Cognitive Impairments in Individuals at Clinical High-Risk for Psychosis: Relationships to Clinical Symptoms and Functioning and Prediction of Functional Outcome

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Abstract

Introduction: Traditionally, research in the clinical-high risk (CHR) for psychosis population has focused on a dichotomous measure of transition to psychosis. In light of declining transition rates, it is becoming increasingly important to focus on continuous measures of outcome such as functional status. Moreover, studies have almost exclusively utilised clinically presenting/help-seeking samples, limiting the generalisability of findings. Utilising a sample of CHR participants primarily recruited from the general population, this study aimed to investigate the relationship between cognitive performance, clinical symptoms and functioning at baseline; and baseline predictors of functional outcome at 6- and 12-months follow-up.

Methods: Data was available for 129 CHR individuals at baseline, 86 CHR individuals at 6-month follow-up and 69 CHR individuals at 12-month follow-up. 46 CHR-negative (CHR-N) participants (n = 40 at follow-up) who did not meet CHR criteria and 55 healthy controls (HCs) were also included. All participants were assessed on clinical, functional and cognitive variables at baseline. Functional outcome was assessed using the global assessment of functioning (GAF) score at follow-up.

Results: Emotion recognition response time (RT), either alone or in combination with other cognitive variables, was associated with clinical symptoms and functioning at baseline. Over half of CHR individuals were classified as having a poor functional outcome (PFO) at 6- and 12-months with functioning remaining relatively stable over time. PFO at 6-month follow-up was predicted by impairments in attention and processing speed, working memory, global functioning and role functioning at baseline. PFO at 12-month follow-up was predicted by reduced attention accuracy and poor global functioning at baseline. The areas under the curve for the 6- and 12-month prediction models were 0.911 and 0.818, respectively, demonstrating high discriminative abilities.

Discussion: These findings emphasise the importance of focusing on a broader outcome of interest in individuals at CHR for psychosis, rather than the arbitrary threshold of psychosis transition. At baseline, neurocognitive and social cognitive performance were predictive of clinical symptoms and functioning whilst reduced neurocognitive

performance and functional impairments at baseline predicted PFO at follow-up. These findings highlight the importance of such predictive factors for detecting false positives as well as the potential benefits of interventions incorporating vocational and educational rehabilitation and cognitive remediation. Furthermore, given that the majority of the CHR sample were recruited from the general population, clinical early detection teams should extend their services into the community in order to improve access to such interventions.

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Abbreviations

APS	Attenuated Psychotic Symptoms
ARMS	At-Risk Mental State
BACS	Brief Assessment of Cognition in Schizophrenia
BS	Basic Symptoms
CAARMS	Comprehensive Assessment of At-Risk Mental States
CHR	Clinical High-Risk
CNB	Penn Computerized Neurocognitive Battery
COGDIS	Cognitive Disturbances scale
COPER	Cognitive-Perceptive Basic Symptoms scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
ER40	Penn Emotion Recognition Task
FEP	First Episode Psychosis
GAF	Global Assessment of Functioning
GF	Global Functioning
ICD	International Statistical Classification of Diseases
LNB2	Penn Letter-N-Back Test
MINI	Mini-International Neuropsychiatric Interview
PCA	Perceptual-Cognitive Anomalies
PCPT	Penn Continuous Performance Test
PQ	Prodromal Questionnaire
SPI-A	Schizophrenia Proneness Instrument, Adult version
UHR	Ultra-High Risk

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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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1.0 Introduction

1.1 Schizophrenia - definition and epidemiology.

Schizophrenia, the most severe manifestation of psychosis, is a debilitating mental illness characterised by a loss of contact with reality and disturbances in thinking, speech, perception, emotion and behaviour. Worldwide, it has been ranked as the severest disorder, in terms of disability, out of 220 mental and physical health disorders (Salomon et al., 2012). Indeed, individuals with schizophrenia tend to die 20 years earlier, on average, than the general population partly due to an increased rate of suicide - an approximate lifetime risk of 5% (Hor & Taylor, 2010) and under-diagnosis of physical health conditions (Laursen, Nordentoft, & Mortensen, 2014). Overall, the total societal cost of schizophrenia in England is estimated at £11.8 billion per year (Andrew, Knapp, McCrone, Parsonage, & Trachtenberg, 2012).

