-overlap (APN), the average distance (AD), the average distance between means (ADM) and the figure of merit (FOM). Whereas internal validation measures evaluate the connectedness, compactness and separation of the different clusters, stability validation measures assess the consistency of a clustering result by comparing it with the clusters obtained after removing each column, one at a time. In general, smaller values reflect better performance, with the exception of silhouette width and Dunn index where larger values are preferable. This information was used to inform the third step whereby data-driven agglomerative hierarchical clustering was applied to the component scores via the *stats* package [47], using Ward's method and squared Euclidean distance, in order to produce two clusters. Cross-validated linear discriminant analysis, using the 20 original standardised cognitive scores as independent variables, was performed with the *caret* package [60] to evaluate the classification accuracy of the final clustering solution.

For the CHR-P group, the resulting clusters were compared on demographic, functional, clinical and cognitive characteristics using Welch's *t*-tests, Mann-Whitney *U* tests, Pearson's chi-square tests and Fisher's exact tests. We also conducted a series of hierarchical multiple linear regression analyses to examine effects of cluster membership on cognitive domains and functional variables after controlling for the potential effects of clinical (CAARMS and SPI-A severity) and demographic (age, sex, education) variables in order to examine the possibility that differences by cluster were better accounted for by overall

symptom severity or demographic characteristics. In these models, clinical and demographic variables were entered in step 1 and cluster membership was entered in step 2. Binary logistic regression analyses were also employed to determine whether cluster membership could predict clinical and functional outcomes. The overall variance explained was measured by the Nagelkerke pseudo R^2 statistic (R^2N) while diagnostic accuracy was determined using the area under the receiver operating characteristic (ROC) curve (AUC).

4.4 Results

4.4.1 Demographic data

CHR-P individuals had significantly fewer years of education, greater symptom severity, higher likelihood of comorbid mood and anxiety disorders and poorer functioning compared to CHR-N and HC participants (Table 8). Relative to the total sample, CHR-P individuals were also significantly younger while FEP patients displayed significantly higher CAARMS severity, antipsychotic and anxiolytic medication use as well as poorer global functioning. Among the CHR-P group, 45 (30.8%) met CAARMS criteria, 36 (24.7%) met SPI-A criteria and 65 (44.5%) met both. Moreover, the FEP group comprised participants with SCID DSM-IV schizophrenia (n = 10; 66.7%), psychotic disorder not otherwise specified (n = 3; 20.0%), schizoaffective disorder (n = 1; 6.7%) and schizophreniform disorder (n = 1; 6.7%).

Table 8 - Demographic, clinical and functional characteristics of the total sample (N = 261) at baseline

	CHR-P (1) (N = 146)	FEP (2) (N = 15)	CHR-N (3) (N = 47)	HC (4) (N = 53)	*p*	Effect size[a]	Post hoc test[b]
Age (years), mean (SD)	21.47 (4.22)	24.40 (4.37)	22.94 (4.80)	22.42 (3.36)	.003	η^2_p = 0.051	2,3,4 > 1
Sex, female n (%)	104 (71.2)	7 (46.7)	30 (63.8)	36 (67.9)	.241	*V* = 0.127	··
Education (years), mean (SD)	15.12 (3.10)	15.25 (2.84)	16.45 (3.44)	16.47 (2.85)	.010	η^2_p = 0.043	3,4 > 1
CAARMS severity, median (range)	28 (0-74)	79 (38-122)	6 (0-24)	0 (0-12)	< .001	η^2_p = 0.404	2 > 1 > 3 > 4
SPI-A severity, median (range)	7 (0-74)	15 (0-109)	0 (0-7)	0 (0-2)	< .001	η^2_p = 0.336	1,2 > 3,4
GAF, median (range)	58 (21-95)	41 (18-79)	70 (43-94)	88 (67-97)	< .001	η^2_p = 0.343	4 > 3 > 1 > 2
Social functioning (current), median (range)	8 (3-10)	··	8 (6-9)	9 (8-10)	< .001	η^2_p = 0.229	4 > 3 > 1
Role functioning (current), median (range)	8 (3-9)	··	8 (5-9)	9 (5-9)	< .001	η^2_p = 0.199	4 > 3 > 1
PAS average, median (range)	1.28 (0-3.43)	··	0.86 (0-3.86)	0.43 (0-1.64)	< .001	η^2_p = 0.189	1 > 3 > 4
Comorbidity, n (%)							
Anxiety disorder	104 (71.2)	··	22 (46.8)	0 (0)	< .001	*V* = 0.568	1 > 3 > 4
Mood disorder	97 (66.4)	··	14 (29.8)	0 (0)	< .001	*V* = 0.552	1 > 3 > 4
Alcohol abuse/dependence	46 (31.5)	··	11 (23.4)	0 (0)	< .001	*V* = 0.297	1,3 > 4
Substance abuse/dependence	24 (16.4)	··	3 (6.4)	0 (0)	.002	*V* = 0.221	1 > 4
Eating disorder	13 (8.9)	··	1 (2.1)	0 (0)	.023	*V* = 0.170	1 > 4

Psychological treatment, n (%)							
Current	25 (17.1)	5 (33.3)	5 (10.6)	0 (0)	.002	*V* = 0.243	2 > 3,4 & 1 > 4
Past	66 (45.2)	5 (33.3)	15 (31.9)	3 (5.7)	< .001	*V* = 0.323	1,2,3 > 4
Medication, n (%)							
Antidepressants	53 (36.3)	9 (60.0)	13 (27.7)	0 (0)	< .001	*V* = 0.354	2 > 3,4 & 1 > 4
Mood stabilisers	4 (2.7)	0 (0)	0 (0)	0 (0)	.592	*V* = 0.111	··
Antipsychotics	4 (2.7)	7 (46.7)	0 (0)	0 (0)	< .001	*V* = 0.526	2 > 1,3,4
Anxiolytics	10 (6.8)	5 (33.3)	1 (2.1)	0 (0)	< .001	*V* = 0.304	2 > 1,3,4

Note: CHR-P, clinical high-risk for psychosis; FEP, first episode 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; GAF, Global Assessment of Functioning; PAS, Premorbid Adjustment Scale

[a] Effect sizes were eta squared (η^2_p) for Kruskal-Wallis *H* tests (small effect = 0.01, medium effect = 0.06, large effect = 0.14) and Cramer's *V* for Pearson's chi-square or Fisher-Freeman-Halton tests (small effect = 0.1, medium effect = 0.3, large effect = 0.5)

[b] 1 = CHR-P, 2 = FEP, 3 = CHR-N, 4 = HC

4.4.2 Principal component analysis

The KMO measure verified the sampling adequacy for the PCA (KMO = 0.70) with all values for individual items ≥ 0.52, which is above the acceptable limit of 0.50. Bartlett's test of sphericity, x^2 (190) = 3795.385, p < .001, indicated that correlations between items were sufficiently large for PCA. Five principal components were extracted and, in combination, explained 68% of the variance in cognitive performance (Figure 4; Supplementary Tables 6 & 7). These were labelled verbal fluency (α = .89), emotion recognition (α = .82), attention (α = .93), working memory (α = .88) and general cognitive function (α = .68).

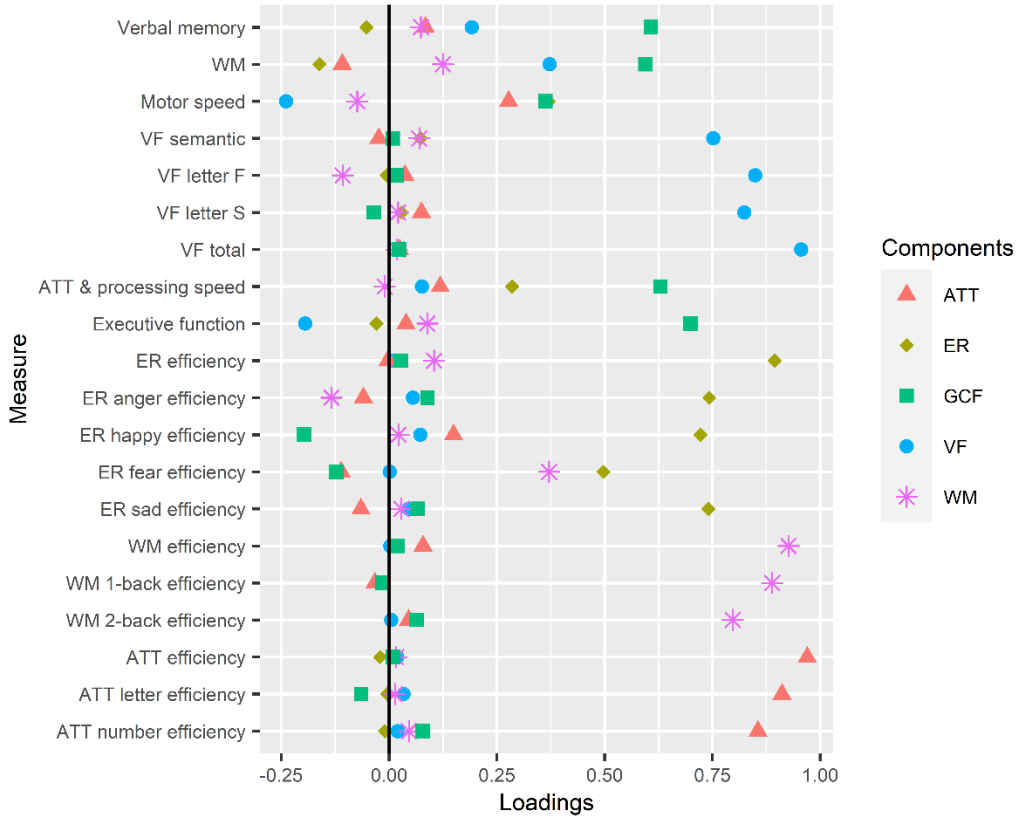

Figure 4 - Component loading plot for the total sample (N = 261). ATT attention, ER emotion recognition, GCF general cognitive function, VF verbal fluency, WM working memory

4.4.3 Agglomerative hierarchical cluster analysis

The resulting dataset contained statistically meaningful clusters (H = 0.24). All internal validation measures and two out of four stability validation criteria favoured agglomerative hierarchical clustering with two clusters. The dendrogram was cut to produce two clusters and subjects were assigned cluster membership accordingly (Supplementary Figure 5). Cluster 1 comprised 111

(42.5%) cognitively impaired participants while cluster 2 comprised 150 (57.5%) cognitively spared participants. Linear discriminant analysis with 10-fold repeated (100 times) cross-validation, using the 20 original standardised cognitive scores as independent variables, confirmed that we were able to predict the cluster membership of new cases with a mean accuracy of 88.8%.

Cluster 1 comprised 93.3% (n= 14) of FEP individuals and 45.9% (n = 67) of CHR-P participants (Figure 5). In addition, similar percentages of CHR-N and HC individuals were assigned to cluster 1 (CHR-N: 29.8%; HC: 30.2%).

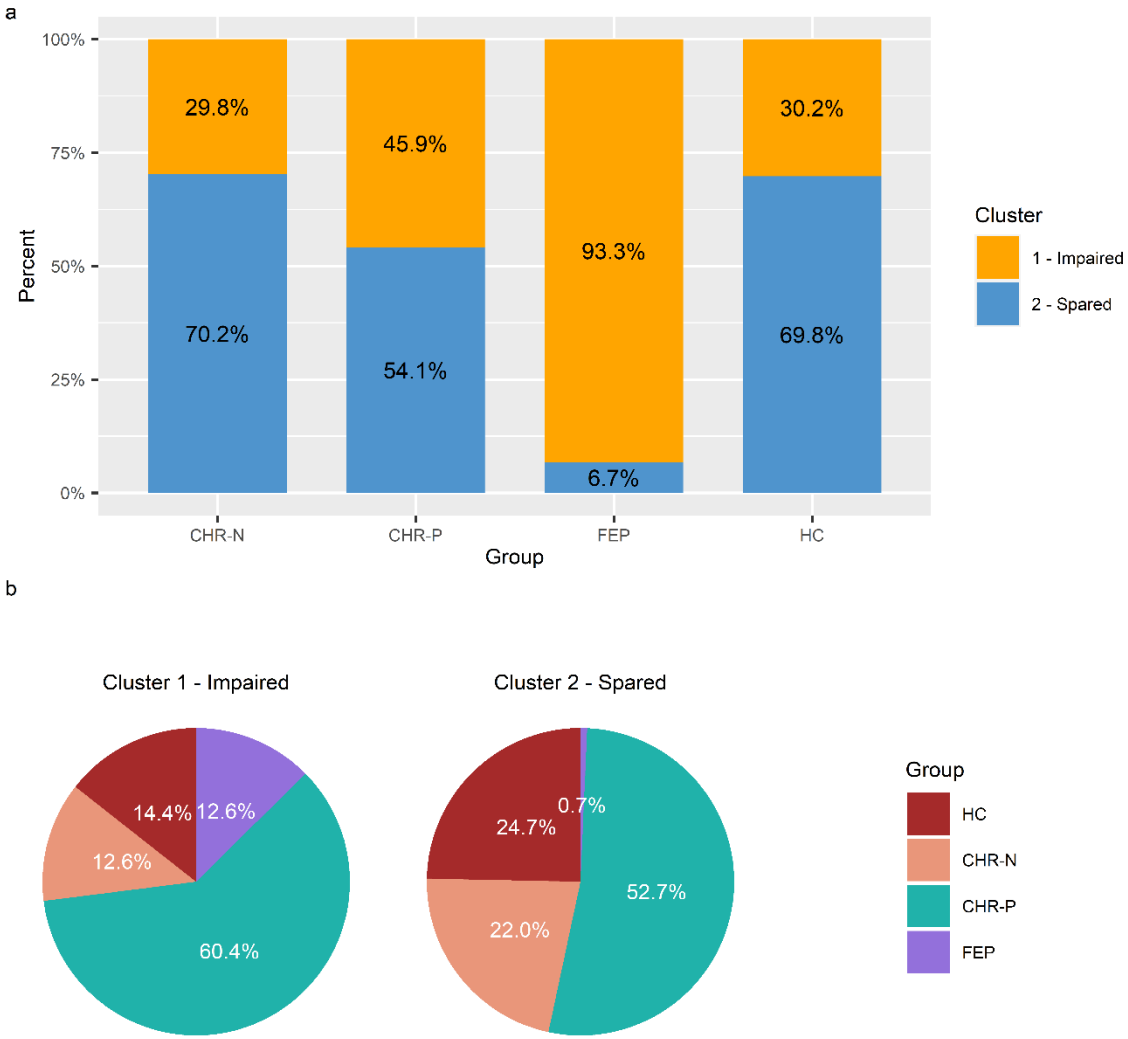

Figure 5 - The distribution of (a) clusters within each diagnostic group and (b) diagnostic groups within each cluster for the total sample (N = 261). CHR-P, clinical high-risk for psychosis; FEP, first episode psychosis; CHR-N, clinical high-risk-negative; HC, healthy control

4.4.4 Cluster comparisons at baseline

CHR-P individuals in cluster 1 displayed significantly lower premorbid IQ and poorer performance across all 20 cognitive tests compared to those in cluster 2 ($p < .01$), with medium to large effect sizes (Supplementary Table 8), and were characterised by poorer social, role and premorbid functioning ($p < .01$) but not global functioning (Table 9; Figure 6). Male CHR-P participants were also significantly more likely ($p < .001$) to be allocated to cluster 1 (47.8%) than cluster 2 (12.7%). After controlling for clinical symptoms and demographic characteristics, cluster membership remained significantly associated with premorbid IQ ($t = 2.565$; $p = .011$), all 20 cognitive domains ($t = 2.033$ to 7.166; $p < .05$), social functioning ($t = 2.375$; $p = .019$) and premorbid functioning ($t = -3.997$; $p < .001$), but not role functioning ($t = 1.548$; $p = .124$). Furthermore, the proportion of CHR-P participants meeting CAARMS criteria, SPI-A criteria or both did not differ between the clusters ($p = .667$).

Table 9 - Demographic, clinical and functional characteristics of the CHR-P group by cognitive cluster at baseline (N = 146) and follow-up (N = 122)

BASELINE	Cluster 1 Impaired (N = 67)	Cluster 2 Spared (N = 79)	*p*	Effect size[a]
Age (years), mean (SD)	21.36 (4.63)	21.56 (3.86)	.288	r = 0.088
Sex, female n (%)	35 (52.2)	69 (87.3)	<.001	ϕ = 0.386
Education (years), mean (SD)	14.96 (3.43)	15.25 (2.80)	.421	r = 0.067
CAARMS severity, median (range)	29 (0-74)	28 (0-72)	.212	r = 0.103
SPI-A severity, median (range)	6 (0-61)	7 (0-74)	.883	r = 0.012
GAF, median (range)	55 (21-87)	60 (21-95)	.094	r = 0.139
Social functioning (current), median (range)	7 (3-10)	8 (3-10)	<.001	r = 0.296
Role functioning (current), median (range)	7 (4-9)	8 (3-9)	.002	r = 0.255
PAS average, median (range)	1.36 (0-3.43)	0.86 (0-2.57)	<.001	r = 0.405
Comorbidity, n (%)				
Anxiety disorder	49 (73.1)	55 (69.6)	.640	ϕ = 0.039
Mood disorder	50 (74.6)	47 (59.5)	.054	ϕ = 0.160
Alcohol abuse/dependence	18 (26.9)	28 (35.4)	.266	ϕ = 0.092
Substance abuse/dependence	11 (16.4)	13 (16.5)	.995	ϕ = 0.001
Eating disorder	4 (6.0)	9 (11.4)	.252	ϕ = 0.095
Psychological treatment, n (%)				
Current	15 (22.4)	10 (12.7)	.120	ϕ = 0.129
Past	27 (40.3)	39 (49.4)	.273	ϕ = 0.091
Medication, n (%)				
Antidepressants	25 (37.3)	28 (35.4)	.815	ϕ = 0.019
Mood stabilisers	2 (3.0)	2 (2.5)	1.000	ϕ = 0.014
Antipsychotics	3 (4.5)	1 (1.3)	.333	ϕ = 0.098
Anxiolytics	4 (6.0)	6 (7.6)	.754	ϕ = 0.032
FOLLOW-UP	**Cluster 1 Impaired (N = 57)**	**Cluster 2 Spared (N = 65)**	***p***	**Effect size[a]**
GAF, median (range)	52 (21-88)	68 (33-88)	.012	r = 0.227
Poor functional outcome, n (%)	41 (71.9)	31 (47.7)	.007	ϕ = 0.246
Social functioning (current), median (range)	8 (2-10)	8 (4-9)	.021	r = 0.209
Role functioning (current), median (range)	8 (4-9)	8 (5-9)	.139	r = 0.134
CAARMS severity, median (range)	15 (0-71)	12 (0-82)	.886	r = 0.013
CAARMS persistence, n (%)	17 (29.8)	21 (32.3)	.768	ϕ = 0.027
Transitions[b], n (%)	9 (15.8)	5 (7.7)	.162	ϕ = 0.127

Note: CHR-P, clinical high-risk for psychosis; CAARMS, Comprehensive Assessment of At-Risk Mental States; SPI-A, Schizophrenia Proneness Instrument, Adult version; GAF, Global Assessment of Functioning; PAS, Premorbid Adjustment Scale

[a] Effect sizes were Rosenthal's *r* for Mann-Whitney *U* tests and Phi (ϕ) for Pearson's chi-square or Fisher's exact tests (small effect = 0.1, medium effect = 0.3, large effect = 0.5)

[b] 19 non-transitioned CHR-P individuals have yet to reach the 3-year follow-up

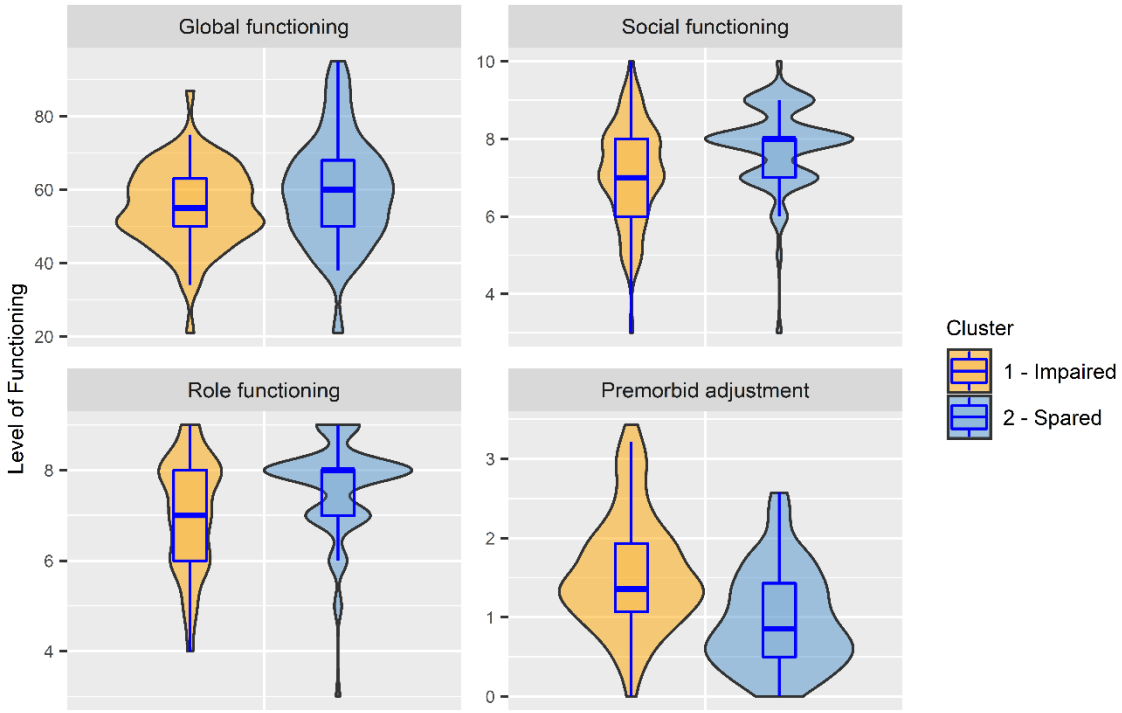

Figure 6 - Level of functioning across cognitive clusters for the CHR-P group (N = 146)

4.4.5 Cluster comparisons and outcome prediction at follow-up

CHR-P individuals in cluster 1 displayed significantly poorer global and social functioning at follow-up 6- and/or 12-months later compared to those in cluster 2 ($p < .05$). Within the CHR-P group, poor functional outcome was also significantly more likely ($p = .007$) in cluster 1 (71.9%) compared to cluster 2 (47.7%).

In a binary logistic regression analysis, cluster membership explained 8.0% of the variance in functional outcome ($p = .007$, AUC = 0.625, sensitivity = 56.9% and specificity = 68.0%). Based on the odds ratio, poor functional outcome was 2.81 times higher if participants were assigned to cluster 1 rather than cluster 2. This association remained significant after adjusting for GAF score at baseline (adjusted odds ratio = 2.52, $p = .030$). In contrast, cluster membership could not predict clinical outcomes in terms of CAARMS persistence ($p = .768$) or transition to psychosis ($p = .170$).

4.4.6 Additional analyses

The PCA and cluster analysis were repeated following the exclusion of the small sample of FEP participants in order to verify the stability and interpretability of our results. Overall, results remained unchanged, albeit with slightly smaller effect sizes (see Supplementary Results & Supplementary Figures 6-9).

4.5 Discussion

Using a data-driven hierarchical clustering approach in conjunction with PCA, we identified a two-cluster solution, comprising a cognitively spared and cognitively impaired subgroup, in a sample consisting of CHR-P and FEP participants as well as CHR-N participants and HCs. While the majority of FEP individuals were assigned to the cognitively impaired cluster, CHR-P individuals were almost equally distributed. At both baseline and follow-up, CHR-P individuals classified as cognitively impaired displayed significantly poorer functioning than their cognitively spared counterparts with cluster membership able to predict functional but not clinical outcome.

4.5.1 Hierarchical clustering on principal components

In the present study, PCA was applied prior to clustering in order to reduce data dimensionality, thereby reducing information redundancy and maximising explanatory variance [61]. Verbal fluency, emotion recognition, attention, working memory and general cognitive function were the five principal components that explained 68% of the variance in cognitive performance across the entire sample. Interestingly, Lam et al. [62] observed a similar cognitive component structure in both CHR-P and HC samples, indicating that our components constitute reproducible dimensions of cognitive performance.

The emergence of a two-cluster solution is in agreement with previous studies involving schizophrenia-spectrum disorders [14, 20, 28, 63, 64]. However, three- or four-cluster solutions are more typically reported in mixed samples of FEP and HC participants [26, 27]. Furthermore, the only study to investigate cognitive subgroups in CHR-P participants obtained a four-cluster solution [29]. It is possible that our two-cluster solution partially reflects the novel combination of FEP and CHR-P participants as well as the application of basic symptom criteria

to recruit CHR-P individuals. Nevertheless, this solution has resulted from replicable cognitive components [62], supporting the validity of our findings.

Finally, it is important to note that the majority of CHR-P participants in the current study were recruited from the community and not through dedicated clinical pathways. Community-recruitment strategies represent an important aspect of early detection and intervention [65, 66]. Indeed, there may be a substantial number of young people at CHR-P in the community who are not seen by specialised early detection services [65]. Therefore, community-recruitment strategies are particularly advantageous in their ability to detect more representative samples, ensuring that findings can be generalised to the entire population of individuals at CHR-P.

4.5.2 Characterising within-group cognitive heterogeneity

In line with Velthorst et al. [29], our CHR-P group exhibited substantial cognitive heterogeneity, with 45.9% of individuals assigned to the cognitively impaired subgroup. On the other hand, cognitive heterogeneity was less apparent in our FEP group, contrasting with previous findings in larger samples [26, 27]. Approximately 16% fewer CHR-N participants were classified as cognitively impaired relative to CHR-P participants, indicating that cognitive impairment is somewhat more prevalent in the CHR-P state. Interestingly, a considerable proportion of HCs (30.2%) were also allocated to the cognitively impaired subgroup, supporting previous findings [26]. Overall, these results support the notion of a cognitive continuum [12, 16, 67], at least among CHR-P, CHR-N and HC populations.

4.5.3 Cluster comparisons in the CHR-P group

Cognitively impaired CHR-P individuals displayed significantly poorer performance across all domains with large effect sizes for verbal memory, verbal fluency and attention and processing speed. Indeed, cognitive scores fell mostly within 0.5-1.0 SDs below HC data for cognitively impaired participants. Deficits in facial emotion recognition were also significantly greater in cognitively impaired individuals with medium effect sizes, indicating that cluster

membership was driven by the degree of impairment across both neurocognitive and social cognitive domains.

Within the CHR-P group, cognitively impaired individuals had significantly poorer functioning than cognitively spared individuals. While role functioning and global functioning were significantly reduced at baseline and follow-up, respectively, social functioning was impaired at both time points, in line with previous findings [29]. Lower levels of premorbid functioning and premorbid IQ were also observed in the cognitively impaired vs. cognitively spared subgroup, consistent with previous studies across the psychosis spectrum [15, 18, 25, 27]. These findings, in addition to the larger number of male participants in our cognitively impaired subgroup, may support the existence of a neurodevelopmental contribution towards pronounced cognitive impairments in CHR-P participants [68], in line with previous results in psychosis patients [69].

In contrast, positive symptom severity did not significantly differ between cognitive subgroups. Cluster analyses have produced mixed findings, reporting either no significant differences across cognitive subgroups in the schizophrenia spectrum [18, 25, 28, 63] or greater positive symptom severity in the most cognitively impaired cluster [12, 15, 26, 27]. Furthermore, the proportion of CHR-P participants meeting CAARMS criteria, SPI-A criteria or both did not differ between the cognitive subgroups, contrasting with previous reports of lesser cognitive deficits in individuals meeting basic symptom, as opposed to UHR, criteria [70].

4.5.4 Outcome prediction in the CHR-P group

Importantly, we were also able to predict functional outcome from cluster membership, with cognitively impaired CHR-P individuals significantly more likely to experience poor functional outcome at follow-up. Conversely, cluster membership was unable to predict clinical outcomes in terms of APS persistence or transition to psychosis. This contrasts with Velthorst et al. [29] whereby impaired cognition in CHR-P individuals predicted transition to psychosis. Nevertheless, our findings suggest that early interventions targeting cognition, such as cognitive remediation, should be tailored towards cognitively impaired

CHR-P participants in order to alleviate cognitive deficits and consequently improve functional outcome [71].

4.5.5 Limitations

Certain limitations should be considered. Firstly, the sample size of FEP participants was small, limiting our ability to accurately characterise cognitive heterogeneity in this group. Furthermore, negative symptoms were not assessed in the current study while cognition was only assessed at baseline. Therefore, we were unable to ascertain the full impact of clinical symptomatology on cluster assignment as well as the stability of cognitive subgroups over time. Finally, cluster membership explained only 8.0% of the variance in functional outcome. This could, in part, be explained by our measure of functioning. For example, the GAF scale confounds functioning with symptom severity, the latter being unrelated to functioning in the current study. Nevertheless, this measure was chosen over social and role functioning scales as these scores were mostly limited in range.

4.6 Conclusions

We employed cluster analysis to investigate cognitive subgroups in CHR-P participants using a community-recruitment approach, social cognitive measures and functional outcome prediction. We identified two discrete cognitive subgroups and found support for considerable cognitive heterogeneity within the CHR-P group. Cognitively impaired and cognitively spared CHR-P individuals could be distinguished on measures of functioning at baseline and follow-up, with cluster membership able to predict functional outcome. These findings emphasise the key role cognition plays in functioning and suggest that cluster assignment is driven by cognitive performance, rather than clinical symptoms. In addition, the current findings may support the role of cognitive enhancement therapies, such as cognitive remediation, in CHR-P individuals with impaired cognition. Indeed, data-driven approaches such as cluster analysis could effectively stratify heterogenous clinical populations along dimensions of interest and thus represent an important step towards personalised psychiatry. Future research should attempt to replicate these findings in larger samples, over longer follow-up periods and also investigate whether these cognitive

subgroups are differentially associated with neurobiological measures, such as measures of cortical thickness and volume as well as electrophysiological parameters.

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Chapter 5 Computerised cognitive training during early-stage psychosis improves cognitive deficits and gamma-band oscillations: A pilot study

This chapter contains a full-length manuscript, the shorter version of which is available as a published letter to the editor:

Haining, K., Grent-'t-Jong, T., Chetcuti, B., Gajwani, R., Gross, J., Kearns, C., Krishnadas, R., Lawrie, S. M., Molavi, S., Paton, C., Queirazza, F., Richardson, E., Schultze-Lutter, F., Schwannauer, M., & Uhlhaas, P. J. (2022). Computerised cognitive training during early-stage psychosis improves cognitive deficits and gamma-band oscillations: A pilot study. *Schizophrenia Research*, *243*, 217–219. https://doi.org/10.1016/j.schres.2022.04.001

The supplementary material for Chapter 5 is presented in Appendix D.

5.1 Abstract

Aim: Schizophrenia is characterised by deficits in cognition and oscillatory activity, especially in the gamma-band range. Such impairments are already present during early stages, including in the clinical high-risk for psychosis (CHR-P) state and first-episode psychosis (FEP). Although cognitive training can alleviate cognitive deficits and enhance gamma-band activity in schizophrenia patients, evidence for its effectiveness in CHR-P and FEP participants is limited. Therefore, we sought to assess whether neuroplasticity-based computerised cognitive training could improve cognition and enhance gamma-band activity in CHR-P and FEP participants.

Methods: Thirteen participants (n = 5 CHR-P; n = 8 FEP) completed 10 hours of computerised cognitive training comprised of visual processing exercises. Before and after the training, participants completed the Brief Assessment of Cognition in Schizophrenia (BACS) and magnetoencephalography (MEG) data were obtained during a visual grating task. In the visual task, participants had to press a button when a speed change was detected in a concentric inward moving visual grating stimulus. Oscillatory activity was examined in the 30-80 Hz frequency range at sensor-level, with significant effects followed up with source-level analyses.

Results: We found significant improvements pre- to post-training in verbal memory (d = 1.43), motor speed (d = 0.68), attention and processing speed (d = 0.79) and BACS composite score (d = 0.88) as well as a significant reduction in executive function (d = 0.62). We also found a significant increase in gamma-band power (~40-44 Hz) at sensor level 250 to 750 ms after stimulus onset which was source localised to frontal, motor and cingulate regions. No behavioural effects were observed in visual task performance.

Conclusions: Our findings suggest that neuroplasticity-based computerised cognitive training can improve cognitive performance, particularly in the domain of verbal memory. In addition, we found significant improvements in gamma-band activity. Overall, our findings implicate improved attentional and motor-related processes in CHR-P and FEP participants following a 10-hour cognitive training intervention.

5.2 Introduction

Cognitive impairment, a central feature of schizophrenia, is strongly associated with poor functional outcomes (Green et al., 2019; Lepage et al., 2014) and is already present in the early stages of psychosis, including in the clinical high-risk for psychosis (CHR-P) state (Catalan et al., 2021) and first-episode psychosis (FEP; Mesholam-Gately et al., 2009). Although antipsychotic medications are largely effective in alleviating the positive symptoms of schizophrenia, they appear to have limited impact on cognition (Nielsen et al., 2015) and functioning (Jääskeläinen et al., 2013). Therefore, cognitive impairment has emerged as a promising target for interventions. In particular, there is a growing interest in non-pharmacological approaches, such as cognitive training.

Neuroplasticity-based cognitive training has been developed in order to improve basic auditory and visual-perceptual processes (Vinogradov et al., 2012). The premise of this approach is that intensive training through progressively more challenging exercises will facilitate synaptogenesis and lead to changes in higher-level cognitive domains (Reddy et al., 2014). Notably, cognitive training may be more beneficial in the early stages of psychosis, owing to the increased capacity for neuroplasticity (Fisher et al., 2013)

Although current findings indicate that computerised cognitive training may be one strategy for targeting cognitive impairments in schizophrenia (Prikken et al., 2019), there is currently only preliminary evidence for its effectiveness in the early stages of psychosis (Fisher et al., 2015; Glenthøj et al., 2017; Loewy et al., 2022). In one randomised controlled trial (RCT), individuals with recent-onset schizophrenia who completed 20-40 hours of neuroplasticity-based auditory training, independently at home via laptop computers, had significant improvements in global cognition, problem solving, verbal memory and working memory, relative to those who played 20-40 hours of computer games (Fisher et al., 2015; Loewy et al., 2022).

Meanwhile, three studies have examined the effects of neuroplasticity-based computerised cognitive training, completed independently at home (or elsewhere), in CHR-P samples (Hooker et al., 2014; Loewy et al., 2016; Piskulic et al., 2015). Loewy et al. (2016) found that CHR-P individuals who completed

auditory training had significant improvements in verbal memory, relative to those who played computer games. However, a similar, albeit smaller RCT by Piskulic et al. (2015) could not detect any significant improvements in cognitive performance. Notably, although these studies expected participants to train for 40 hours, the average training duration was closer to 20 hours. On the other hand, Hooker et al. (2014) conducted a small pilot study and found that CHR-P individuals who completed up to 40 hours of cognitive training had significant improvements in processing speed pre- to post-training. Interestingly, fewer training hours may also be sufficient to produce change in the early stages of psychosis. In a pilot study delivering 10 hours of computerised cognitive training in a group-based format, Rauchensteiner et al. (2011) found that CHR-P individuals had significant improvements in attention and long-term verbal memory from pre- to post-training.

Importantly, neural oscillations may constitute a mechanism for cognitive impairments in schizophrenia (Uhlhaas et al., 2008). Gamma-band oscillations (> 30 Hz) are reduced during perceptual tasks (Uhlhaas & Singer, 2013) and deficits are already present in CHR-P and FEP individuals (Grent-'t-Jong et al, 2020). Although initial findings are encouraging, only three studies have sought to determine whether task-related gamma-band activity can be enhanced by neuroplasticity-based computerised cognitive training approaches in schizophrenia, with all studies focusing on auditory, rather than visual, processing exercises (Dale et al., 2016, 2020; Popov et al., 2012). Notably, these studies employed magnetoencephalography (MEG) which tends to have a substantially higher signal-to-noise ratio than electroencephalography (EEG) for the measurement of visually induced gamma oscillations (Muthukumaraswamy & Singh, 2013).

To our knowledge, no study has yet examined whether task-related gamma-band activity can be enhanced by neuroplasticity-based computerised cognitive training in the early stages of psychosis. Accordingly, the current pilot study sought to assess the impact of a 10-hour neuroplasticity-based computerised cognitive training intervention on cognitive performance and task-related gamma-band activity, as measured by MEG, in a group of participants meeting CHR-P or FEP criteria. Specifically, we focused on gamma-band oscillations in

visual cortex as the main outcome parameter and a targeted cognitive training intervention consisting of visual processing exercises was employed. We hypothesised that cognitive training would improve cognitive performance and increase gamma-band oscillations in visual cortex.

5.3 Methods

5.3.1 Participants

CHR-P participants and the majority of FEP participants were recruited following their participation in the longitudinal Youth Mental Health Risk and Resilience (YouR) study (Uhlhaas et al., 2017). FEP participants were also recruited via referrals from the ESTEEM First Episode Psychosis Service in Glasgow. Overall, 16 early-stage psychosis participants (CHR-P = 6; FEP = 10) were recruited and completed baseline testing (Figure 7). Of these, 13 participants (CHR-P = 5; FEP = 8) completed both pre- and post-testing. A small number of FEP individuals entered the study via patient referral (n = 4) with referred participants comprising 37.5% (n = 3) of the final FEP sample. All participants were in the 16 to 35 age range and provided written informed consent. Ethical approval was obtained from the West of Scotland Research Ethics Service and the University of Glasgow.

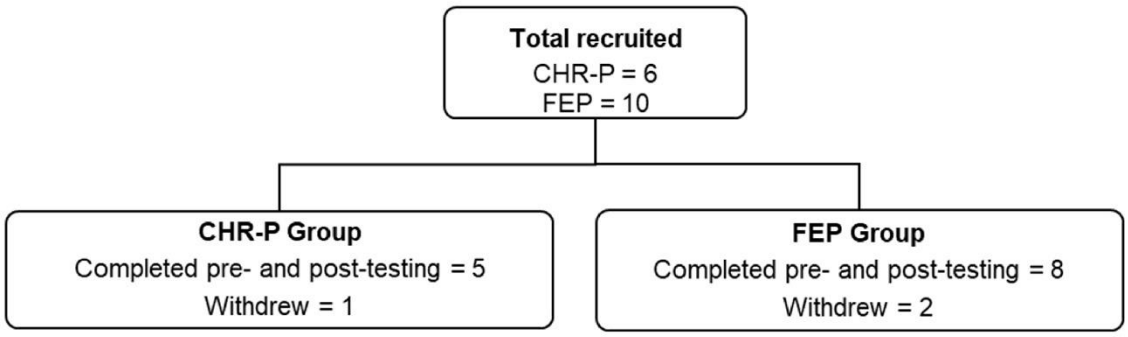

Figure 7 - Study flowchart for participant recruitment

5.3.2 Assessments

Eligibility for the CHR-P group was established using 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 from the Schizophrenia Proneness Instrument, Adult version (SPI-A; Schultze-Lutter et al., 2007). Participants were recruited into the CHR-P group if they met one or both SPI-A criteria (i.e. COGDIS, COPER) and/or at least one of the following CAARMS criteria: attenuated psychotic symptoms (APS), genetic risk and functional deterioration (GRFD), brief limited intermittent psychotic symptoms (BLIPS). Eligibility for the FEP group was established using the Structured Clinical Interview for DSM-IV (SCID; First et al., 2002). FEP participants also received the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). Furthermore, CHR-P and FEP participants both completed the Audio-Visual Abnormalities Questionnaire (AVAQ; Nikitova et al., 2019).