With a lifetime prevalence of approximately 1% (Sisti & Calkins, 2016), schizophrenia typically strikes between the ages of 16 and 35 with males displaying an earlier onset than females by about 5 years (Linden, 2011). As well as reporting a median incidence rate of 15.2 per 100,000 persons per year, systematic reviews of studies published between 1965 and 2002 (McGrath et al., 2004b; McGrath, Saha, Chant, & Welham, 2008) concluded that individuals were more likely to develop schizophrenia if they were male versus female (in the order of 1.4:1); lived in urban sites rather than mixed urban/rural sites; and were migrants as opposed to native-born individuals.

1.2 The history of schizophrenia.

Although the term “schizophrenia” was coined relatively recently, descriptions of associated symptoms have been documented since antiquity; grouped under various disorders including phrenesis, melancholia and mania (Jablensky, 2010). Case descriptions dating back to the mid-19th century show that European psychiatrists had begun elucidating disorders of unknown cause, typically affecting the young and often resulting in a dramatic deterioration of intellect with little hope of recovery or remission. In France, Morel (1860) used the term “dementia praecox*”* to refer to such disorders whereas, in Scotland, Clouston (1904) proposed the idea of an “adolescent insanity”. In Germany, Kahlbaum (1874) and

his protégé Hecker (1871) added the diagnostic categories "catatonia" and "hebephrenia", respectively. Whereas catatonia described patients immobilised by psychological factors, hebephrenia referred to patients with erratic, bizarre and regressed behaviours.

Noting the commonalities between catatonia and hebephrenia, German physician Emil Kraepelin (1899, 1919) added the term "paranoia" to describe highly suspicious patients and grouped these three mental disorders under the heading coined by Morel 40 years before - dementia praecox. He distinguished dementia praecox from "manic-depressive insanity" (now bipolar disorder) which was characterised by an episodic course, absence of mental deterioration and a more positive outcome – a distinction referred to as "The Kraepelin Dichotomy" (Lake, 2012).

However, Swiss psychiatrist Eugen Bleuler (1911) disagreed with Kraepelin's dementia praecox. On observation of his patients, he noticed that the disorder was not confined to adolescence and early adulthood and did not inevitably result in cognitive deterioration – in fact, remission could be achieved. He is credited with introducing the term schizophrenia, derived from the Greek words "schizo" (split) and "phren" (mind), to describe the fragmentation of mental functions (Schlosser, Garrett, & Vinogradov, 2014). While Kraepelin viewed schizophrenia as a single disease, Bleuler believed it comprised a group of closely related illnesses (Baldwin, 2016). He broadened Kraepelin's narrow definition by dividing the symptoms of schizophrenia into two distinct categories: fundamental and accessory (Buller & Sapin, 2016; Nickl-Jockschat & Abel, 2016). The fundamental symptoms, referred to as Bleuler's 4 As, were purported to be pathognomonic in that they were unique to schizophrenia, occurring in all patients. These are loosening of association, affective incongruence, ambivalence and autism – now regarded as negative symptoms. On the other hand, accessory symptoms such as hallucinations and delusions – now classified as positive symptoms - could occur in a variety of different disorders and therefore, were not essential for a schizophrenia diagnosis.

This emphasis on negative rather than positive symptoms later reversed. Jaspers (1946) believed that the core defect in schizophrenia was impairment of empathic communication and that "un-understandability" of individual experience was pathognomonic. Influenced by Jaspers, Kurt Schneider (1959) defined 11 first-rank symptoms which he considered to be diagnostic of schizophrenia. These comprise audible thoughts; voices arguing; voices

commenting on one's action; influence playing on the body, somatic passivity; thought withdrawal; thoughts ascribed to others (thought insertion); diffusion or broadcasting of thoughts; "made" feelings; "made" impulses (drives); and "made" volitional acts (Mellor, 1970). In contrast to the Bleulerian approach, Schneider's first-rank symptoms are closely related to positive symptoms.

Kraepelinian chronicity, Bleulerian negative symptoms and Schneiderian positive symptoms have been incorporated into the diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM; from DSM-I to DSM-IV) and the *International Statistical Classification of Diseases* (ICD; from ICD-6 to ICD-10), although the specific emphasis placed on these three aspects has changed over time (Altamura, Fagiolini, Galderisi, Rocca, & Rossi, 2014). In the ICD-10 (World Health Organisation [WHO], 1992), DSM-III (American Psychiatric Association [APA], 1980) and DSM-IV (APA, 1994), the presence of one first-rank symptom was deemed symptomatically sufficient for a schizophrenia diagnosis (Nordgaard, Arnfred, Handest, & Parnas, 2008). Since then, doubts have been raised regarding the predictive utility of first-rank symptoms. Specifically, Soares-Weiser et al. (2015) reviewed 20 studies and reported that first-rank symptoms differentiated schizophrenia from all other diagnoses with a sensitivity of 57% and a specificity of 81.4%. Therefore, in the current DSM-5 (APA, 2013) and available draft of the ICD-11 (Luciano, 2015), at least two first-rank symptoms and at least one psychotic symptom is required for a schizophrenia diagnosis (Tandon et al., 2013).

1.3 Positive and negative symptoms of schizophrenia.

The idea of referring to schizophrenia symptoms as either positive or negative originated in the 1800s when neurologist Hughlings Jackson (1931) used the terms to describe deficits experienced by his patients. He believed that positive symptoms reflected an excess or distortion of normal function whereas negative symptoms represented a diminution or loss of normal function (Andreasen, 2010).

The concept of positive and negative symptoms was operationalised in the type I/type II model of schizophrenia proposed by Crow (1980). Type I schizophrenia is characterised by positive symptoms (including hallucinations, delusions and thought disorders); arises from dopaminergic overactivity; responds well to antipsychotic medication; and has favourable

long-term prognosis. Conversely, Type II schizophrenia is characterised by negative symptoms (social withdrawal, lack of affect and reduced motivation); arises from structural brain abnormalities; responds poorly to antipsychotic medication; and has poor long-term outcome (Beck, Rector, Stolar, & Grant, 2009; Jablensky, 2010). Crow (1985) later amended the original model by replacing the diametric "types" with a positive and a negative dimension, acknowledging that both symptoms can co-occur in the same individual.

More recently, the authors of the DSM-5, have considered the addition of a further classification category – cognitive symptoms – which includes difficultly in sustaining attention; low psychomotor speed; poor abstract thinking; and poor problem solving. However, this has been rejected due to a lack of evidence and so, cognitive symptoms remain part of the negative symptoms in the DSM-5 (Ebenezer, 2015).

1.4 The course of schizophrenia.

Schizophrenia develops through four sequential phases: the premorbid, prodromal, psychotic and stable phases (Ray, 2017; Tandon, Nasrallah, & Keshavan, 2009). Typically, negative symptoms are predominant in the nonpsychotic period whereas positive symptoms manifest during psychotic episodes (Kandel et al., 2000). The initial premorbid phase is characterised by subtle and nonspecific problems with cognition, motor and social functioning. Next is the prodromal phase, heralding the onset of attenuated (subthreshold) psychotic symptoms (APS) or basic symptoms (BS) with an associated decline in functioning. The length of this phase varies from a mean of 2 years (McGorry & Edwards, 1997) up to 5 years (Häfner, 2003; Häfner et al., 1992). Psychotic symptoms become apparent in the following psychotic phase which marks the formal onset of schizophrenia. In this phase, patients experience repeated episodes of psychosis separated by intermittent blocks of remission. Decline in functioning is generally greatest during the first 5 years after the first psychotic episode. The final, stable phase is characterised by a reduction of psychotic symptoms and an increase in both negative symptoms and stable cognitive/social deficits. Notably, varying degrees of remission, sometimes amounting to permanent recovery, can be achieved at each stage (Torgalsbøen & Rund, 2002).

1.5 Genetic and environmental risk factors.

The two-hit hypothesis of schizophrenia suggests that early developmental risk factors (i.e. genetic predisposition, environmental stressor) function as a “first hit”, rendering an individual susceptible to a “second hit” later in development (Fatemi & Folsom, 2009). This second hit (i.e. an environmental factor) is necessary to trigger the onset of the disorder.

1.5.1 Genetics.

1.5.1.1 Pre-molecular genetics.

Twin, family and adoption studies have demonstrated that having a close biological relative with schizophrenia is the strongest risk factor for developing a psychotic disorder (Henriksen, Nordgaard, & Jansson, 2017). Monozygotic twins, who share 100% of their genes, have an increased propensity to develop schizophrenia compared to dizygotic twins, who share 50% of their genes. Recently, utilising data from the Danish Twin Register, Hilker et al. (2018) estimated the heritability of schizophrenia to be 79%. Pooling European twin studies from 1963-1987, Gottesman (1991) found a concordance rate of 48% for monozygotic twins and 17% for dizygotic twins in line with later European and Japanese twin studies from 1992-1999 (Cardno & Gottesman 2000). Gottesman (1991) also conducted a meta-analysis of family studies, noting that risk for third-degree relatives (2%) was only slightly greater than the general population risk; second-degree relatives had a risk of around 5%; while first-degree relatives had a risk close to 10%. In order to separate genetic and rearing environment effects, adoption studies are critical. In one of the first large adoption studies, Heston (1966) identified 47 adopted children whose biological mother had a diagnosis of schizophrenia and found that 10.6% later developed the disorder themselves in contrast to 0% of 50 control adoptees.