Before and after the cognitive training intervention, CHR-P and FEP participants also completed the Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004). In order to minimise practice effects, we used different versions of the verbal memory and executive function tests at the post-training assessment.

5.3.3 Neuroimaging – stimuli and task

Before and after the cognitive training intervention, CHR-P and FEP participants underwent MEG scanning whilst performing a visual grating task (Hoogenboom et al., 2006) that has been shown to elicit robust and reliable high-frequency activity (Tan et al., 2016). Each trial started with the presentation of a fixation point (Figure 8). Following a baseline period of 1.5 s, participants were presented with a circular sinewave grating that contracted towards a central fixation. Participants were asked to press a button with their right index finger if they detected an increase in stimulus velocity within 1.0 s of its occurrence. Such speed changes randomly occurred between 0.75 and 3.0 s post-stimulus onset on 90% of the trials (i.e. 10% were catch trials with no acceleration). In total, participants performed 3 blocks of 80 trials. Stimulus presentation was controlled using Presentation software (Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com).

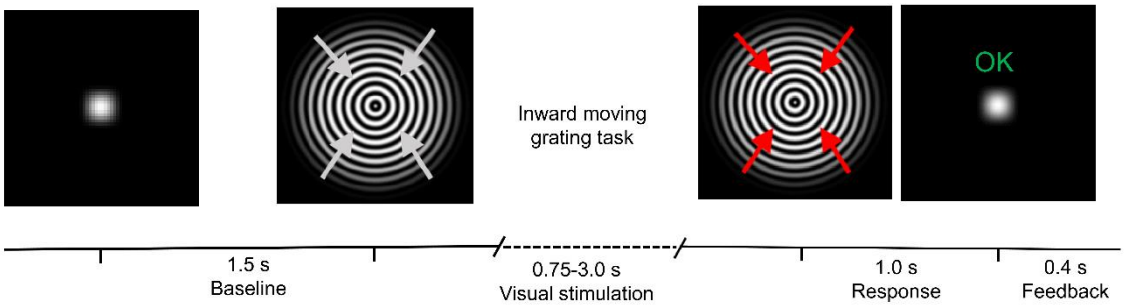

Figure 8 - Visual grating task paradigm. Participants had to press a button when a speed change was detected in a concentric inward moving visual grating stimulus. Stimulus presentation ended after button press, or at 3.0 s when either no acceleration occurred or the participant did not press the button (missed trial). Performance feedback was provided following each trial.

5.3.4 Neuroimaging – data acquisition

MEG data were acquired using a whole-head, 248-channel magnetometer system (Magnes 3600 WH, 4D Neuroimaging, San Diego, CA) at a sampling rate of 1017.25 Hz with a low-pass filter at 400 Hz. T1-weighted anatomical scans were acquired pre-training using a 3D magnetisation-prepared rapid gradient-echo (MPRAGE) sequence (slices = 192; echo time = 2.6 ms; repetition time = 2250 ms; inversion time = 900 ms; flip angle = 9°; voxel size = 1 mm^3; field of view = 256 × 256 × 176 mm^3) on a 3T Siemens Trio Tim magnetic resonance imaging (MRI) scanner (Siemens, Erlangen, Germany) for participant-specific source localisation of MEG activity.

5.3.5 Cognitive training intervention

We utilised BrainHQ (Posit Science, San Francisco; www.brainhq.com) – a commercially available computerised cognitive training programme widely used in cognitive training studies. Participants completed 10 sessions of computerised cognitive training, each 60 minutes in duration, over approximately 3 weeks. Training was completed at home using a computer or laptop, with the exception of one participant who used a mobile phone. Each session was comprised of eight different visual processing exercises: Visual Sweeps, Double Decision, Target Tracker, Eye for Detail, Hawk Eye, Divided Attention, Mind's Eye and Scene Crasher (Supplementary Table 9). In order to meet the session quota of 1 hour, each exercise was repeated three times.

Throughout the programme, participants were driven to make progressively more accurate discriminations about the spectral-temporal fine-structure of visual stimuli under conditions of increasing working memory load. Task difficulty was continually adjusted to maintain performance at approximately 80% accuracy on an ongoing trial-by-trial basis using an n-up/m-down algorithm to participant responses. Thus, as a user gets trials correct, task difficulty increases; conversely as the user gets trials incorrect, task difficulty decreases. Correct responses were rewarded with stars (reflecting *z*-score performance) and animations. Training activity was monitored via an online administrative portal and participants received regular reminders by email or text.

5.3.6 Statistical analysis

Data were analysed using IBM SPSS Statistics for Windows, version 18 (IBM Corp., Armonk, N.Y., USA), with the exception of MEG data which were analysed in MATLAB version R2020b (MathWorks Inc., Natick, MA) using the open-source Fieldtrip toolbox (Oostenveld et al., 2011; http://fieldtriptoolbox.org). Statistical significance was set at $p < .05$ (two-tailed).

BACS raw scores on each neurocognitive domain were converted into standardised *z*-scores using the means and standard deviations of sex-specific healthy controls whose data were obtained from a normative sample (Keefe et al., 2008). The BACS composite score was created by averaging the *z*-scores obtained from the six primary measures and then converting this value into a standardised *z*-score as before.

The CHR-P and FEP groups were compared on demographic, functional and clinical characteristics at baseline using Mann–Whitney *U* tests and Fisher's exact tests. For the main analyses, CHR-P and FEP groups were combined to examine the effects of cognitive training in the early stages of psychosis. To determine changes over time, difference scores (post-training minus pre-training) were computed for cognitive performance on the BACS and behavioural performance on the visual grating task. Normality of the difference scores was assessed using the Shapiro-Wilk test. A paired *t*-test was used on those variables meeting the assumption of normality. Otherwise, a non-parametric Wilcoxon signed rank test was used. A similar approach was used to examine improvement over repeated

play for each BrainHQ exercise (see Supplementary Methods). A power analysis (power = .80, α [two-sided] = .05, n = 13, paired-samples *t*-test) in R version 4.0.3 (R Core Team, 2020), using the *pwr* package (Champely, 2020), revealed a minimum detectable effect size of $d = 0.85$.

MEG data pre-processing included correct response trials only with non-overlapping 2.8 s segments (including 1.0 s baseline), time-locked to the onset of the stimulus (i.e. the visual grating). Power line noise was attenuated by applying a discrete 50 Hz Fourier transform filter (including the first two harmonics) and faulty sensors with large signal variance or flat signals were removed and interpolated using nearest-neighbour averaging. Data were denoised relative to 23 reference channels and down-sampled to 300 Hz. Artifact cleaning was performed using semi-automatic removal of trials contaminated by excessive transient muscle activity, slow drift or superconducting quantum interference device (SQUID) jumps; and independent component analysis (ICA)-based removal of eye blink, eye movement and heartbeat artifacts.

Time-frequency representations (TFRs) at sensor-level were computed for planar-orientation transformed MEG data (Bastiaansen & Knösche, 2000). A sliding window fast Fourier transform (FFT) approach was used with a fixed window of 450 ms and a step-size of 50 ms across the length of the epochs. Power of all frequencies between 1 and 91 Hz were computed for the full-length data segments padded with zeros up to 4.0 s, using a frequency resolution of 1 Hz and frequency smoothing of 2 Hz, and by multiplying the data with a Hanning taper before averaged power estimation. We tested sensor-level TFR data for within-group differences in gamma (30-80 Hz) power, averaged across 250 to 750 ms. Specifically, we used Monte-Carlo permutation-based dependent samples *t*-tests (2000 permutations), with cluster-based correction for multiple comparisons. Clusters were formed when at least two neighbouring sensors reached a cluster-forming threshold of $p < .05$ (two-tailed). For significant clusters, we calculated an effect size (Cohen's *d*) by averaging the TFR data over the channels, time points and frequencies that comprised the cluster.

Next, source estimation of gamma-band activity changes was performed using the dynamic imaging of coherent sources (DICS) beamforming approach (Gross et al., 2001), based on significant effects at sensor-level. Source estimation was

performed on a 3D grid (5 mm spacing) based on the Montreal Neurological Institute (MNI) template brain, with the grid linearly warped to individual anatomy. Source-level power estimates for each grid point (voxel) were computed from the cross-spectral density matrix using normalised lead fields and common spatial filters over both time windows of interest combined (i.e. baseline [-500 to 0 ms] and post-stimulus [250 to 750 ms]) in order to reduce noise common to both windows. We tested source-level data for within-group differences using Monte-Carlo permutation-based dependent samples *t*-tests (2000 permutations), with false discovery rate (FDR) correction for multiple comparisons. We also calculated an effect size (Cohen's *d*) for the significant voxels that survived correction.

At both sensor- and source-level, power was expressed as relative change (relch) from baseline activity (−500 to 0 ms).

5.4 Results

5.4.1 Demographic data

There were no significant differences between CHR-P and FEP participants on demographic, clinical and functional variables at baseline (Table 10). Among the CHR-P group, 1 (20.0%) met CAARMS criteria, 2 (40.0%) met SPI-A criteria and 2 (40.0%) met both. The FEP group consisted of participants with SCID DSM-IV schizophrenia (n = 4; 50.0%), schizophreniform disorder (n = 2; 25%), schizoaffective disorder (n = 1; 12.5%) and psychotic disorder not otherwise specified (n = 1; 12.5%).

One out of 6 (16.7%) CHR-P participants withdrew from the study following pre-training assessments compared to 2 out of 10 (20%) FEP participants, giving an overall attrition rate of 18.8%. Across both groups, the mean training duration was 22.15 days (SD = 14.55).

Table 10 - Demographic, clinical and functional characteristics of the total sample (N = 13)

	CHR-P (N = 5)	FEP (N = 8)	*p*	Effect Size[a]
Age (years), mean (SD)	24.40 (4.22)	23.88 (3.80)	1.000	r = 0.000
Sex, female n (%)	3 (60.0)	3 (37.5)	.592	ϕ = 0.220
Education (years), mean (SD)	16.90 (1.25)	14.88 (2.53)	.127	r = 0.451
CAARMS severity, median (range)	23 (8-48)	..	..	..
SPI-A severity, median (range)	11 (0-25)	..	..	..
Age at onset of FEP, mean (SD)	..	22.13 (3.80)	..	..
PANSS, median (range)				
Positive	..	13 (6-26)	..	..
Negative	..	17 (7-28)	..	..
Cognitive/disorganisation	..	14 (9-24)	..	..
Excitement	..	5 (4-8)	..	..
Emotional distress	..	8.5 (4-15)	..	..
Total score	..	59 (33-89)	..	..
GAF, median (range)	58 (47-77)	44 (34-60)	.093	r = 0.489
AVAQ, median (range)				
Total frequency	29 (10-95)	52 (14-136)	.622	r = 0.163
Total distress	13 (4-62)	22 (8-88)	.524	r = 0.183
Psychological therapy, n (%)				
Current	0 (0)	3 (37.5)	.231	ϕ = 0.433
Past	2 (40.0)	3 (37.5)	1.000	ϕ = 0.025
Current medication, n (%)				
Antidepressants	1 (20.0)	2 (25.0)	1.000	ϕ = 0.058
Antipsychotics	0 (0)	4 (50.0)	.105	ϕ = 0.527
Anxiolytics	2 (40.0)	1 (12.5)	.510	ϕ = 0.318
Training duration (days)	18.25 (13.21)	28.40 (14.42)	.065	r = 0.509
No. of MEG trials included Pre (SD)	183.80 (36.13)	169.13 (43.73)	.622	r = 0.163
No. of MEG trials included Post (SD)	201.20 (7.53)	173.88 (30.94)	.093	r = 0.488

Note. CHR-P, clinical high-risk for psychosis; FEP, first-episode psychosis; CAARMS, Comprehensive Assessment of At-Risk Mental States; SPI-A, Schizophrenia Proneness Instrument, Adult version; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; AVAQ, Audio-Visual Abnormalities Questionnaire; MEG, magnetoencephalography.
[a] Effect sizes were Rosenthal's *r* for Mann-Whitney *U* tests (small effect = 0.1, medium effect = 0.3, large effect = 0.5) and Phi (ϕ) for Fisher's exact tests (small effect = 0.1, medium effect = 0.3, large effect = 0.5)

5.4.2 Training effects on cognition and behaviour

Individuals with early-stage psychosis had significant improvements in verbal memory ($p < .001$, $d = 1.43$), motor speed ($p = .030$, $d = 0.68$), attention and processing speed ($p = .015$, $d = 0.79$) and BACS composite score ($p = .008$, $d = 0.88$) as well as a significant reduction in executive function ($p = .044$, $d = 0.62$) from pre- to post-training (Table 11). There were also significant improvements on all eight BrainHQ exercises over repeated play ($p < .01$), with large effect sizes (Supplementary Figure 10 & Supplementary Table 10). In regard to the visual grating task completed during MEG scanning, there were no significant differences in behavioural performance.

Table 11 - Cognitive and behavioural performance pre- to post-training (N = 13)

	Pre		Post		*p*	Effect Size[a]
	Mean	SD	Mean	SD		
Cognitive Performance						
Verbal memory	-0.77	1.32	0.32	1.29	< .001	*d* = 1.43
Working memory	-0.80	0.79	-0.33	1.05	.082	*d* = 0.53
Motor speed	-0.10	1.22	0.42	1.08	.030	*d* = 0.68
Verbal fluency	-0.03	0.69	0.22	1.02	.258	*d* = 0.33
Attention & processing speed	-0.03	1.33	0.32	1.30	.015	*d* = 0.79
Executive function	0.93	0.93	0.31	0.70	.044	*d* = 0.62
BACS composite	-0.23	0.95	0.33	1.12	.008	*d* = 0.88
Behavioural Performance (Visual Grating Task)						
Accuracy, % correct	88.69	14.01	90.83	9.01	.182	*r* = 0.37
Mean response time, ms	596.21	79.10	600.64	100.69	.871	*d* = 0.07
Response variance[b], ms	158.62	44.37	149.75	52.57	.474	*d* = 0.21

Note. BACS, Brief Assessment of Cognition in Schizophrenia
[a] Effect sizes were Cohen's *d* for paired-samples *t*-tests (small effect = 0.2, medium effect = 0.5, large effect = 0.8) and Rosenthal's *r* for Wilcoxon signed rank tests (small effect = 0.1, medium effect = 0.3, large effect = 0.5)
[b] Response variance equals standard deviation of response times across trials.

5.4.3 Training effects on gamma-band oscillations

The total number of MEG trials included in the analysis did not significantly differ for CHR-P and FEP participants at either pre- or post-training (Table 10). At sensor-level (Figure 9A), the cluster-based permutation test revealed a

significant increase in gamma-band activity pre- to post-training at sensors covering left central-frontal scalp regions in a latency range of 250 to 750 ms after stimulus onset and a frequency range of approximately 40 to 44 Hz (cluster $t(12) = 145.01$, $p = .013$, $d = 1.41$, 95% CI [0.008 to 0.018]).

Therefore, we performed whole-head source estimation of 40 to 44 Hz gamma power between 250 and 750 ms (Figure 9B, C). We found a significant increase in gamma-band activity pre- to post-training in frontal, motor and cingulate regions ($t(12) = 3.90$, $d = 1.08$).

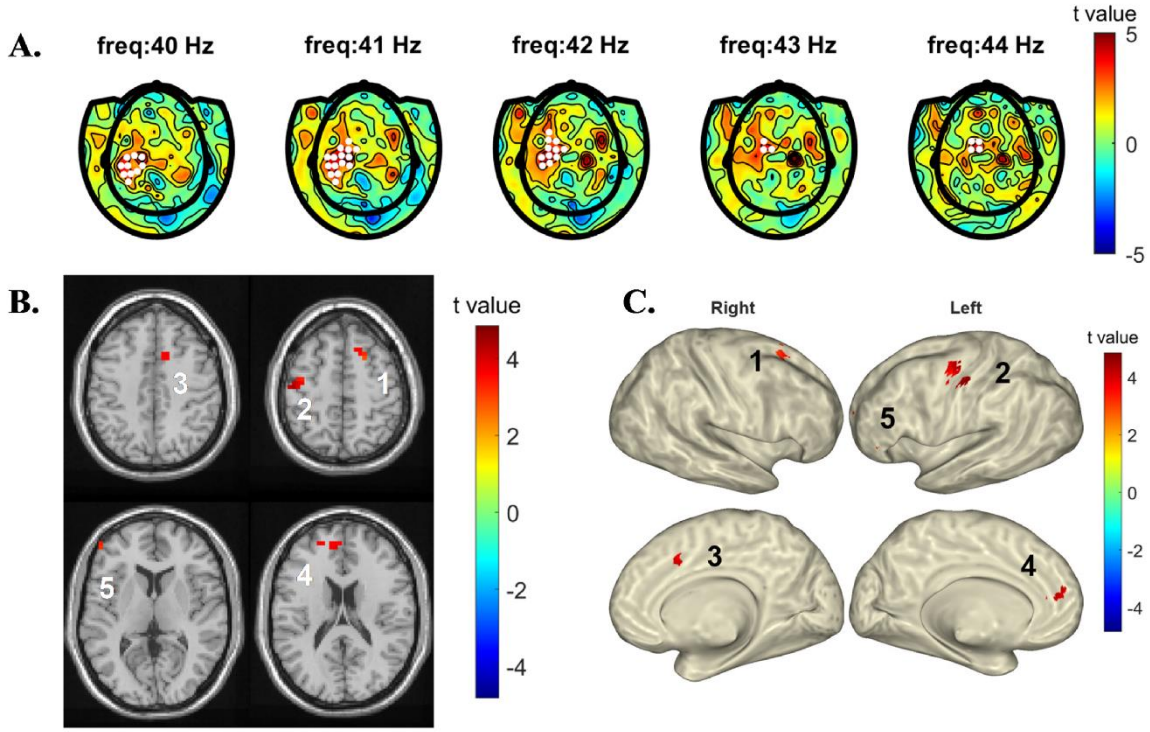

Figure 9 - Sensor- and source-level magnetoencephalography (MEG) data. (A) Topography of the change in low gamma power from pre- to post-training. White dots indicate sensors significant after cluster correction. Slice (B) and surface (C) plot representations of low gamma source-power differences pre- to post-training (FDR corrected). Colour bars indicate the distribution of *t*-values, with red colours (positive *t*-values) indicating an increase in gamma power. ROI 1: Right supplementary motor area (RSMA), right dorsal superior frontal gyrus (RdSFG) and right middle frontal gyrus (RMFG); ROI 2: Left precentral gyrus (PreCG) and left postcentral gyrus (LPoCG); ROI 3: Right median cingulate and paracingulate gyri (RDCG); ROI 4: Left anterior cingulate and paracingulate gyri (LACG), left medial superior frontal gyrus (LmSFG) and left dorsal superior frontal gyrus (LdSFG); ROI 5: Left middle frontal gyrus (LMFG) and left inferior frontal gyrus, triangular part (IFGtriang).