1.5.1.2 Molecular genetics.

The genetic architecture of schizophrenia is highly polygenic, with specific contributions from common genetic variants of small effect and rare genetic variants of larger effect. Of note, many of the discovered associations are not specific to schizophrenia; in contrast, they indicate a genetic vulnerability to several psychiatric disorders including major

depressive disorder (MDD), attention deficit hyperactivity disorder (ADHD) and bipolar disorder (Anttila et al., 2018).

Genome-wide association studies (GWASs) of single nucleotide polymorphisms (SNPs) have provided convincing evidence for common genetic variants with small odds ratios (ORs), generally < 1.2 (Rees, O'Donovan, & Owen, 2015). Given the modest effect size, GWASs screen hundreds of thousands to millions of common genetic variants in order to provide adequate statistical power. One seminal GWAS (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) of > 35,000 cases identified 108 independent loci associated with schizophrenia, 83 of which were novel findings. Overall, SNPs in the extended major histocompatibility complex (MHC) locus on chromosome 6 – an area known to play a central role in immune function - were most significantly associated with schizophrenia. Consistent with pathophysiological hypotheses, loci containing the dopamine D2 receptor (*DRD2* – the ultimate schizophrenia candidate gene) and several glutamate receptors were also associated with the disorder.

Collectively, common genetic variants are estimated to explain between a quarter and a half of the variance in genetic liability – leaving a large proportion unaccounted for (International Schizophrenia Consortium, 2009). Studies of copy number variation (CNV), single nucleotide variants (SNVs) and small insertion and deletions (indels) additionally link rare genetic variants, with large ORs of ~2-20, to the aetiology of schizophrenia (Rees et al., 2015).

Rare, *de novo* or inherited CNVs are defined as deletions and duplications of the genomic sequence that typically range in length from 1 kilobase (kb) to several megabase (Mb) pairs (Kirov, 2015). Large (> 100 kb), rare (< 1% in the population) CNVs are increased 1.15-fold in individuals with schizophrenia compared to controls (International Schizophrenia Consortium, 2008). Specifically, robust associations have been uncovered between schizophrenia and the following large, rare CNVs: deletions at 1q21.1, Neurexin 1 (NRXN1), 3q29, 15q13.3 and 22q11.2 as well as duplications at 16p13.1 and 16p11.2 (Henriksen et al., 2017). They affect multiple genes (apart from NRXN1) which are important for cell signalling, brain development and glutamate transmission.

Whole-exome sequencing studies have further implicated rare genetic variants in schizophrenia. This technique identifies DNA variants within the 1% protein-coding regions or genes (exons) of the genome (exome), permitting evaluation of gene mutations at single-base resolution. Purcell et al. (2014) explored rare SNVs and indels using exome sequencing and identified a polygenic burden, arising from rare (< 1 in 10,000) mutations distributed across many genes from a selection of 2,546 genes previously linked to schizophrenia by GWAS, CNV and *de novo* SNV studies. Specifically, the total count for mutations was 1527 in schizophrenia subjects versus 1383 in controls.

However, the absence of 100% concordance between monozygotic twins and the failure of GWAS to identify major genetic candidates implies a potential aetiologic role of a variety of environmental factors in the development of schizophrenia.

1.5.2 Prenatal/perinatal environmental risk factors.

1.5.2.1 Obstetric complications.

Obstetric complications, particularly those associated with hypoxia, contribute to schizophrenia susceptibility, albeit with a modest effect (ORs ~2; Geddes & Lawrie, 1995). In a meta-analysis utilising population-based data, M. Cannon, Jones, and Murray (2002) distinguished three groups of complications significantly associated with schizophrenia: (1) pregnancy complications (bleeding, diabetes, preeclampsia and rhesus incompatibility); (2) abnormal fetal growth and development (low birth weight, congenital malformations and small head circumference); and (3) delivery complications (asphyxia, uterine atony and emergency caesarean section). A previous individual patient meta-analysis (Geddes et al., 1999), involving 12 studies on 700 schizophrenia participants and 835 controls, specifically identified premature rupture of membranes, gestational age < 37 weeks and use of resuscitation or an incubator as significant risk factors for developing schizophrenia. Additional associations between schizophrenia and birth weight < 2500 grams or use of forceps during delivery were of borderline significance. Such obstetric complications even confer risk to individuals in the prodromal phase of schizophrenia. According to Kotlicka-Antczak et al. (2017), a history of at least one obstetric complication is associated with an increased risk of transition to the full-blown disorder (OR of 6.57).

1.5.2.2 Infections.

Prenatal infections such as influenza, rubella, *Toxoplasma gondii* and type 2 herpes virus are considered plausible risk factors for schizophrenia. P. R. Nielsen, Meyer, and Mortensen (2016) recently reported that any maternal hospitalisation for infection during pregnancy was associated with a 1.32-fold increased risk of schizophrenia in offspring. This effect remained significant after adjustment for parental history of psychiatric admission and degree of urbanicity although relative risk was attenuated to 1.16-fold. Studies using prenatal serum samples, however, have documented that prenatal exposure to rubella and first trimester exposure to influenza confers a 10-20-fold and 7-fold increase in risk of later schizophrenia, respectively (Brown, 2006). One prevalent hypothesis suggests that stimulation of the cytokine response could be responsible for mediating the relationship between infection and schizophrenia. Certainly, maternal levels of tumour necrosis factor-alpha (TNF-α) – a major proinflammatory cytokine - have been associated with psychotic disorders among offspring (Buka et al., 2001).

1.5.2.3 Nutrition.

The strongest evidence relating maternal malnutrition during pregnancy to schizophrenia in offspring derives from analysis of data obtained from two major famines. Those conceived to the most malnourished mothers during the Dutch Hunger Winter of 1944-45 (Lumey, Stein, & Susser, 2011) and the Chinese Famine from 1959-61 (St Clair et al., 2005) showed a twofold increased risk of schizophrenia. Several micronutrient deficiencies, including folate, essential fatty acids, retinoids, iron and vitamin D, have been hypothesised to mediate this association. In particular, levels of vitamin D appear to inversely correlate with negative and depression symptoms in those with psychosis (Nerhus et al., 2016) while vitamin D supplementation (≥ 2000 international units/day) during the first year of life has been shown to reduce the risk of developing schizophrenia in Finish male infants (McGrath et al., 2004a).

1.5.2.4. Season of birth.

Schizophrenia often affects persons born during the late winter and early spring – a phenomenon known as the seasonality effect (Carlson, 2013). Possible explanations include maternal exposure to winter-borne viruses and low prenatal vitamin D. In a meta-analysis of eight studies from the northern hemisphere, a pooled OR of 1.07 and a population attributable risk of 3.3% for winter/spring births was detected (Davies, Welham, Chant, Torrey, & McGrath, 2003). However, while the seasonality effect is robust in the northern hemisphere, a meta-analysis performed on data from 11 southern hemisphere studies (in Australia, South Africa and the Reunion Islands) did not support an effect (McGrath & Welham, 1999), corroborating findings from a plethora of studies.

1.5.2.5 Place of birth.

The relative risk of developing schizophrenia when born in an urban vs. rural environment is about 2.4 according to major population-based studies in the Netherlands (Marcelis, Navarro-Mateu, Murray, Selten, & Van Os, 1998) and Denmark (Mortensen et al., 1999). Since urban birth was relatively frequent in both studies, a substantial population attributable risk of approximately 30% was calculated for this variable. Factors attributable to urbanicity, such as air pollution, toxins, vitamin D deficiency and stress, are assumed to underlie this effect (Zwicker, Denovan-Wright, & Uher, 2018). However, most people who are born in urban areas are also brought up there, making it difficult to disentangle prenatal and perinatal effects from those operating later in childhood. In fact, Pedersen and Mortensen (2001) stated that a dose-response relationship, between years spent in an urban environment during upbringing and later emergence of schizophrenia, accounts for 15% of relevant cases.

1.5.3 Later environmental risk factors.

1.5.3.1 Substance abuse.

Risk factors associated with psychosis later in development are largely substance use-related. On investigation of Danish national registers, S. M. Nielsen, Toftdahl, Nordentoft, and Hjorthøj (2017) found that abuse of cannabis, alcohol, hallucinogens, sedatives and other substances significantly increased the risk of developing schizophrenia. Cannabis and alcohol presented as the strongest factors, increasing risk by 5 and 3 times, respectively.

Interestingly, the risk remained significant even 10–15 years following a diagnosis of substance abuse. The relationship between premorbid cannabis use and schizophrenia is evidenced by the positive dose-response relationship between cannabis use and psychosis (Marconi, Di Forti, Lewis, Murray, & Vassos, 2016) and the earlier onset of psychosis, by up to 2.7 years, in those with a history of cannabis use compared to those with no history (Donoghue et al., 2014). Of course, not all individuals using cannabis develop schizophrenia, leading to the proposition that cannabis use is only a risk factor in a subgroup of genetically vulnerable subjects, specifically through interference with the neurodevelopmental role of endocannabinoid (Mallet, Ramoz, Le Strat, Gorwood, & Dubertret, 2017).