5.5 Discussion

We examined the impact of a neuroplasticity-based computerised cognitive training intervention among individuals in the early stages of psychosis. In line with our hypothesis, cognitive training led to significant improvements in cognitive performance, especially in global cognition and the domain of verbal memory. Furthermore, cognitive training led to a significant increase in gamma-band activity across frontal, motor and cingulate regions.

In terms of cognitive performance, we found medium to large improvements in global cognition, verbal memory, attention and processing speed and motor speed, concurring with previous studies employing neuroplasticity-based computerised cognitive training interventions in FEP (Fisher et al., 2015; Loewy et al., 2022) and CHR-P (Choi et al., 2017; Hooker et al., 2014; Loewy et al., 2016) samples. The largest effect size was found for verbal memory, with all participants either equalling or improving their pre-training score at post-training. Unexpectedly, we also found a significant decrease in executive function between pre- and post-training which may be partly attributable to the discontinue rule used in this test whereby non-administered items were treated as incorrect. Furthermore, we found significant improvements on all BrainHQ exercises over repeated play, with large effect sizes, suggesting that our cognitive training intervention successfully trained basic visual-perceptual processes and engaged intact learning mechanisms.

Interestingly, we also found increased gamma-band activity in brain areas associated with attentional and motor-related processes pre- to post-training. Therefore, one possibility is that cognitive training led to improved task (motor) preparation, improved top-down attentional control and a switch from reactive to proactive cognitive control strategies during the visual grating task. Proactive control is engaged when goal-relevant information is actively maintained, prior to the occurrence of a cognitively demanding event, in order to optimally bias attention, perception and response systems (Braver, 2012). Meanwhile, reactive control is engaged when goal-relevant information and attention are recruited as a “late correction” mechanism, following the detection of a response cue. In contrast to reactive control, proactive control places significant demands on working memory capacity and requires a strong attentional focus. Therefore, it

is possible that the cognitive training exercises required participants to recruit the attentional and working memory resources needed to effectively sustain proactive strategy use.

Furthermore, our finding of increased gamma-band activity in central-frontal brain regions pre- to post-training is in agreement with previous studies in schizophrenia populations that utilised neuroplasticity-based computerised cognitive training interventions to investigate changes in auditory processing (Dale et al., 2016, 2020; Popov et al., 2012). Interestingly, however, these studies found improvements in high gamma-band activity (~60-117 Hz) whereas the current study found improvements in low gamma-band activity (~40-44 Hz), perhaps reflecting the use of different MEG paradigms.

Overall, our findings illustrate the potential benefits of a 10-hour neuroplasticity-based computerised cognitive training intervention, delivered in real-world settings. Typically, studies employing neuroplasticity-based computerised cognitive training in the early stages of psychosis expect participants to complete 20 to 40 hours of cognitive training (Choi et al., 2017; Fisher et al., 2015; Hooker et al., 2014; Loewy et al., 2016, 2022; Piskulic et al., 2015). Although more studies are needed to clarify the optimal dosage, our findings indicate that just 10 hours of training is sufficient to induce cognitive change, in line with findings from an earlier pilot study (Rauchensteiner et al., 2011). Furthermore, our attrition rate of 18.8% was relatively low when compared to previous studies (Fisher et al., 2015; Loewy et al., 2016, 2022; Piskulic et al., 2015).

A major limitation of the current study is the small sample size. Although our analysis was powered to detect improvements in both global cognition and verbal memory, we were unable to examine the differential effects of cognitive training in CHR-P individuals as compared to FEP individuals or participant characteristics that moderated the response to training. Furthermore, we focused on cognitive performance and gamma-band activity at pre- and post-training. Therefore, it is unclear whether symptoms and/or functioning improved at post-training and also whether the effects were durable over time. In addition, we did not include an active control group and therefore, we cannot draw any specific conclusions about the benefits of cognitive training over other

interventions or the natural fluctuation of cognition and gamma-band activity in the early stages of psychosis.

In conclusion, our study demonstrates the feasibility of a neuroplasticity-based computerised cognitive training intervention in the early stages of psychosis, indicating that 10 hours of training may be sufficient to induce cognitive gains and enhance gamma-band activity. Importantly, our findings can be used to guide and inform intervention design and implementation and also support the pursuit of large RCTs, especially those that investigate the oscillatory dynamics associated with cognitive training in both chronic schizophrenia and the early stages of psychosis.

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Chapter 6 General discussion

The overarching aim of this thesis was to investigate cognitive and clinical correlates of early-stage psychosis including associations with functioning and the feasibility of a computerised cognitive training intervention. The studies in this thesis were driven by identified gaps in existing research literature including the lack of community-recruited samples, the limited application of more advanced machine learning methods to study cognition and the need to better understand emerging digital mental health approaches that could potentially complement existing early detection and intervention strategies. Overall, our findings build upon the existing literature in this field and provide insights which have implications for both research and clinical practice.

6.1 Summary of the main findings

In Chapter 2, we aimed to investigate the prevalence of suicidality and non-suicidal self-harm in CHR-P (n = 130) and FEP (n = 15) participants recruited from the community via a web-based screening platform. Moreover, we aimed to examine predictors of current suicidal ideation in the CHR-P group. Our approach enhanced existing literature by including a more representative sample of CHR-P and FEP participants, recruited outside clinical pathways. The prevalence of suicidality and non-suicidal self-harm was considerable in both groups with current suicidal ideation most commonly disclosed (FEP = 73.3%; CHR-P = 34.6%). In a binary logistic regression analysis, lifetime suicide attempts, lower CAARMS severity, impaired social functioning and greater comorbidity were found to significantly predict current suicidal ideation in the CHR-P group (AUC = 0.80). Overall, these findings highlight the need to develop and enhance novel detection approaches, similar to the web-based screening platform utilised in this study, to identify CHR-P and FEP individuals in the community who (1) may be at risk of adverse outcomes and (2) are likely to benefit from early intervention strategies.

In Chapters 3 and 4, we built upon the existing literature by harnessing more advanced machine learning methods to study cognition in a sample of CHR-P participants (n = 146) primarily recruited from the community via a web-based screening platform. Traditionally, the relationship between cognitive

impairment and functioning is studied using methods which do not regularise parameters, use cross-validation or compare above-chance performing models to simpler alternatives. Furthermore, efforts to elucidate the relationship between cognitive impairment and functional outcome are hindered by considerable cognitive heterogeneity. Therefore, in Chapter 3, we leveraged supervised machine learning methods (i.e. feature selection and classification) and techniques (i.e. cross-validation, regularisation and simpler control models) to examine the relationship between cognitive impairment and functioning while in chapter 4, we employed unsupervised machine learning methods (i.e. dimensionality reduction and clustering) to examine cognitive heterogeneity and its association with both clinical and functional outcome.

To the best of our knowledge, we showed for the first time in a CHR-P sample that: 1) machine learning classifiers utilising cognitive variables, alongside clinical and functional variables, could predict functional outcome with above-chance performance (mean AUC = 0.72; Chapter 3); and 2) cognitive subgroups formed by cluster analysis could be used to predict functional outcome (AUC = 0.63; Chapter 4). Notably, cognitive variables alone were found to explain just 12% of the variance in baseline functioning (Chapter 3) and cognitive heterogeneity was found to be substantial (Chapter 4). Taken together, these findings demonstrate a consistent relationship between cognitive performance and functioning and emphasise the need for personalised early interventions adapted to the profile of cognitive impairment. Importantly, in Chapter 3, machine learning classifiers based on baseline functioning alone outperformed our complex machine learning classifiers (AUC= 0.76). This leads us to question whether the potential gains that such complex methods bring are sufficient to justify their use over simpler alternatives.

In chapter 5, we conducted a pilot study to examine whether neuroplasticity-based computerised cognitive training could improve cognitive performance and enhance gamma-band activity in early-stage psychosis. This study built upon the existing literature by providing, for the first time, an investigation into the oscillatory correlates of cognitive training in the early stages of psychosis. Specifically, we found that CHR-P (n = 5) and FEP (n = 8) individuals who completed 10 hours of neuroplasticity-based computerised cognitive training had

significant improvements in cognitive performance, especially in the domain of verbal memory, as well as a significant increase in low gamma-band activity across frontal, motor and cingulate regions. Taken together, these findings demonstrate the feasibility of delivering neuroplasticity-based computerised cognitive training to individuals with early-stage psychosis in real-world settings and provide novel insights regarding the oscillatory correlates of cognitive training.

6.2 Adverse outcomes in the early stages of psychosis

A consistent finding across Chapters 2, 3 and 4 was that a considerable proportion of our CHR-P participants experienced notable impairments at baseline and/or follow-up assessments. At baseline, 72.6% of CHR-P individuals had poor functioning, 45.9% were cognitively impaired and 34.6% had suicidal ideation. Psychiatric comorbidity was also substantial. Indeed, 71.2% of individuals presented with a comorbid anxiety disorder and 66.4% presented with a comorbid mood disorder. Furthermore, 59.3% of individuals had poor functional outcome at 6- and/or 12-month follow-up. These findings concur with previous research investigating suicidality and self-harm (DeVylder et al., 2012; Gill et al., 2015), cognitive impairment (Velthorst et al., 2019), psychiatric comorbidity (Salazar de Pablo et al., 2020) and functioning (Carrión et al., 2011, 2013) in help-seeking CHR-P samples, wherein recruitment is typically focused on individuals referred to specialised CHR-P clinics. Notably, our CHR-P individuals were mainly recruited from the community and therefore, our findings indicate that a lack of help-seeking behaviour does not reduce the possibility of additional clinical need.

Despite experiencing several notable impairments, less than 18% of our CHR-P participants were engaged in psychological treatment when the baseline assessment was conducted. In addition, the number of CHR-P individuals taking medication for a mental health problem was considerably lower when compared to the number of CHR-P individuals presenting with a comorbid psychiatric disorder. Therefore, community-recruited CHR-P participants represent a vulnerable group who would likely benefit from early intervention strategies and routine risk monitoring.

To date, transition to psychosis has been the primary outcome of interest in CHR-P studies. Notably, 14 CHR-P individuals transitioned to psychosis during our 36-month follow-up period, giving an overall transition rate of 9.6%. Interestingly, all CHR-P individuals who transitioned entered the study via the web-based screening platform and therefore, the transition rate for community-recruited CHR-P individuals was 10.8%. These transition rates are relatively low compared to the recent meta-analytical estimate of 25% within 3 years (Salazar de Pablo, Radua, et al., 2021). However, the majority of studies included in this meta-analysis focused solely on SIPS (49%) or CAARMS (39%) criteria at intake whereas the studies included in this thesis used both CAARMS and SPI-A criteria at intake. Therefore, given that CAARMS criteria were developed to detect a more imminent risk of psychosis than SPI-A criteria, it is possible that our low transition rates are reflective of an insufficient follow-up duration and lack of longer-term follow-up data. Indeed, of the non-transitioned CHR-P individuals who are beyond the 36-month follow-up period (n = 121), only 49.6% completed at least one follow-up assessment in the final year of follow-up (i.e. 24-, 30- or 36-month follow-up).

Traditionally, CHR-P individuals who do not transition to psychosis are viewed as "false positives". However, according to our findings, CHR-P individuals who do not transition experience several adverse outcomes beyond transition to psychosis – including suicidality and self-harm and impairments in cognitive performance and functioning – which would likely benefit from treatment.

Importantly, another consistent finding across Chapters 2 and 4 was that a considerable proportion of our FEP participants experienced notable impairments at baseline. Specifically, we found that 73.3% of FEP individuals had suicidal ideation (Chapter 2) and 93.3% were cognitively impaired (Chapter 4). These proportions were relatively high when compared to previous research investigating suicidality and self-harm (Sicotte et al., 2021) and cognitive impairment (Sauvé et al., 2018; Uren et al., 2017) in FEP samples recruited from specialised early intervention in psychosis services. Of note, Chapter 2 reports on a community-recruited sample of FEP participants while Chapter 4 reports on a mixed sample of FEP participants (46.7% referred). In the mixed sample, 33.3% were engaged in psychological treatment and 46.7% were taking antipsychotic

medication whereas, in the community-recruited sample, 20.0% were engaged in psychological treatment and 13.3% were taking antipsychotic medication. Overall, these findings indicate that FEP individuals require timely clinical attention and support, not only for their heightened psychotic symptoms but also for a broader range of adverse outcomes.

6.3 Digital detection and intervention strategies

Across Chapters 2 to 5, we have highlighted the feasibility of using digital detection and intervention strategies in the early stages of psychosis. Specifically, Chapters 2 to 4 harnessed a web-based screening platform to recruit CHR-P and FEP individuals from the community whereas Chapter 5 examined the impact of a computerised cognitive training intervention in a small sample of CHR-P and FEP participants.

In terms of early detection, the web-based screening platform allowed us to recruit CHR-P and FEP individuals from the general population who may not otherwise present to clinical services. Instead, these individuals may only present to clinical services when symptoms escalate and a crisis point is reached. Indeed, Staines et al. (2021) recently found that our CHR-P sample were characterised by a longer duration of risk symptoms when compared to CHR-P samples recruited via clinical pathways, despite demonstrating similar levels of impairment. Specifically, our CHR-P sample had been experiencing APS for 43 months, on average, and basic symptoms for 51 months, on average. Therefore, it is possible that our digital detection strategy overcame several key barriers to help-seeking including stigma and embarrassment about help-seeking and poor mental health literacy (Gulliver et al., 2010). Overall, our findings suggest that novel digital detection approaches could potentially provide the first entry points for clinical services and psychoeducation in hard-to-reach groups.

In terms of early intervention, we have shown that remotely delivering computerised cognitive training to CHR-P and FEP individuals is feasible and results in an acceptable attrition rate. This has implications in terms of the accessibility and dissemination of digital interventions in real-world settings. For example, individuals with early-stage psychosis who live in remote and/or under-

resourced areas, or who are unwilling or unable to attend a clinic, are likely to benefit from the convenient and accessible nature of digital interventions, such as computerised cognitive training. In the future, with continued refinement, such approaches have the potential to address health disparities and promote health equity. Furthermore, participants' progress can be monitored online and support can be provided by email or text which might reduce the need for local infrastructures, potentially resulting in cost savings.

Importantly, we demonstrated, for the first time, that computerised cognitive training could increase gamma-band activity in the early stages of psychosis, in line with previous research involving schizophrenia patients (Dale et al., 2016, 2020; Popov et al., 2012). Together, these findings highlight the importance of studying intervention-specific neural response patterns in order to better understand the functional implications of different training modalities (e.g. visual vs. auditory training) and training durations (e.g. 10 hours vs. 20 hours). Notably, we did not assess whether computerised cognitive training was related to improvements in functioning over time as has been shown in previous CHR-P studies (Choi et al., 2017; Piskulic et al., 2015). However, since verbal memory was a particularly strong predictor of functioning in Chapter 3 and also the most improved cognitive domain in Chapter 5, it is possible that our computerised cognitive training intervention would have led to improvements in functioning among individuals with early-stage psychosis.

Moreover, our findings also indicate that digital interventions, such as computerised cognitive training, should adopt a more tailored and personalised approach to treatment. Indeed, 44.6% of CHR-P individuals had never experienced suicidality or self-harm, 54.1% were cognitively spared and 20.3% had good functioning at baseline and follow-up. Therefore, standardised approaches to treatment may not be effective in CHR-P populations and instead, certain treatments may only work for specific subgroups. For example, computerised cognitive training may be better suited to CHR-P individuals with impaired, rather than spared, cognition. In this situation, following a standardised approach to treatment is unlikely to benefit cognitively spared individuals and may, in turn, obscure meaningful treatment effects. Notably, we did not pre-select individuals with cognitive impairment for our pilot study on

computerised cognitive training. Interestingly, however, the two individuals who did not demonstrate improvements in their BACS total score pre- to post-training also had the highest BACS total scores at pre-training (i.e. they were the only participants to score over 300 points), again emphasising the need for digital interventions adapted to the profile of impairment.

Overall, our findings align with the Digital Health and Care Strategy set out by the Scottish Government (Scottish Government, 2018). Specifically, this strategy recognises that health and wellbeing can be improved and transformed through the use of digital technology:

> The issue is not whether digital technology has a role to play in addressing the challenges we face in health and care, and in improving health and wellbeing: the issue is that it must be central, integral and underpin the necessary transformational change in services in order to improve outcomes for citizens. (Scottish Government, 2018, Joint Foreword, para.2)

Furthermore, as outlined in the updated Digital Health and Care Strategy (Scottish Government, 2021), digital solutions have much to offer in the current climate as society recovers from the Covid-19 pandemic and takes steps to tackle climate change. For healthcare staff, digital detection and intervention strategies can address backlogs and increase capacity while for service users, such strategies can increase accessibility and reduce treatment delays. In addition, greater use of remote technology reduces the need for travel and therefore plays an important role in addressing the climate crisis.

6.4 Developing accurate models

In Chapters 2 to 4, we used traditional statistical methods, such as logistic regression, and/or machine learning methods to determine factors associated with current suicidal ideation and baseline functioning as well as predictors of functional outcome at 6- and/or 12-month follow-up. The resulting models were significant and mostly demonstrated acceptable discriminative abilities (i.e. AUCs between 0.70 and 0.80). Specifically, we found that cognitive variables, either alone or in combination with clinical and functional variables, were associated with baseline functioning and could be used to predict functional

outcome. On the other hand, cognitive variables were not associated with clinical variables (i.e. current suicidal ideation) and could not be used to predict clinical outcomes (i.e. CAARMS persistence or transition to psychosis).

Importantly, however, our findings also highlight several key issues which must be addressed before such models can be implemented in clinical settings. Firstly, across our models, a substantial proportion of the variance was unaccounted for. In Chapter 2, clinical and functional variables together explained 32.4% of the variance in current suicidal ideation in our CHR-P sample, in line with previous CHR-P studies in which clinical variables have been found to explain 19% (Bang et al., 2017) to 26.9% (Pelizza et al., 2019) of the variance in current suicidal ideation. Furthermore, in Chapter 3, we found that cognitive, clinical and functional variables explained 41% of the variance in baseline functioning while cognitive variables alone explained 12%. Similarly, cluster membership explained 8% of the variance in functional outcome in Chapter 4. These findings concur with previous CHR-P studies utilising more traditional methods in which cognitive impairments have been found to explain just 5% to 10% of the variance in baseline functioning (Carrión et al., 2011), less than 4% of the variance in functional outcome (Bolt et al., 2019) and, when combined with clinical and functional variables, 32% to 52% of the variance in functional outcome (Carrión et al., 2013; Glenthøj et al., 2020).

Secondly, current models will ultimately require greater levels of sensitivity and specificity. Sensitivity is defined as the proportion of positive cases that are correctly identified as positive whereas specificity is defined as the proportion of negative cases that are correctly identified as negative (Trevethan, 2017). Although characterised by excellent specificity (82.4%), our suicidal ideation model yielded limited sensitivity (46.7%). This issue has also been noted for suicide prediction models in high-risk populations (Kessler et al., 2020). Indeed, even the utility of suicidal ideation as a test for later suicide is limited by modest sensitivity with one meta-analysis reporting pooled sensitivities of 46% in psychiatric populations and 22% in non-psychiatric populations (McHugh et al., 2019).