1.5.3.2 Childhood adversity.

Childhood adversities, including neglect, abuse (emotional, psychological, physical and sexual), peer bullying, parental loss or divorce and poverty have been strongly implicated in the development of psychotic disorders (Morgan & Gayer-Anderson, 2016). A meta-analysis of 36 studies reported that those with psychosis were 2.72 times more likely to have been exposed to childhood adversity than controls, with an estimated population attributable risk of 33% (Varese et al., 2012). Remarkably, Kelleher et al. (2013b) found that cessation of childhood trauma (physical assault and bullying) predicted subsequent cessation of psychotic experiences in a cohort of 1,112 adolescents.

Regarding symptomatology, childhood adversities may influence the severity of delusions and hallucinations in a dose-response relationship (Muenzenmaier et al., 2015). Indeed, childhood sexual abuse has been linked to auditory hallucinations in females with first-episode schizophrenia (FES; Misiak, Moustafa, Kiejna, & Frydecka, 2016). Various mechanisms have been proposed to mediate the relationship between childhood adversity and psychosis including hypothalamic-pituitary-adrenal (HPA) axis dysregulation, reduced levels of brain-derived neurotrophic factor (BDNF), increased levels of inflammatory markers and metabolic dysregulation (Misiak et al., 2017).

1.5.3.3 Migration.

The risk of schizophrenia for first- and second-generation migrants is between 2 and 4.5 times that of the majority ethnic group under investigation, although the exact risk varies by ethnicity and setting (Tortelli et al., 2015). For example, in the United Kingdom, African-Caribbean migrants are at greatest risk, with rates 9 times higher than White British people (Fearon et al., 2006) while in the Netherlands, more recent North African migrants are at greatest risk, with rates 7 times higher for Moroccan migrants compared to the native Dutch population (Veling et al., 2006).

Ødegaard's (1932) landmark study found a twofold increase in first admission rates for schizophrenia amongst Norwegian migrants who moved to the United States compared with native-born Americans and Norwegians. He hypothesised that those predisposed to schizophrenia were more likely to migrate – a theory known as "selective migration". However, this hypothesis garnered little support as it could not account for the increased risk for schizophrenia found among second-generation migrants. Nowadays, possible explanations centre on postmigration factors including age, sex, socioeconomic status, discrimination, social isolation, trauma and abuse (Hollander et al., 2016).

1.6 Pathophysiological hypotheses.

The contributions of neurochemical alterations and brain abnormalities to the pathophysiology of schizophrenia have been studied intensively.

1.6.1 The dopamine hypothesis.

Dopamine is a key neurotransmitter modulating essential functions of the central nervous system (CNS) including voluntary movement, reward and higher cognitive functions such as memory and goal maintenance (Ledonne & Mercuri, 2017). There are two major classes of metabotropic dopamine receptors: D1-like receptors (D1 and D5) which are primarily excitatory and D2-like receptors (D2, D3, D4) which are primarily inhibitory (Nikolova, Bodgan, & Hariri, 2013). Furthermore, there are three major dopaminergic pathways in the CNS: the nigrostriatal pathway (substantia nigra to striatum); the mesolimbic pathway (ventral tegmental area (VTA) to nucleus accumbens); and the mesocortical pathway (VTA to prefrontal cortex (PFC)).

Formulated by van Rossum (1966), the “original dopamine hypothesis” postulated that hyperactive dopamine D2 receptor neurotransmission contributes to the symptoms of schizophrenia. This premise was based on the observation that first-generation antipsychotics, such as chlorpromazine and haloperidol, block D2 receptors and dopamine agonists, such as amphetamine and methylphenidate, boast psychotomimetic properties (Abi-Dargham & Grace, 2010).

However, this initial hypothesis is problematic for two main reasons: (1) although first-generation antipsychotics effectively treat positive symptoms, they may exacerbate negative and cognitive symptoms and (2) the second-generation antipsychotic clozapine, despite having one of the lowest levels of D2 receptor occupancy of all antipsychotic drugs, is the most efficacious treatment for chronic schizophrenia (Lawrence, First, & Lieberman, 2015; Li, Snyder, & Vanover, 2016).