Moreover, our models predicting functional outcome displayed specificity and sensitivity values between 56% and 68%. Previous studies utilising clinical and/or

functional data to predict functional outcome via machine learning methods have reported similar sensitivity values (i.e. 60.9% to 69.7%) and slightly higher specificity values (i.e. 62.5% to 84%) in help-seeking CHR-P samples (Koutsouleris et al., 2018; Mechelli et al., 2017). Notably, these previous studies solely employed SVM classifiers whereas, in Chapter 3, we provide a direct comparison of five different classifiers including SVM. By assessing a range of classifiers, we were able to evaluate whether performance metrics showed adequate consistency across the different classifiers and to reduce the likelihood of developing a single bespoke, and possibly overfitted, model (Vieira et al., 2020). Notably, we discovered that our cross-site models - trained on the Glasgow data and tested on the Edinburgh data – performed slightly worse, on average, when compared to our mixed-site models, indicating that, despite utilising a range of classifiers, cross-site generalisability was not entirely optimal.

At present, the models in Chapters 2 to 4 appear to have limited clinical value since (1) they may miss a large number of vulnerable individuals and therefore limit the opportunity to provide early intervention to those who require it and/or (2) they may lead to unnecessary interventions in those who would not actually benefit.

Thirdly, Chapter 3 resulted in an unexpected finding which has implications for both research and clinical practice. Although the classifiers using cognitive variables, alongside clinical and functional variables, could predict functional outcome with above-chance performance, they consistently failed to outperform simpler classifiers which solely used baseline functioning variables (i.e. GAF, social functioning and role functioning). Therefore, our findings suggest that evaluating machine learning classifiers against population chance levels rather than participant-specific baselines could, in some instances, provide overly optimistic estimates in terms of their clinical utility.

Overall, our findings suggest that a short assessment of functioning at baseline provides the most simple and acceptable estimate of future functioning. The simplicity of this approach alone provides an argument in its favour over more complicated computational methods, especially for clinical services which may struggle to integrate complex algorithms into the clinical workflow. Certainly, our findings emphasise the need to take baseline functioning scores into

consideration during the clinical decision-making process, as individuals will likely continue to present with poor functioning in the future if appropriate interventions are not undertaken.

6.5 The CHR-N group

Notably, in addition to HCs, the studies in Chapters 2 to 4 also included a comparison group of CHR-N individuals. At present, the majority of CHR-P studies use HCs, who do not endorse any psychiatric disorder, as the sole reference point, which is likely to result in a comparison group that is not necessarily representative of the general population (Millman et al., 2019). Furthermore, given that psychiatric comorbidity is substantial in CHR-P samples (Salazar de Pablo et al., 2020), the inclusion of the CHR-N group allowed us to determine whether our findings related specifically to psychosis-specific processes or instead to co-occurring psychopathology.

In Chapter 2, we found that CHR-P individuals more commonly disclosed current self-harm intention and lifetime suicide attempt relative to CHR-N individuals, indicating that suicidality and self-harm are somewhat more prevalent in the CHR-P state. That said, the proportion of CHR-P and CHR-N individuals who disclosed current suicidal ideation did not significantly differ, in contrast to previous findings (Granö et al., 2013; Pelizza et al., 2020). This may reflect our choice of the CAARMS to measure suicidal ideation. Indeed, although Pelizza et al. (2019) found that CHR-P individuals more commonly disclosed current suicidal ideation relative to CHR-N individuals when suicidal ideation was assessed using the Beck Depression Inventory-II (BDI; Beck et al., 1996) – a self-report questionnaire – they did not find any significant differences when suicidal ideation was assessed using the CAARMS interview.

In Chapter 3, cognitive variables explained 12% of the variance in baseline functioning in our CHR-P group, yet failed to explain any of the variance in baseline functioning in our CHR-N group, leading us to suggest that this relationship may be specific to the CHR-P state. Furthermore, clinical and functional variables explained 17% of the variance in baseline functioning in our CHR-N group. Specifically, these variables were SPI-A mean distress, social functioning and role functioning – variables which also appeared in the combined

CHR-P model. Therefore, impaired functioning and distress related to basic symptoms may warn of future difficulties in any young person, regardless of symptomatology. Indeed, Koutsouleris et al. (2018) similarly found that functioning scores before study inclusion were a transdiagnostic predictor of social outcome at follow-up when examining CHR-P individuals and individuals with recent-onset depression.

Furthermore, in Chapter 4, we found that approximately 16% fewer CHR-N participants were allocated to the cognitively impaired subgroup relative to CHR-P participants, indicating that cognitive impairment is somewhat more prevalent in the CHR-P state. Notably, a sizeable proportion of HC individuals (30.2%) were also allocated to the cognitively impaired subgroup. This finding has implications for group-average approaches relying on HC populations as the sole reference point, with cognitive variability potentially reducing the validity of between-group inferences.

6.6 Limitations

Overall, our CHR-P sample is unlikely to be wholly representative of the general population. In terms of sample characteristics, 71.2% of our YouR-study CHR-P sample were female, 72.6% were UK citizens and 82.2% were engaged in college or university level education. The inclusion of a predominantly WEIRD (Western, Educated, Industrialised, Rich and Democratic) sample may partly reflect our choice of recruitment strategy whereby email invitations were sent out to colleges and universities in Glasgow and Edinburgh. Meanwhile, the over-representation of female participants may partly reflect the gender imbalance in higher education (HESA, 2022) as well as the greater willingness of females to participate in health research (Glass et al., 2015).

The number of FEP participants included in Chapters 2 and 4 was relatively low, especially with regard to the number of CHR-P participants. This low sample size also precluded us from including FEP participants in our machine learning analysis in Chapter 3. As such, we were unable to accurately characterise suicidality and non-suicidal self-harm, cognitive impairment, cognitive heterogeneity and functioning in our FEP group. Furthermore, the number of CHR-P participants who were recruited via referral or transitioned to psychosis

was also relatively low and therefore, we could not effectively examine differences between referred and community-recruited participants or between transitioned and non-transitioned participants. Notably, Chapter 5 also included a small sample of CHR-P and FEP participants, yet this was only ever intended to be a small-scale pilot study in order to test the feasibility of computerised cognitive training in the early stages of psychosis.

Furthermore, as shown in Chapters 3 and 4, approximately 80% of the total CHR-P sample completed a 6- and/or 12-month follow-up assessment, compared to just 55% of the total CHR-N sample. Notably, FEP and HC participants were not invited for follow-up assessments. Therefore, the relationship between cognition and functional outcome could not be examined in CHR-N, FEP or HC groups. That said, in Chapter 3, we intentionally did not perform the LASSO-LARS regression analysis in the HC group at baseline as their GAF scores were consistently high (i.e. 67 to 97), indicating that there would not be enough variation to allow a meaningful link with cognitive, functioning or clinical variables.

In terms of methodology, we used the GAF scale to measure global functioning across Chapters 3 to 5. However, this measure confounds functioning with symptom severity, potentially resulting in low scores even when social and role functioning are relatively spared. Nevertheless, the GAF scale is frequently used to measure functioning and is therefore suited for comparisons with other studies (e.g. Mechelli et al., 2017; Velthorst et al., 2019). Notably, we did utilise distinct measures of social and role functioning throughout Chapters 2 to 4. However, these scores were mostly limited in range (i.e. primarily falling within one point of the median), indicating that these measures may not readily pick up on some of the subtle changes experienced by our CHR-P participants, especially those recruited from the community.

Importantly, negative symptoms were not assessed in Chapters 2 to 5 despite previous CHR-P research suggesting that negative symptoms: (1) are significantly associated with suicidal ideation at baseline (Gill et al., 2015; Pelizza et al., 2020) and social outcome at 12-month follow-up (Glenthøj et al., 2020); and (2) mediate the relationship between neurocognition and social and role functioning at both baseline and 12-month follow-up (Meyer et al., 2014). As such, we could not determine the overall impact of clinical symptomatology on suicidal

ideation, baseline functioning and functional outcome in the CHR-P group. Moreover, we did not routinely collect information on current medication use or engagement in psychological treatment at the follow-up assessments. In Chapter 3, GAF scores at baseline were not significantly affected by medication use and less than 18% of individuals were receiving psychological treatment. Nevertheless, it would still have been useful to examine whether medications and psychological treatments received over the follow-up period exerted any effects on GAF scores at follow-up.

6.7 Future directions

Future research should focus on the design and implementation of digital technologies in order to provide more ecologically valid measures and improve participant engagement, real-world outcomes and access to early interventions. For example, ecological momentary assessment (EMA), where participants track their thoughts, feelings and behaviours in real-time and in naturalistic settings using an app on their mobile device – could potentially provide a more ecologically valid measure of suicidal thoughts and behaviours as well as social and role functioning. Indeed, EMA has the potential to overcome current measurement issues as, unlike the CAARMS, GAF and GF: Social and Role scales, it does not rely on a single retrospective assessment and, as such, is better able to capture subtle fluctuations over time. Passive measures of mobile device activity (e.g. GPS tracking, call logs, app usage) could also provide valuable information and are particularly advantageous since they can be collected continuously without burdening participants. That said, the use of passive mobile phone data warrants important ethical considerations, particularly among individuals with early-stage psychosis (Reilly et al., 2019).

In order to facilitate timely access to early intervention, future studies should investigate the feasibility of novel web-based screening platforms for detecting individuals with early-stage psychosis in the general population. Indeed, previous research by McDonald et al. (2019) indicated that, although characterised by excellent sensitivity (81%), our screening tool had modest specificity (57%) for predicting CHR-P status. Future studies should build upon our web-based screening platform by (1) incorporating known risk factors for the development of psychotic disorders; (2) performing online cognitive testing to detect

cognitive impairment; and (3) collecting speech samples to detect disorganised speech.

Digital technologies for both early detection and early intervention should strive to match the needs and expectations of end-users and therefore, individuals with lived experience of early-stage psychosis should be included in the design process. Following completion of the computerised cognitive training in Chapter 5, we asked participants to complete a short satisfaction survey. According to the survey, 76.9% of participants were "very satisfied" with the research process and felt that the number of cognitive training sessions was "about right" while 23.1% were "somewhat satisfied" with the research process and felt that the number of cognitive training sessions was "too many". Participants mentioned that the training was "new", "cool" and "different" and liked that they could compare their overall performance to other BrainHQ users. However, they also found the training to be "time-consuming" and "repetitive". Such feedback is vital in order to guide and inform the design and implementation of future interventions. As such, researchers should consider involving individuals with lived experience in usability sessions and focus groups before large RCTs are conduced to ensure optimal levels of participant satisfaction and engagement.

Importantly, there are concerns that individuals with early-stage psychosis who reside in low- or middle-income countries may have limited access to electricity, internet and/or digital devices which is likely to form a barrier to the implementation of digital detection and intervention strategies (Bell et al., 2022). That said, smartphone ownership is rapidly increasing in low- and middle-income countries, especially among young people aged 18-34 (Pew Research Center, 2019). Therefore, future studies should seek to recruit participants across diverse contexts, cultures and countries to ensure that findings can be generalised to the entire population and to accelerate the provision of high-quality mental health care in low-resource settings.

Importantly, computerised cognitive training represents just one core feature of cognitive remediation programmes. Other core features are the presence of an active and trained therapist, procedures to develop problem-solving strategies and procedures to facilitate transfer of cognitive gains to real-world functioning (Bowie et al., 2020). In schizophrenia, studies which include all four core

features appear to produce significantly larger improvements in global cognitive performance and overall functioning (Vita et al., 2021) and significantly better acceptability as measured by study drop-out rates (Vita et al., 2022). Therefore, future research in the early stages of psychosis should aim to incorporate these four core features in order to maximise treatment effectiveness. Of course, studies investigating computerised cognitive training alone are still valuable to the field as questions remain in terms of, for example, the effectiveness of different training modalities, the optimal training dosage, the durability of effects and the impact on underlying circuit deficits.

In order to enhance existing models, future studies should also assess the added value of different data combinations by incorporating, for example, negative symptoms and neuroimaging data. Indeed, Koutsouleris et al. (2018) found that machine learning prediction models trained on social and role functioning scores as well as structural neuroimaging data could outperform clinical raters' estimations of social functioning outcomes (combined model AUC = 0.86; clinical rater model AUC = 0.72). Importantly, other neuroimaging modalities, such as MEG and EEG, may be better suited to capturing subtle neural changes in the early stages of psychosis and therefore, future studies should examine the extent to which MEG and/or EEG data can enhance model performance. Most importantly, in order to avoid overoptimistic results, future studies should also adopt more rigorous machine learning methodologies that involve (1) external validation in diverse samples and varied settings; (2) the testing of multiple classifiers; and (3) the inclusion of appropriate benchmark measures.

6.8 Conclusions

This thesis has provided insights with regard to early detection and intervention in the early stages of psychosis. A considerable proportion of our CHR-P and FEP participants experienced suicidality and non-suicidal self-harm, cognitive impairment and poor functioning, emphasising the need for novel early detection and intervention strategies in the community and the importance of studying outcomes beyond transition to psychosis in CHR-P youth. Notably, our findings suggest that digital strategies represent a particularly promising avenue for identifying vulnerable youth in the community who may not otherwise

present to conventional services and also for providing accessible and scalable interventions, such as cognitive training.

Moreover, our findings suggest that cognitive heterogeneity must be taken into account to ensure a more tailored and personalised approach to early intervention and also emphasise the need to develop more accurate models for predicting outcomes. Future research must address the pitfalls and possibilities that currently surround the implementation of digital strategies and prediction models in clinical practice. Large-scale collaborative efforts are now required to bridge the gap between research and practice and, ultimately, to provide effective early detection and intervention strategies and accurate prediction models that have tangible benefits for clinicians, researchers and, most importantly, for young individuals with early-stage psychosis.

Appendix A - Supplementary Material for Chapter 2

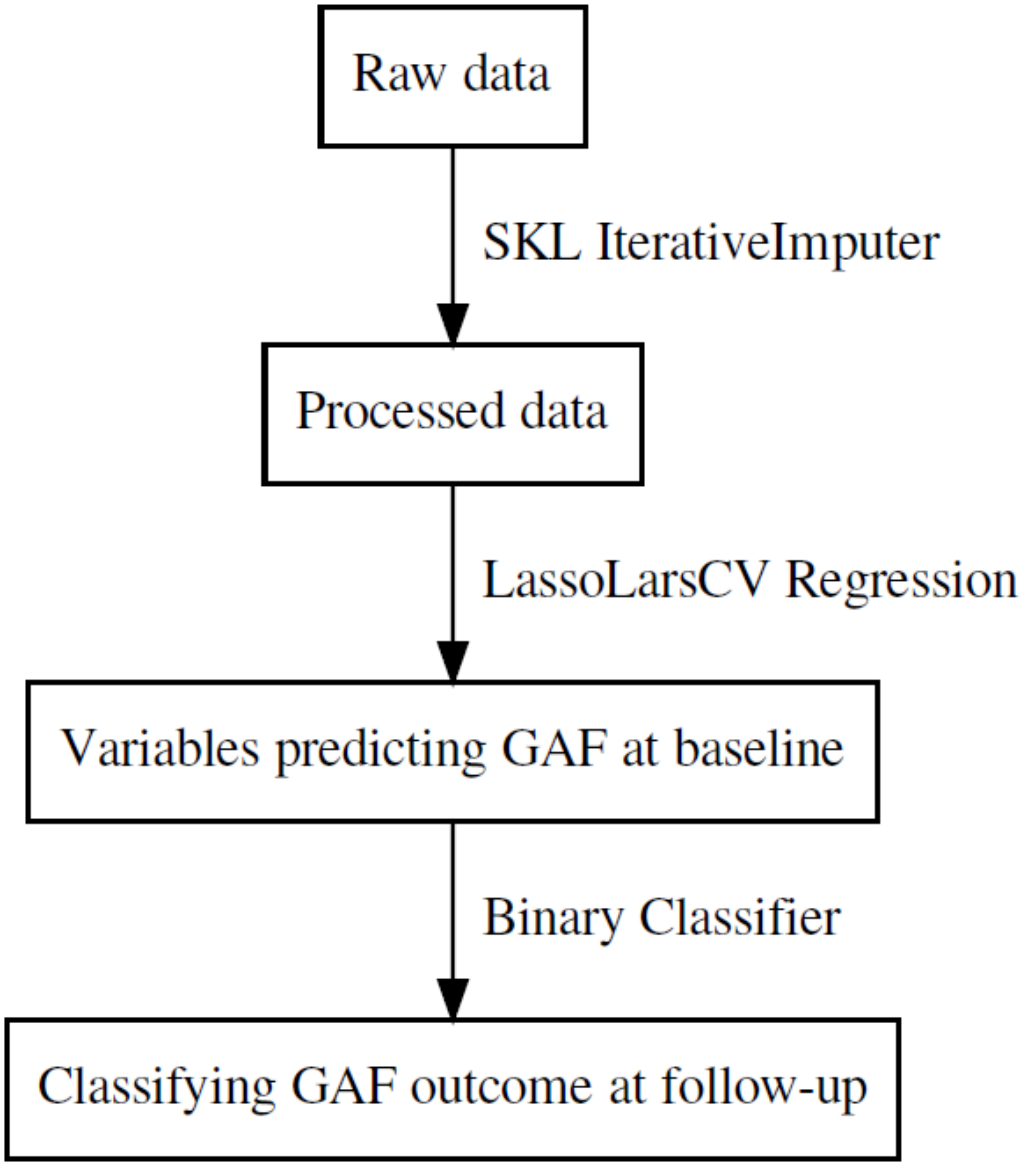
Supplementary Table 1 - Demographic, clinical, functional and cognitive characteristics of CHR-P participants by recruitment pathway (N = 146)

	Community (n = 130)	Referral (n = 16)	*p*	Effect size[a]
Age (years), mean (SD)	21.64 (4.27)	20.06 (3.62)	.121	r = 0.129
Gender, female n (%)	94 (72.3)	10 (62.5)	.397	ϕ = 0.068
Education (years), mean (SD)	15.40 (2.95)	12.88 (3.40)	.001	r = 0.267
Suicidality and self-harm, n (%)				
Self-harm intention (past month)	37 (28.5)	1 (6.3)	.070	ϕ = 0.158
Self-harm behaviour (past month)	7 (5.4)	0 (0)	1.000	ϕ = 0.079
Self-harm behaviour (lifetime)	37 (28.5)	2 (12.5)	.237	ϕ = 0.113
Suicide plan (past month)	12 (9.2)	2 (12.5)	.653	ϕ = 0.035
Suicidal ideation (past month)	45 (34.6)	4 (25.0)	.442	ϕ = 0.064
Suicide attempt (past month)	3 (2.3)	0 (0)	1.000	ϕ = 0.051
Suicide attempt (lifetime)	38 (29.2)	8 (50.0)	.092	ϕ = 0.140
MINI suicidality risk, n (%)				
Low	28 (21.5)	5 (31.3)	.359	ϕ = 0.073
Moderate	21 (16.2)	0 (0)	.129	ϕ = 0.144
High	21 (16.2)	2 (12.5)	1.000	ϕ = 0.031
CAARMS severity, median (range)	29 (0-74)	22 (11-54)	.148	r = 0.120
SPI-A severity, median (range)	7 (0-74)	5 (0-33)	.773	r = 0.024
Comorbidity, median (range)	2 (0-5)	1.5 (0-4)	.480	r = 0.059
ACES total, median (range)	2 (0-8)	1.5 (0-7)	.532	r = 0.052
Psychological treatment, n (%)				
Current	21 (16.2)	4 (25.0)	.479	ϕ =0.073
Past	59 (45.4)	7 (43.8)	.901	ϕ =0.010
Medication, n (%)				
Antidepressants	46 (35.4)	7 (43.8)	.511	ϕ =0.054
Mood stabilisers	4 (3.1)	0 (0)	1.000	ϕ =0.059
Antipsychotics	2 (1.5)	2 (12.5)	.060	ϕ =0.210
Anxiolytics	8 (6.2)	2 (12.5)	.301	ϕ =0.078
Social functioning (current), median (range)	8 (3-10)	7 (5-9)	.070	r = 0.150
Role functioning (current), median (range)	8 (3-9)	6.5 (6-9)	.008	r = 0.218
PAS average, median (range)	1.20 (0-3.43)	1.61 (0.50-3.00)	.030	r = 0.180
Social support, mean (SD)	5.05 (0.89)	5.19 (1.21)	.501	r = 0.056
Insecure attachment, mean (SD)	1.75 (0.46)	1.71 (0.38)	.611	r = 0.042
BACS composite score, mean (SD)	-0.39 (1.64)	-1.79 (1.98)	.012	r = 0.207

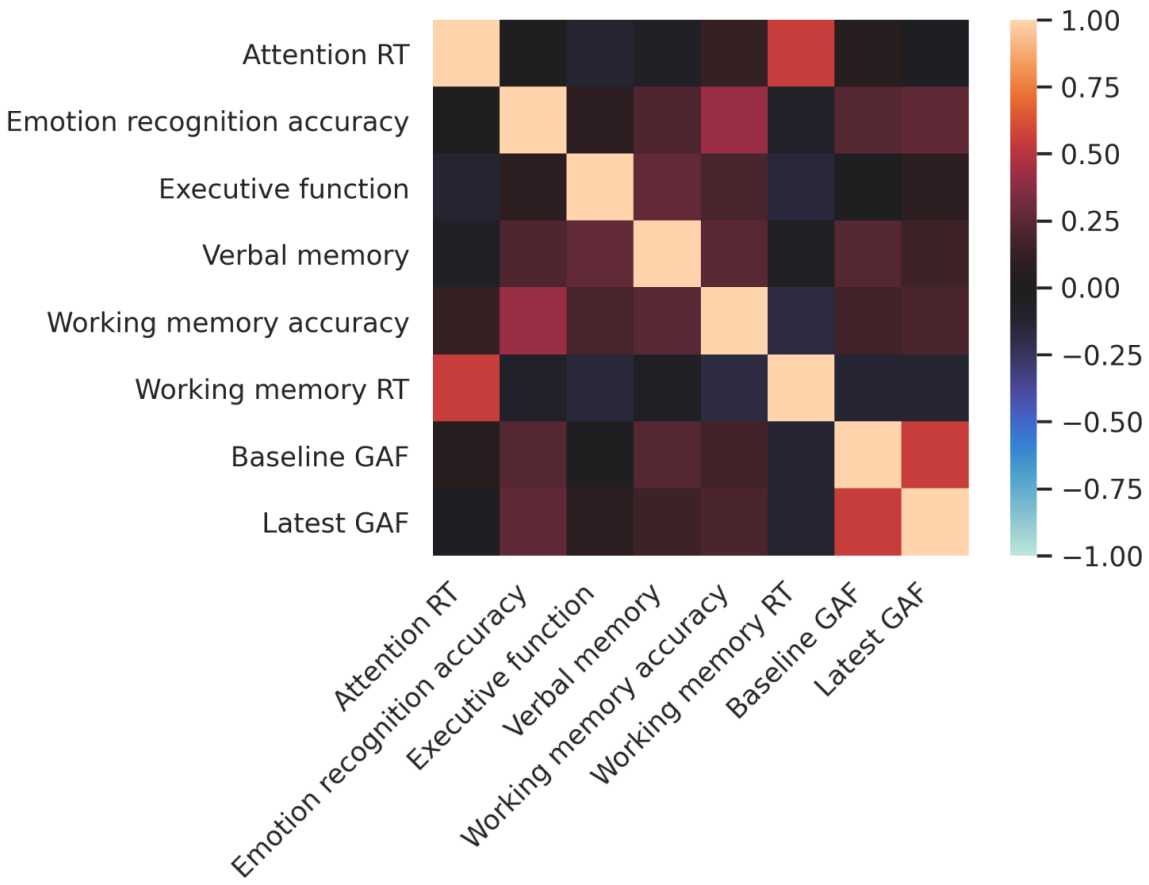
Note. CHR-P, clinical high-risk for psychosis; MINI, Mini-International Neuropsychiatric Interview; CAARMS, Comprehensive Assessment of At-Risk Mental States; SPI-A, Schizophrenia Proneness Instrument, Adult version; ACES, Adverse Childhood Experiences Scale; PAS, Premorbid Adjustment Scale; BACS, Brief Assessment of Cognition in Schizophrenia.

[a] Effect sizes were Rosenthal's r for Mann-Whitney U tests and Phi (ϕ) for Pearson's chi-square or Fisher's exact tests (small effect = 0.1, medium effect = 0.3, large effect = 0.5).

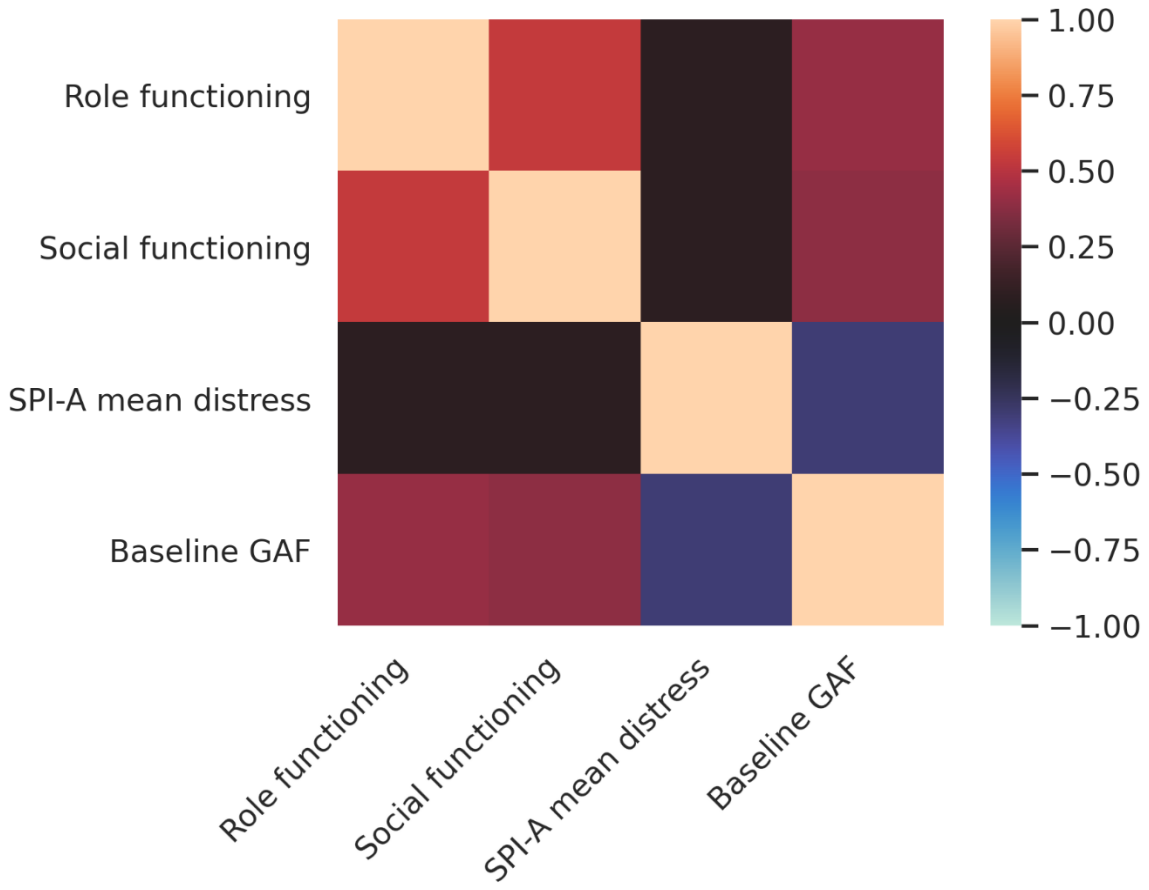
Appendix B - Supplementary Material for Chapter 3



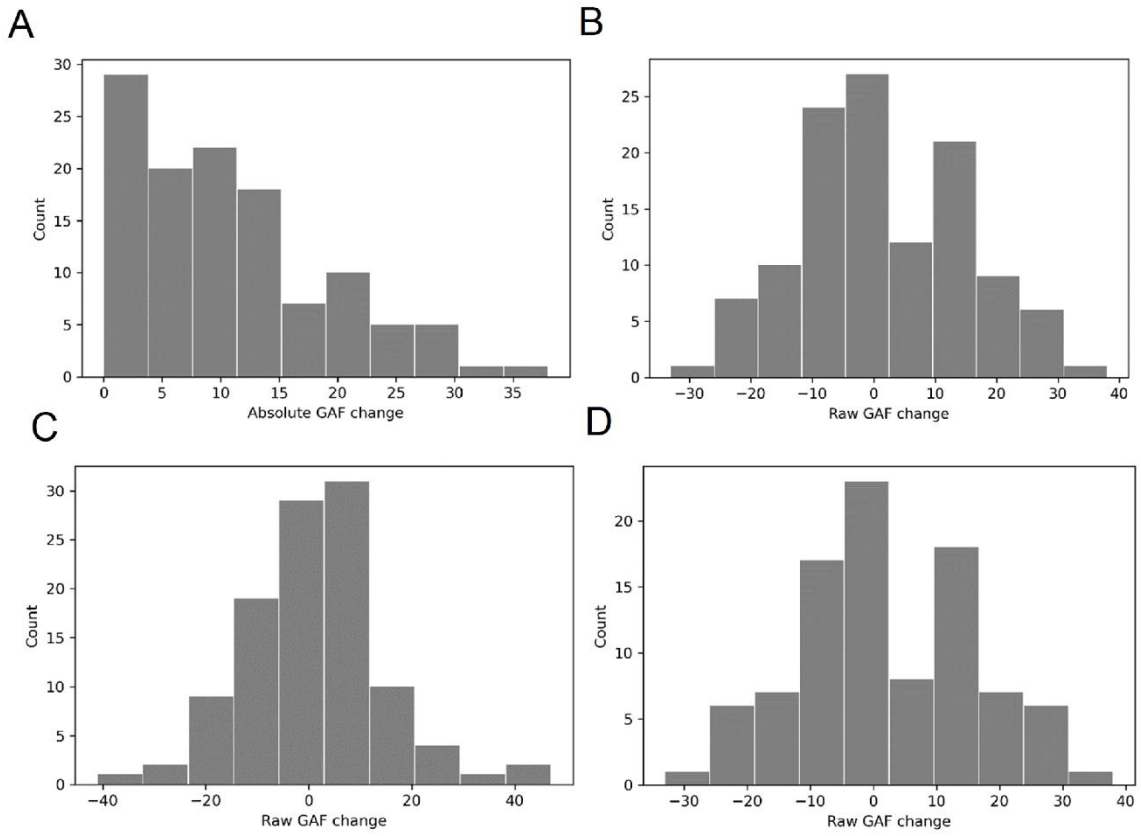
Supplementary Figure 1 - Flowchart showing the sequence of analyses used. Data was first prepared for regression, variables associated with GAF scores at baseline were identified, and GAF outcomes were classified using those variables.



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 = 118); (B) raw change in GAF scores between baseline and 6-12 month follow-up (N = 118); (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 2 - 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 Experiences 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 3 - 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 Experiences Scale; GAF, Global Assessment of Functioning; PAS, Premorbid Adjustment Scale; RT, response time.
Here, importance (i) for variable j is calculated using the *R*2 score for the fitted model, and new *R*2 scores ($S_{k,j}$) obtained after randomly shuffling variable column j for k iterations in the following manner:

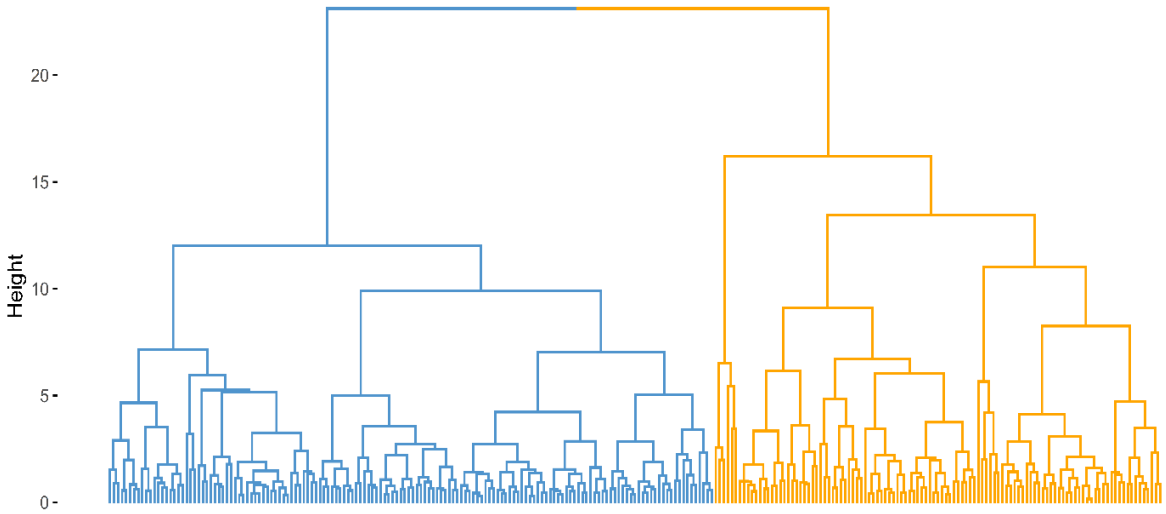
$$i_j = s - \frac{1}{K}\sum_{k=1}^{K} s_{k,j}$$

Supplementary Table 4 - 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 Experiences 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 C - Supplementary Material for Chapter 4



Supplementary Figure 5 - Cluster dendrogram displaying cluster 1 (impaired; orange) and cluster 2 (spared; blue) for the total sample (N = 261). Cluster analysis was conducted using the dist and hclust functions from the *stats* package

Supplementary Table 5 - Cognitive domains assessed by the BACS and CNB

BACS cognitive domain	Task	Procedure	Measure	Range
Verbal memory	List learning (version 1)	Participants are read a list of 15 words and then asked to recall as many as possible, in any order. Procedure repeated over five consecutive trials.	Number of words correctly recalled	0-75
Working memory	Digit sequencing task	Participants are read clusters of numbers (e.g. 961) that steadily increase in length. They are asked to recall the numbers in order, from lowest to highest.	Number of correct responses	0-28
Motor speed	Token motor task	Participants are given 100 plastic tokens and asked to place as many as possible in a container, two at a time. Time limit = 60 seconds.	Number of tokens correctly placed in the container	0-100
Verbal fluency	Semantic fluency	Participants are asked to generate as many words as possible within a specific category (i.e. animals). Time limit = 60 seconds.	Number of animals named	0-time variant
	Letter fluency	In two separate trials, participants are asked to produce as many words as possible beginning with a given letter (i.e. F and S). Time limit (per trial) = 60 seconds.	Number of words generated	0-time variant
Attention and processing speed	Symbol coding task	Participants are asked to write the numerals one through nine as matches to non-meaningful symbols on a response sheet as quickly as possible, based on a key provided to them. Time limit = 90 seconds.	Number of correct items	0-110
Executive function	Tower of London (version A)	Participants are shown two pictures (A and B) simultaneously - each showing three balls of different colours uniquely arranged on three pegs. They are asked to estimate the minimum number of times that the balls in picture A would have to be moved in order to match the arrangement in picture B.	Number of correct responses	0-22
CNB cognitive domain	**Task**	**Procedure**	**Measure**	**Range**
Attention	Continuous Performance Test-number and letter version (PCPT-nl)	Participants are presented with a series of red vertical and horizontal lines (seven segment displays) that flash in a digital numeric frame (akin to a digital clock). Participants are asked to press the spacebar when the lines form a complete number (initial 3 mins) or a complete letter (next 3 mins). Each stimulus is shown for 300 ms followed by a blank screen for 700 ms, allowing the participant 1 s to respond per trial.	Number of true positive responses	0-120
			Median response time for true positive responses	0-1000ms

Working memory	Letter-N-Back (LNB2)	Participants are presented with a continual series of flashing letters, one at a time, and asked to press the spacebar according to three different rules. In the 0-back condition, the spacebar must be pressed whenever the letter "X" appears. In the 1-back condition, the spacebar must be pressed whenever the current letter matches the previous letter. In the 2-back condition, the spacebar must be pressed whenever the current letter matches the letter before the previous letter. Each stimulus is shown for 500 ms followed by a blank screen for 2000 ms, allowing the participant 2.5 s to respond per trial.	Number of correct responses	0-45
			Median response time for correct responses	0-2500ms
Emotion recognition	Emotion Recognition Task (ER40)	Participants are presented with 40 colour photographs of faces, one at a time, and asked to determine the specific emotion being expressed from five possible choices: happy, sad, anger, fear or no emotion. Participants respond by clicking on their chosen emotion with the mouse.	Number of correct responses	0-40
			Median response time for correct responses	0-time variant

Note: BACS, Brief Assessment of Cognition in Schizophrenia; CNB, Penn Computerized Neurocognitive Battery

Supplementary Table 6 - Pattern matrix for the total sample (N = 261)

Measure	Oblimin rotated component loadings				
	VF	ER	ATT	WM	GCF
Verbal memory	0.19	-0.05	0.08	0.07	**0.61**
WM	0.37	-0.16	-0.11	0.12	**0.59**
Motor speed	-0.24	0.37	0.28	-0.07	0.36
VF semantic	**0.75**	0.07	-0.02	0.07	0.01
VF letter F	**0.85**	-0.01	0.04	-0.11	0.02
VF letter S	**0.82**	0.03	0.08	0.02	-0.04
VF total	**0.96**	0.02	0.02	0.02	0.02
ATT & processing speed	0.08	0.29	0.12	-0.01	**0.63**
Executive function	-0.19	-0.03	0.04	0.09	**0.70**
ER efficiency	0.01	**0.89**	0.00	0.10	0.03
ER anger efficiency	0.06	**0.74**	-0.06	-0.13	0.09
ER happy efficiency	0.07	**0.72**	0.15	0.02	-0.20
ER fear efficiency	0.00	**0.50**	-0.11	0.37	-0.12
ER sad efficiency	0.05	**0.74**	-0.07	0.03	0.07
WM efficiency	0.00	0.01	0.08	**0.93**	0.02
WM 1-back efficiency	-0.02	-0.02	-0.03	**0.89**	-0.02
WM 2-back efficiency	-0.01	0.05	0.05	**0.80**	0.06
ATT efficiency	0.02	-0.02	**0.97**	0.02	0.01
ATT letter efficiency	0.03	0.00	**0.91**	0.01	-0.06
ATT number efficiency	0.02	-0.01	**0.86**	0.05	0.08
Eigenvalues	3.26	3.04	2.79	2.65	1.96
% of variance	16	15	14	13	10
α	.89	.82	.93	.88	.68

Note: Component loadings over .40 appear in bold. VF, verbal fluency; ER, emotion recognition; ATT, attention; WM, working memory; GCF, general cognitive function

Supplementary Table 7 - Structure matrix for the total sample (N = 261)