Impairment in higher cognitive functions, such as working memory, is a severe, enduring and core symptom of schizophrenia (Laruelle & Abi-Dargham, 2003). Functional brain imaging studies have suggested that these symptoms may be associated with a dysfunction of the PFC where the dopamine D1 receptor is abundantly expressed (Tsang et al., 2015). Indeed, Sawaguchi and Goldman-Rakic (1994) induced deficits in a working memory task by infusing D1 receptor antagonists into the PFC of nonhuman primates. Similarly, Müller, von Cramon, and Pollmann (1998) administered human participants with either a mixed D1/D2 receptor agonist or a selective D2 agonist and noted that the former facilitated working memory whereas the latter had no effect.

The “revised dopamine hypothesis” attempts to account for negative and cognitive symptoms as well as positive symptoms. It posits that (1) hyperactivity of dopamine D2 receptor neurotransmission in the mesolimbic pathway results in the positive symptoms of schizophrenia and (2) hypofunctionality of dopamine D1 receptor neurotransmission in the mesocortical pathway is responsible for the negative and cognitive symptoms of schizophrenia (Brisch et al., 2014; Desbonnet, 2016; Patel, Cherian, Gohil, & Atkinson, 2014). Moreover, disrupted feedback loops have been implicated in the current hypothesis (Weinberger, 1987). Normally, activity in the mesocortical pathway inhibits the

mesolimbic pathway whereas in schizophrenia, there is reduced activity in the mesocortical pathway which leads to disinhibition and overactivity in the mesolimbic pathway.

1.6.2 The glutamate hypothesis.

Glutamate is the main excitatory neurotransmitter in the CNS (Fatemi & Folsom, 2016). Mediated through activation of either ionotropic or metabotropic receptors, glutamatergic neural transmission plays a central role in neuronal plasticity, neurotoxicity, development, learning and memory (Gasbarri & Pompili, 2014). Three major types of ionotropic glutamate receptors can be distinguished: NMDA (N-methyl-D-aspartate), AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate) and kainic acid. The glutamate hypothesis proposes that hypofunction of glutamate signalling, via NMDA receptors, particularly in the frontal cortex, is responsible for the development of the positive, negative and cognitive symptoms of schizophrenia (Coyle, 2012; Kantrowitz & Javitt, 2010).

NMDA receptor antagonists, such as phencyclidine (PCP) and ketamine, produce psychotomimetic effects in healthy human subjects and experimental animals (Krystal & Moghaddam, 2010; Perez & Lodge, 2014) while worsening psychotic symptoms in those with schizophrenia (Malhotra et al., 1997). Additionally, administration of ketamine at subanaesthetic doses correlates with impaired performance on tasks measuring executive functions, spatial and verbal working memory and verbal declarative memory (Krystal et al., 2000; Rowland et al., 2005). Garnering further support for this hypothesis, NMDA receptor deficits have been observed in post-mortem brain tissue derived from individuals with schizophrenia (Stone et al., 2008) and in the brain tissue of those living with the disorder using single-photon emission tomography (SPET) imaging (Pilowsky et al., 2006). Another imaging technique, proton magnetic resonance imaging (^{1}H-MRS), has evidenced decreased *in vivo* glutamate levels in the medial frontal brain region of those with schizophrenia when compared to healthy individuals (Marsman et al., 2013).

1.6.3 The GABA hypothesis.

In comparison to glutamate, gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the CNS (Fatemi & Folsom, 2016). Acting on either ionotropic

($GABA_A$) or metabotropic ($GABA_B$) receptors, GABA is implicated in cortical maturation, synaptic plasticity, and cognition (Ebenezer, 2015). An abundance of evidence indicates that dysfunctional GABAergic inhibition and the consequent imbalance between excitation and inhibition in the cerebral cortex is linked to schizophrenia (Gonzalez-Burgos & Lewis, 2012; Lewis, Curley, Glausier, & Volk, 2012; Nakazawa et al., 2012).

Postmortem brain studies of those with schizophrenia have consistently shown that glutamic acid decarboxylase 67 (GAD67), the enzyme that converts glutamate to GABA, is reduced in a subpopulation of GABAergic neurons (Guidotti et al., 2000; Hashimoto et al., 2003, 2008; Volk, Austin, Pierri, Sampson, & Lewis, 2000). In particular, GAD67 is reduced in about 50% of parvalbumin (PV)-expressing GABA interneurons in layer 2/3 of the PFC (Hashimoto et al., 2003). Reduced concentrations of the transporter protein GABA-transporter-1 (GAT-1), which is responsible for GABA reuptake in the presynaptic neuron (Volk et al., 2002; Woo, Whitehead, Melchitzky, & Lewis, 1998), and increased expression of the α2 subunits of the $GABA_A$ receptor, which mediates most of GABA's physiological activities, have additionally been observed in the brain tissue of schizophrenia patients (Sieghart et al., 1999).