Measure	Oblimin rotated component loadings				
	VF	ER	ATT	WM	GCF
Verbal memory	0.36	0.08	0.31	0.27	**0.69**
WM	**0.47**	-0.02	0.16	0.23	**0.67**
Motor speed	-0.02	0.40	0.35	0.22	0.39
VF semantic	**0.77**	0.22	0.25	0.19	0.21
VF letter F	**0.85**	0.11	0.25	0.03	0.20
VF letter S	**0.85**	0.19	0.33	0.16	0.19
VF total	**0.98**	0.20	0.33	0.17	0.27
ATT & processing speed	0.31	0.38	0.35	0.30	**0.70**
Executive function	-0.01	0.04	0.18	0.25	**0.68**
ER efficiency	0.18	**0.93**	0.25	**0.41**	0.14
ER anger efficiency	0.17	**0.70**	0.09	0.13	0.13
ER happy efficiency	0.19	**0.76**	0.29	0.28	-0.07
ER fear efficiency	0.07	**0.59**	0.12	**0.47**	-0.01
ER sad efficiency	0.17	**0.75**	0.14	0.28	0.14
WM efficiency	0.16	0.35	**0.45**	**0.97**	0.28
WM 1-back efficiency	0.09	0.27	0.30	**0.86**	0.20
WM 2-back efficiency	0.15	0.34	0.38	**0.85**	0.28
ATT efficiency	0.31	0.21	**0.98**	0.39	0.25
ATT letter efficiency	0.29	0.20	**0.91**	0.35	0.17
ATT number efficiency	0.30	0.21	**0.90**	0.40	0.30

Note: Component loadings over .40 appear in bold. VF, verbal fluency; ER, emotion recognition; ATT, attention; WM, working memory; GCF, general cognitive function

Supplementary Table 8 - Cognitive characteristics of the CHR-P group by cognitive cluster at baseline (N = 146)

Measure	Cluster 1		Cluster 2		*p*	Effect size[a]
	Impaired (N= 67)		Spared (N = 79)			
	Mean	SD	Mean	SD		
Premorbid IQ[b]	108.23	7.64	111.39	6.00	.007	*d* = 0.460
Verbal memory	-0.72	1.10	0.24	1.11	< .001	*d* = 0.873
WM	-0.60	1.31	0.41	1.31	< .001	*r* = 0.377
Motor speed	-1.13	1.22	-0.30	1.07	< .001	*d* = 0.729
VF semantic	-0.63	0.93	0.44	1.04	< .001	*d* = 1.087
VF letter F	-0.67	0.93	0.28	1.01	< .001	*r* = 0.458
VF letter S	-0.78	1.08	0.37	1.29	< .001	*r* = 0.446
VF total	-0.80	0.91	0.56	1.11	< .001	*r* = 0.575
ATT & processing speed	-1.12	0.82	0.14	1.09	< .001	*r* = 0.581
Executive function	-0.44	1.45	0.33	1.14	< .001	*r* = 0.290
ER efficiency	-0.87	1.15	0.06	0.62	< .001	*r* = 0.472
ER anger efficiency	-0.42	1.04	0.20	0.57	< .001	*r* = 0.360
ER happy efficiency	-0.83	1.09	-0.10	0.76	< .001	*r* = 0.391
ER fear efficiency	-0.36	1.33	0.13	0.59	< .001	*r* = 0.337
ER sad efficiency	-0.58	1.08	0.15	0.64	< .001	*r* = 0.393
WM efficiency	-0.47	1.10	0.13	0.63	< .001	*r* = 0.314
WM 1-back efficiency	-0.37	1.24	0.14	0.72	.005	*r* = 0.231
WM 2-back efficiency	-0.43	0.89	0.07	0.60	< .001	*r* = 0.302
ATT efficiency	-0.78	1.40	0.20	0.68	< .001	*r* = 0.443
ATT letter efficiency	-0.50	1.22	0.29	0.78	< .001	*r* = 0.394
ATT number efficiency	-0.73	1.45	0.25	0.60	< .001	*r* = 0.396

Note: VF, verbal fluency; ER, emotion recognition; ATT, attention; WM, working memory; GCF, general cognitive function

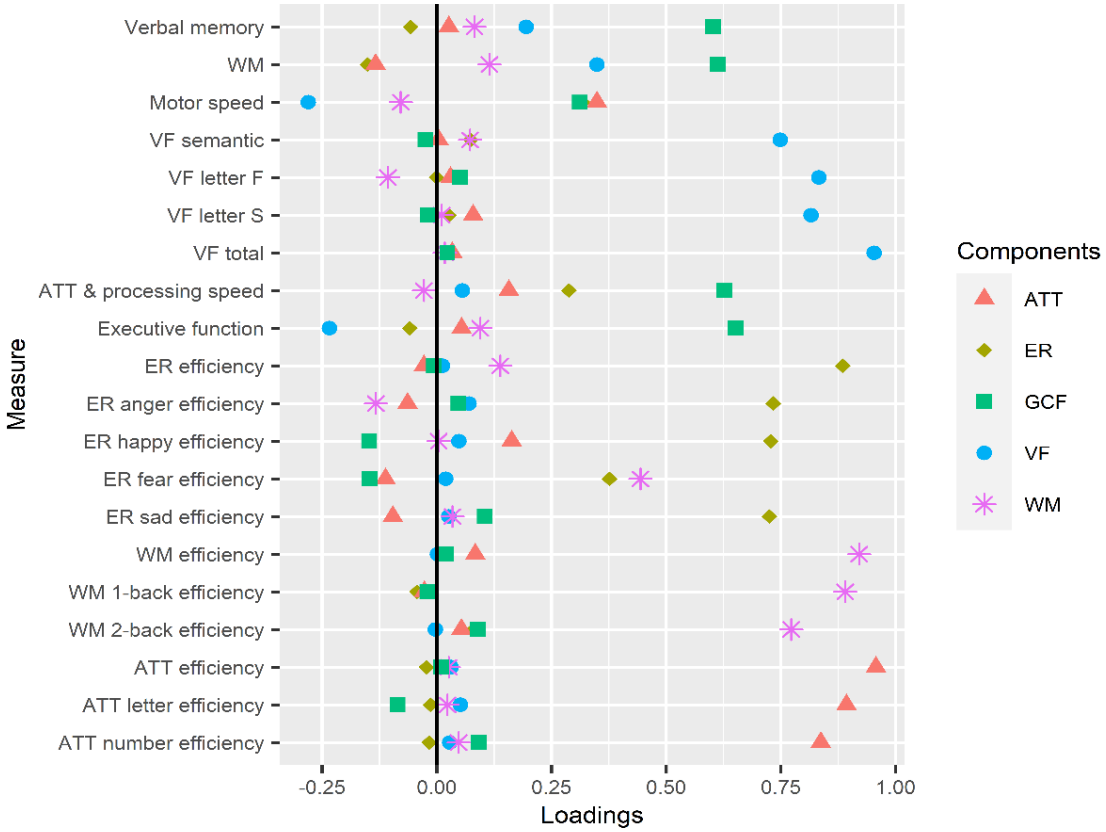
[a] Effect sizes were Rosenthal's *r* for Mann-Whitney *U* tests (small effect = 0.1, medium effect = 0.3, large effect = 0.5) and Cohen's *d* for Welch's *t*-tests (small effect = 0.2, medium effect = 0.5, large effect = 0.8)

[b] This measure was not included in the PCA or cluster analysis

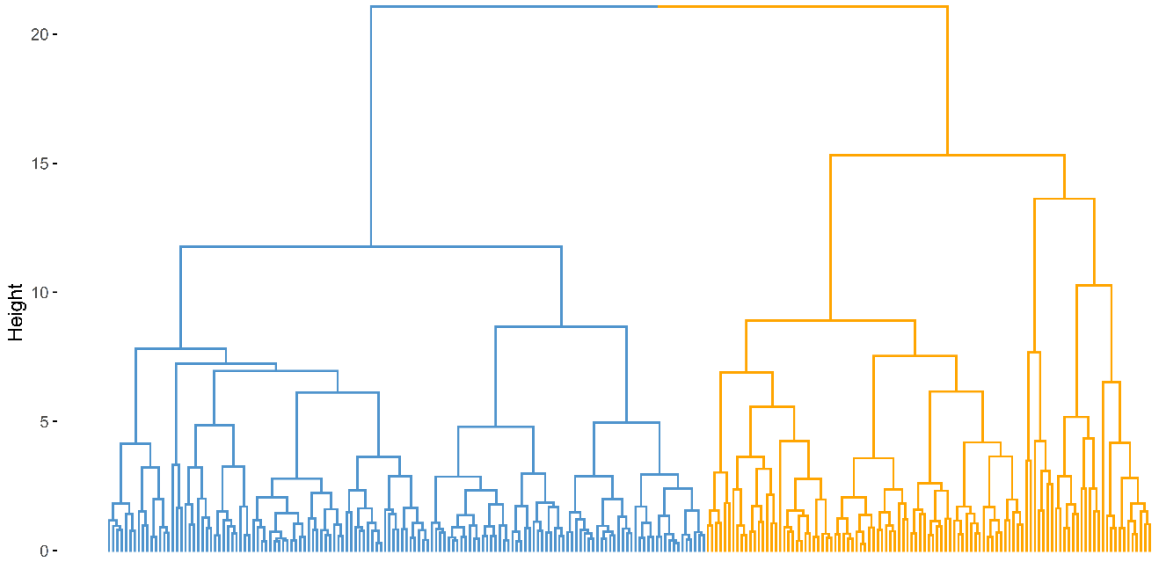
Supplementary Results

Following exclusion of the FEP group, the aforementioned principal components were re-extracted and, in combination, explained 67% of the variance in cognitive performance (Supplementary Figure 6). As before, agglomerative hierarchical clustering with 2 clusters was favoured, resulting in the emergence of a cognitively impaired (n = 105; 42.7%) and spared (n = 141; 57.3%) cluster (Supplementary Figure 7). Linear discriminant analysis confirmed that we were able to predict the cluster membership of new cases with a mean accuracy of 87.5%. Cluster 1 comprised 50.0% of CHR-P participants, 31.9% of CHR-N participants and 32.1% of HCs (Supplementary Figure 8).

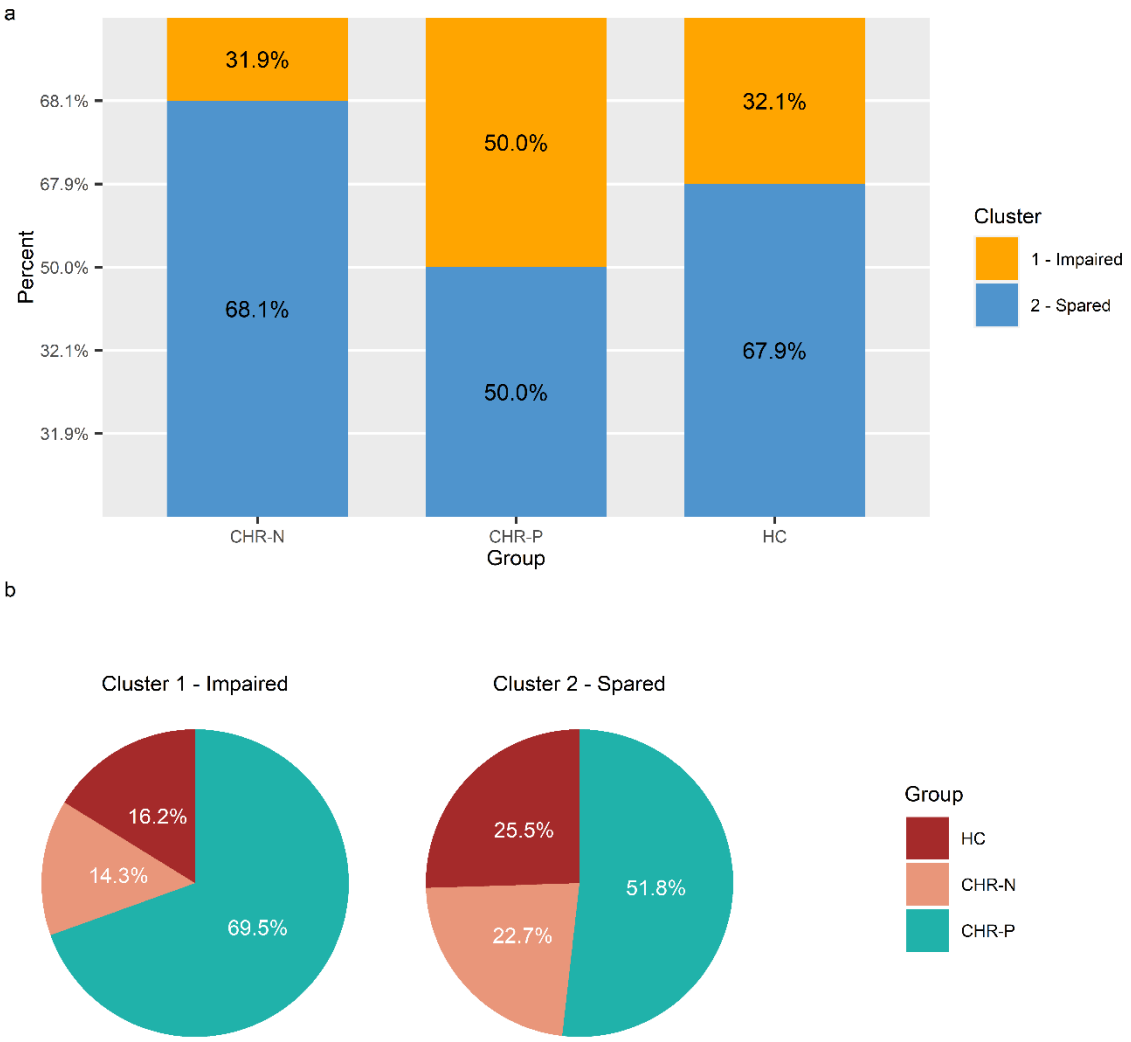
Group differences remained relatively unchanged, with CHR-P individuals in cluster 1 displaying significantly poorer performance across all 20 cognitive tests ($p < .05$) as well as impairments in social ($p = .036$; $r = 0.174$), role ($p = .029$; $r = 0.180$) and premorbid ($p = < .001$, $r = 0.337$) functioning (Supplementary Figure 9). Male CHR-P participants were still significantly more likely ($p < .001$; $\phi = 0.303$) to be allocated to cluster 1 (42.5%) than cluster 2 (15.1%). Similar impairments were also evident at follow-up with poor functional outcome significantly more likely ($p = .006$, $\phi = 0.247$) in cluster 1 (71.0%) than cluster 2 (46.7%) and CHR-P individuals in cluster 1 displaying poorer global ($p = .020$; $r = 0.210$) and social ($p = .045$; $r = 0.182$) functioning. Finally, cluster membership explained 8.1% of the variance in functional outcome ($p = .007$, AUC = 0.626, sensitivity = 61.1% and specificity = 64.0%) but was unable to predict CAARMS persistence ($p = .788$) or transition to psychosis ($p = .290$).



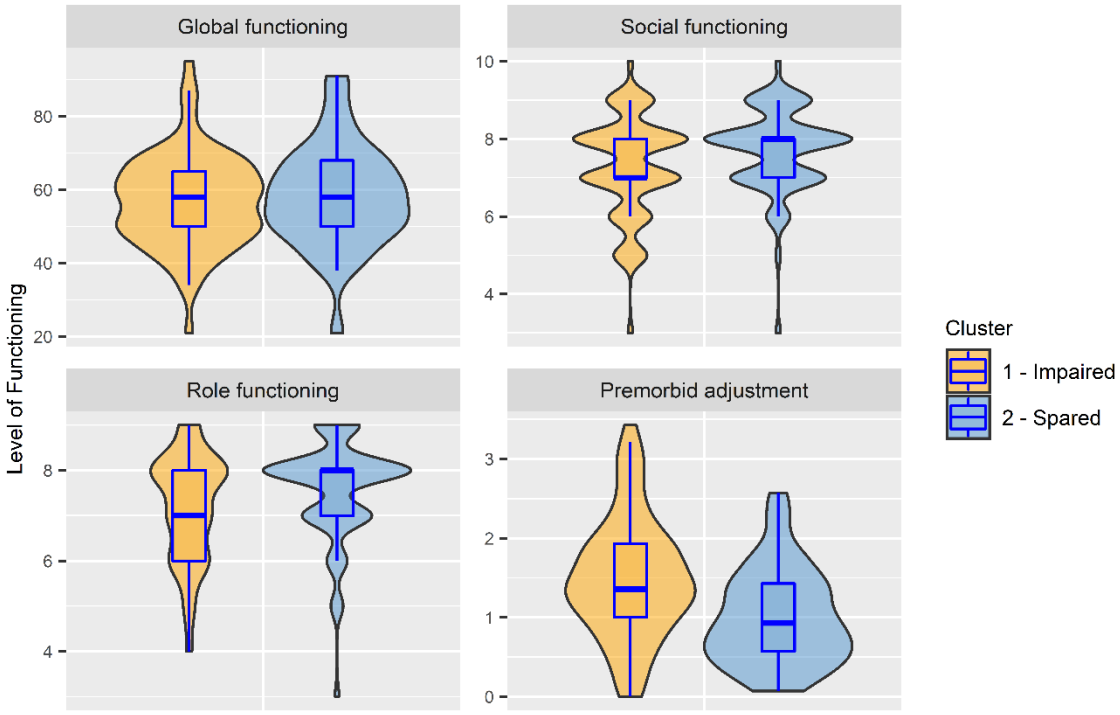
Supplementary Figure 6 - Component loading plot following exclusion of the FEP group (N = 246). ATT, attention; ER, emotion recognition; GCF, general cognitive function; VF, verbal fluency; WM, working memory



Supplementary Figure 7 - Cluster dendrogram displaying cluster 1 (impaired; orange) and cluster 2 (spared; blue) following exclusion of the FEP group (N = 246). Cluster analysis was conducted using the dist and hclust functions from the *stats* package



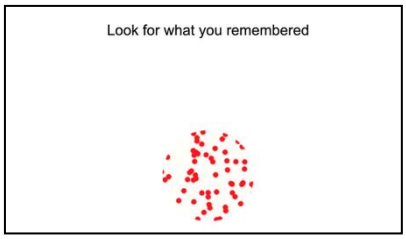
Supplementary Figure 8 - The distribution of (a) clusters within each diagnostic group and (b) diagnostic groups within each cluster following exclusion of the FEP group (N = 246). CHR-P, clinical high-risk for psychosis; CHR-N, clinical high-risk-negative; HC, healthy control

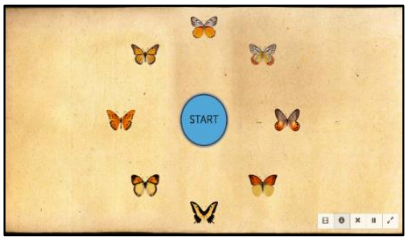
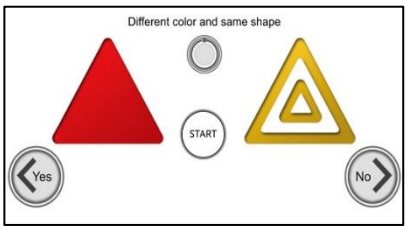
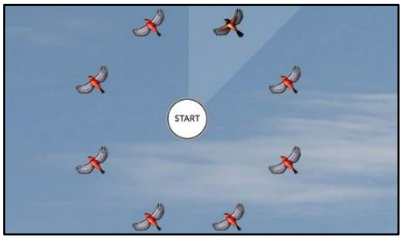
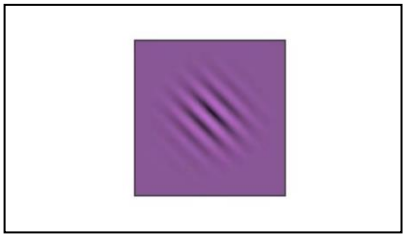


Supplementary Figure 9 - Level of functioning across cognitive clusters for the CHR-P group (N = 146), formed following exclusion of the FEP group. CHR-P individuals in cluster 1 were characterised by poorer social, role and premorbid functioning ($p < .05$) but not global functioning ($p = .528$).

Appendix D - Supplementary Material for Chapter 5

Supplementary Table 9 - Brief summary of the eight BrainHQ exercises

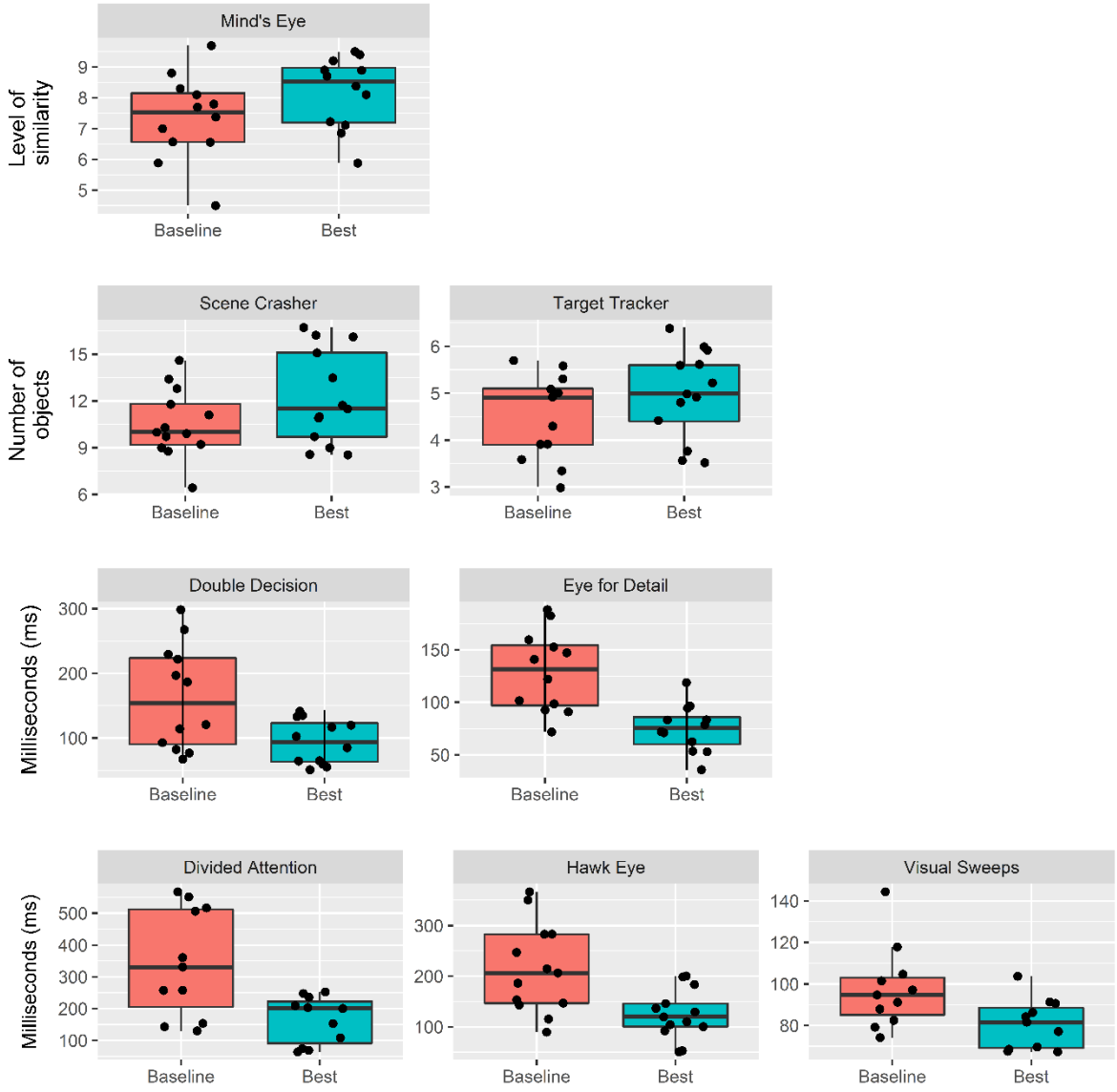
Exercise	Exercise Category	Procedure	Measure	Example
Mind's Eye	Visual distractor suppression	Participants are presented with a target image (e.g. patterns or moving dots). Next, a set of similar images flash on the screen, one at a time. Participants must click on the location where an image appeared that matched the target image.	Score reflects discrimination threshold. Higher scores are better. Min = 1 Max = 15	
Scene Crasher	Visual memory via a change-detection paradigm	Several objects (e.g. sheep or keys) flash on the screen and subsequently disappear. The same scene reappears but with one additional object added. Participants must click on the object that was added to the scene.	Score reflects the number of objects remembered. Higher scores are better. Min = 1 Max = 20	
Target Tracker	Visual working memory capacity via a multiple object tracking paradigm	Participants track target objects (e.g. bubbles, puffer fish or jellyfish) as they move around the screen whilst ignoring identical distractors. Participants must click on the target objects when they stop moving.	Score reflects the number of objects tracked. Higher scores are better. Min score = 1 Max score = 10	
Double Decision	Useful field of view and visual speed of processing	One of two vehicles is briefly displayed in the middle of the screen, along with a Route 66 road sign in the periphery. Participants must choose which vehicle they saw and then select the section of the screen that contained the Route 66 sign.	Score reflects exposure duration in milliseconds. Lower scores are better. Min = 32 ms Max = 3162 ms	

Eye for Detail	Visuospatial working memory and eye movement speed	Three to five images briefly appear, one at a time, in different positions on the screen. Of the images, some match precisely whereas others are similar but not the same. Participants must click on the locations where the matching images appeared.	Score reflects exposure duration in milliseconds. Lower scores are better. Min = 25 ms Max = 5012 ms	
Divided Attention	Colour-shape-fill inhibitory control	Participants are presented with certain criteria and two shapes. Criteria include matching colours, shapes and/or fill interiors. Participants must click the left arrow if the shapes match the criteria or the right arrow if they do not.	Score reflects exposure duration in milliseconds. Lower scores are better. Min = 32 ms Max = 2048 ms	
Hawk Eye	Divided and selective attention via a visual search paradigm	A flock of birds flash on the screen and subsequently disappear. Participants must select the section of the screen that contained the bird that was different from the others.	Score reflects exposure duration in milliseconds. Lower scores are better. Min = 10 ms Max = 10000 ms	
Visual Sweeps	Visual speed of processing via a time-order judgement paradigm	Participants are presented with two Gabor motion patterns, one after the other. Each one can sweep either inwards or outwards. Participants must indicate the direction of the motion by clicking the inward and/or outward arrows.	Score reflects exposure duration in milliseconds. Lower scores are better. Min = 32 ms Max = 1000 ms	

Note. Exercises that are measured in milliseconds (ms) reflect the exposure duration of the stimuli, not response time.

Supplementary Methods

BrainHQ data were analysed using R version 4.0.3 (R Core Team, 2020). For each unique level combination of each exercise, we recorded the baseline score (i.e. the score for the first time the level was played) and the best score (i.e. the best score achieved over repeated play). Since all participants played each unique level combination of each exercise three times, the best score would arise during either repetition two or three. For each participant, a mean baseline score and a mean best score were then calculated for each exercise by collapsing across all levels. Outliers were identified by the Tukey method (1.5 × interquartile range: IQR). This resulted in the removal of one participant's data from three exercises (Mind's Eye, Double Decision, Eye for Detail) and two participants' data from two exercises (Divided Attention, Visual Sweeps). To determine improvement over repeated play, difference scores (baseline score – best score) were computed for BrainHQ performance on the eight visual processing exercises. Normality of the difference scores was assessed using the Shapiro-Wilk test. A paired *t*-test was used on those variables meeting the assumption of normality. Otherwise, a non-parametric Wilcoxon signed rank test was used.



Supplementary Figure 10 - Baseline and best scores for the eight visual processing exercises completed in BrainHQ. For Mind's Eye, Scene Crasher and Target Tracker (rows 1 & 2), higher scores indicate better performance whereas for the remaining tasks (rows 3 & 4), lower scores indicate better performance. Data are collapsed across users and across all levels of the exercise. Black dots indicate mean performance for a single user. Exercises that are measured in milliseconds (ms) reflect the exposure duration of the stimuli, not response time.

Supplementary Table 10 - Baseline and best scores on BrainHQ exercises (N = 13)

	Baseline		Best		*p*	Effect Size[a]
	Mean	SD	Mean	SD		
Mind's Eye	7.36	1.38	8.18	1.16	< .001	*d* = 1.76
Scene Crasher	10.54	2.18	12.19	3.01	< .001	*d* = 1.26
Target Tracker	4.51	0.89	4.97	0.95	< .001	*d* = 1.81
Double Decision	162.86	80.35	94.06	34.42	< .001	*d* = 1.37
Eye for Detail	129.05	38.29	75.14	22.53	< .001	*d* = 1.89
Divided Attention	343.32	169.45	165.25	74.31	.003	*r* = 0.81
Hawk Eye	214.17	87.50	124.81	48.53	< .001	*d* = 1.30
Visual Sweeps	97.74	19.81	80.73	11.90	.002	*d* = 1.28

Note. For Mind's Eye, Scene Crasher and Target Tracker, higher scores indicate better performance whereas for the remaining tasks, lower scores indicate better performance.
[a] Effect sizes were Cohen's *d* for paired-samples *t*-tests (small effect = 0.2, medium effect = 0.5, large effect = 0.8) and Rosenthal's *r* for Wilcoxon signed rank tests (small effect = 0.1, medium effect = 0.3, large effect = 0.5)

Glossary of Measures

Adverse Childhood Experiences Scale (ACES; Felitti et al., 1998; Murphy et al., 2014)

A 25-item self-report questionnaire used to assess experiences of abuse (emotional, physical and sexual), neglect (emotional and physical) and household dysfunction during the first 18 years of life. Household dysfunction encompasses household substance abuse, household mental illness, mother treated violently, parental separation or divorce and incarcerated household member. Each question is answered either on a 5-point scale ("never", "once, twice", "sometimes", "often", "very often") or in a dichotomous manner ("yes"/"no"). The total number of adverse childhood experiences can be calculated per participant out of a possible total of 10.

Audio-Visual Abnormalities Questionnaire (AVAQ; Nikitova et al., 2019)

An 85-item self-report questionnaire used to assess abnormalities in auditory and visual processing. Participants are asked to indicate how often they have experienced each item in the past year on a 4-point scale (0 = "never", 1 = "sometimes", 2 = "often", 3 = "nearly always"). If participants respond with a rating of 1 to 3, they are also asked to rate the distress level associated with that item on a 4-point scale (0 = "no distress" to 3 = "a lot of distress"). Total frequency and distress scores can be calculated per participant by summing the relevant items and excluding the five catch items that are included to detect random responding.

Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004)

A pen and paper battery assessing six neurocognitive domains: verbal memory, working memory, motor speed, verbal fluency, attention and processing speed and executive function. The tests used to assess these domains are outlined in Supplementary Table 5, Appendix C. In order to minimise practice effects and facilitate repeated testing, alternate versions are available for two BACS tests – verbal memory and executive function. Raw test scores can subsequently be

converted into standardised domain and composite scores with correction for sex (and age if applicable).

Comprehensive Assessment of At-Risk Mental States (CAARMS; Yung et al., 2005)

A semi-structured interview used to detect and assess young people at UHR of developing psychosis. The positive symptom domain comprises four symptom subscales – unusual thought content, non-bizarre ideas, perceptual abnormalities and disorganised speech. Questions are rated for symptom presence within the past 12 months. For each domain, intensity of symptoms is rated on a 7-point scale (0 = "never, absent" to 6 = "psychotic and severe"), frequency of symptoms is rated on a 7-point scale (0 = "absent" to 6 = "continuous") and distress is rated on a scale from 0 to 100. Symptom severity can be calculated per participant by multiplying the intensity score by the frequency score for each of the four domains and summing these products, with higher scores indicating greater symptom severity. A mean distress rating can also be calculated per participant, with higher scores indicating greater distress.

Global Assessment of Functioning (GAF) scale (American Psychiatric Association, 2000)

Interviewer-rated scale used to assess a person's overall level of functioning in the past month in terms of both symptoms and functioning. This 100-point scale is divided into 10-point intervals (e.g. 51-60 and 61-70) with anchor descriptors. For example, a score between 51 and 60 would be given to an individual with moderate symptoms or moderate difficulty in social, work or school functioning. Higher scores indicate more satisfactory levels of overall functioning.

Global Functioning: Social (GF: Social) and Global Functioning: Role (GF: Role) scales (Cornblatt et al., 2007)

Interviewer-rated scales used to assess social and role functioning. The GF: Social scale assesses the quality and quantity of peer relationships, peer conflict, age-appropriate intimate relationships and involvement with family members whereas the GF: Role scale assesses school, work or homemaking

performance and level of support required. In both scales, scores range from 1 (“extreme dysfunction”) to 10 (“superior functioning”) with anchor descriptors provided for each point on the scale. Each scale generates three separate scores: current level of functioning in the past month, highest level of functioning in the past year and lowest level of functioning in the past year.

Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998)

A short, structured interview for the major Axis I psychiatric disorders in DSM-IV and ICD-10. Specifically, the MINI screens for 17 major Axis I disorders with additional modules for suicidality and antisocial personality disorder (an Axis II disorder). The focus is on current diagnoses, although lifetime diagnoses are also explored in certain modules. Questions require a “yes” or “no” response. For most modules, one or two screening questions are used to rule out the diagnosis when answered negatively. When answered positively, more detailed symptom questions are asked to investigate additional diagnostic criteria. The total number of diagnostic categories met can subsequently be determined per participant.

National Adult Reading Test (NART; Nelson, 1982)

A 50-item pronunciation test used to estimate premorbid IQ. Participants are asked to read aloud 50 irregular words (e.g. ache, thyme, quadruped) of increasing difficulty. This is taken as an indicator of past learning achievement and therefore represents an indirect measure of premorbid IQ. The number of words incorrectly pronounced, or the NART error score, can be entered into the following regression equation (Bright et al., 2018) to estimate the premorbid Weschler Adult Intelligence Scale - Fourth Edition (WAIS-IV; Wechsler, 2008) full scale IQ score:

$$\text{Predicted WAIS-IV FSIQ} = -0.9775 \times \text{NART error score} + 126.41$$

Penn Computerized Neurocognitive Battery (CNB; Moore et al., 2015)

A series of computerised tests that measure accuracy and speed of performance in major cognitive domains, including attention, working memory and emotion

recognition. The tests used to assess these domains are outlined in Supplementary Table 5, Appendix C. Raw accuracy and speed scores can be converted into standardised scores. Efficiency scores, which combine accuracy and speed, can also be calculated.

Perceptual and Cognitive Anomalies (PCA) questionnaire (McDonald et al., 2019)

A 9-item self-report questionnaire used to assess basic symptoms. Participants indicate whether each item was present in the past 12 months using a binary response ("true"/"false"). If the participant answers "true", they are also asked to rate the associated distress level on a 4-point scale (0 = "none" to 3 = "severe"). The total number of items endorsed can be calculated per participant and those with a cut-off score of 3 or more can be invited for further clinical assessments.

Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987)

A semi-structured interview used to assess symptom severity in the past week. We adopted a five-factor scoring model (van der Gaag et al., 2006; Woodward et al., 2014), yielding scores for positive symptoms (6 items), negative symptoms (7 items), cognitive/disorganisation (9 items), excitement (4 items) and emotional distress (4 items). Each item is rated by the interviewer on a 7-point scale (1 = "absent" to 7 = "extreme"). Total scores can be calculated per participant by summing the relevant items, with higher scores indicating greater symptom severity.

Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982)

A retrospective interview used to assess premorbid functioning across childhood (6-11 years), early adolescence (12-15 years) and late adolescence (16-18 years). Specifically, participants are asked questions related to the following five domains: sociability and withdrawal, peer relationships, scholastic performance, adaptation to school and (where appropriate) socio-sexual aspects of life. Within each life period, each domain is rated by the interviewer on a 7-point scale from 0 (normal adjustment) to 6 (severe impairment). A mean rating of premorbid

functioning can be calculated per participant, with higher scores reflecting more severe impairment.

Prodromal Questionnaire 16-item version (PQ-16; Ising et al., 2012)

A 16-item self-report questionnaire used to screen individuals for psychosis risk. Specifically, it consists of 9 items on perceptual abnormalities/hallucinations, 5 items on unusual thought content/delusional ideas/paranoia and 2 items on negative symptoms. Participants indicate whether each item was present in the past 12 months using a binary response ("true"/"false"). If the participant answers "true", they are also asked to rate the associated distress level on a 4-point scale (0 = "none" to 3 = "severe"). The total number of items endorsed can be calculated per participant and those with a cut-off score of 6 or more can be invited for further clinical assessments.

Psychosis Attachment Measure (PAM; Berry et al., 2006)

A 16-item self-report measure used to assess insecure attachment, with 8 items assessing anxious attachment and 8 items assessing avoidant attachment. Items refer to thoughts, feelings and ways of behaving in close interpersonal relationships and participants rate the extent to which each item, or statement, applies to them using a 4-point scale (0 = "not at all" to 3 = "very much"). A mean rating of insecure attachment can be calculated per participant, with higher scores reflecting greater insecure attachment.

Schizophrenia Proneness Instrument, Adult version (SPI-A; Schultze-Lutter et al., 2007)

A semi-structured interview used to detect and assess basic symptoms. Basic symptoms are clustered in two partially overlapping subsets relating to the COPER (10 items) and COGDIS (9 items) criteria. Questions are rated for symptom presence within the past 3 months on a 7-point scale (0 = "absent" to 6 = "extreme"). Symptoms may also be rated as 7 ("has always been present in same severity"), 8 ("definitely met, but severity unknown") or 9 ("symptom definition questionably met"). Distress is rated on a scale from 0 to 100 for each basic symptom endorsed. Symptom severity can be calculated per participant by

summing the scores for each basic symptom, with higher scores indicating greater symptom severity. For this calculation, scores of 7 and 9 are re-scored to 0 and scores of 8 are re-scored to 1. A mean distress rating can also be calculated per participant, with higher scores indicating greater distress.

Significant Others Scale (SOS; Power et al., 1988)

A self-report scale used to measure actual and ideal levels of social support provided by significant others. Significant others include partner (if applicable), a close relative and a close friend. For each significant other, participants rate the actual and ideal frequency of social support, on a 7-point scale (1 = "never" to 7 = "always"), for 3 emotional support items and 2 practical support items. A mean rating of actual and/or ideal social support can be calculated per participant, with higher scores reflecting greater social support.

Structured Clinical Interview for DSM-IV (SCID; First et al., 2002)

A semi-structured interview guide for making the major DSM-IV Axis I diagnoses. Diagnostic modules include Module A: mood episodes, Module B: psychotic symptoms, Module C: psychotic disorders and Module D: mood disorders. There are four possible ratings for each symptom: 1 = "absent", 2 = "subthreshold", 3 = "threshold" and ? = "inadequate information". Other criteria, such as those referring to diagnostic exclusion rules (e.g. "not better accounted for by bereavement") as well as algorithmic statements (e.g. "AT LEAST THREE 'B' SXS ARE CODED '3'") have three possible ratings: 1 = "false", 3 = "true" and ? = "inadequate information". Most disorders are assessed for both current and lifetime time frames. If diagnostic criteria are met for a disorder, age at onset and/or total number of episodes can also be explored.

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