Ultimately, GABA interneurons play a pivotal role in the brain's rhythm-generating networks, where synchrony of neural oscillations is essential for memory, perception and consciousness (Uhlhaas & Singer, 2010). GABA abnormalities may instigate alterations in neural synchrony, aberrant neural oscillations in the gamma frequency band and working memory impairments, resembling those observed in schizophrenia (Yang & Tsai, 2017).

1.6.4 Dopamine, glutamate and GABA: A revised hypothesis.

Recent evidence increasingly supports a primarily glutamatergic and GABAergic dysfunction in schizophrenia, with dopaminergic imbalance as a secondary consequence.

Incoming activity from glutamate neurons in the PFC is modulated by GABAergic interneurons which in turn, innervate glutamate pyramidal neurons that project to the VTA (Linden, 2011). In healthy individuals, excitation and inhibition via glutamate and GABA, respectively, are sufficiently balanced in the system. In schizophrenia, glutamate released in the PFC acts on hypofunctional NMDA receptors on PV-expressing GABA

interneurons. This results in a reduced release of GABA on the dendrites of glutamate pyramidal neurons in the cortex, leading to downstream disinhibition of glutamate release in the VTA. The increased glutamate released in the VTA stimulates the dopaminergic mesolimbic pathway, enhancing dopamine production (Ebenezer, 2015).

Belforte et al. (2010) performed a restricted deletion of the NMDA receptor in corticolimbic interneurons in early postnatal and post-adolescent mice. As well as producing schizophrenia-related symptoms, this resulted in reduced expression of GAD67 and parvalbumin; disinhibition of cortical excitatory neurons; and reduced neuronal synchrony in early postnatal but not post-adolescent mice. Therefore, along with secondary dopaminergic alterations, NMDA hypofunction early in life may predispose individuals to develop psychotic symptoms in adolescence.

1.6.5 The neurodevelopmental hypothesis.

The neurodevelopmental hypothesis of schizophrenia states that abnormal brain development during the prenatal and perinatal periods, resulting from genetic and environmental factors, underlies the later emergence of psychosis during adulthood (McGrath, Féron, Burne, Mackay-Sim, & Eyles, 2003).

Consistent with this view, a multitude of brain abnormalities have been documented in the prodromal and early stages of schizophrenia which are similar to, but milder than, those seen in the late stages of the disorder (Chung & Cannon, 2015). Structural magnetic resonance imaging (MRI) studies have reported evidence of grey matter volume loss and cortical thinning across thalamocortical circuitry; gyrification abnormalities; and enlargement of the lateral ventricles throughout the prodromal, first-episode and chronic course of schizophrenia (Dietsche, Kircher, & Falkenberg, 2017; Gao et al., 2018; Sasabayashi et al., 2017). Interestingly, formal thought disorders and hallucinations are correlated with grey matter volume loss in the superior temporal lobe while functioning correlates with volume loss in the left PFC (Onay, Yapıcı Eser, Ulaşoğlu Yıldız, Aslan, & Talı, 2017).

Anatomical and functional connectivity alterations have also been demonstrated across the various stages of schizophrenia. Anatomically, there is disconnectivity and lack of alignment in white matter tracts in frontal and temporoparietal brain regions whereas functionally, there is aberrant activity of the default mode network (DMN), numerous cognitive control networks and several independent brain regions (Nelson, Bassett, Camchong, Bullmore, & Lim, 2017). White matter pathology has been implicated in these connectivity alterations. For example, reduced oligodendrocytes - which synthesise myelin - were discovered in diffusion tensor imaging (DTI) and post-mortem studies. In addition, recent evidence links fronto-temporal abnormalities to specific symptoms of schizophrenia; predominantly auditory verbal hallucinations (Oestreich, McCarthy-Jones, Whitford, & Bank, 2016).

1.7 Cognitive impairment in schizophrenia.

Cognitive deficits are a hallmark feature of schizophrenia with approximately 80% of diagnosed individuals experiencing either neurocognitive or social cognitive deficits or both. (Paquin, Wilson, Cellard, Lecomte, & Potvin, 2014). Neurocognition is the ability to effectively perceive, attend to and remember information whereas social cognition focuses on how people process, store and apply information about other people and social situations. Herein, the term "cognition" will be used to refer to both neurocognition and social cognition.

In general, individuals with schizophrenia perform, on average, 1 standard deviation below HCs on a range of cognitive tasks (Dickinson, Ramsey, & Gold, 2007). The neurocognitive domains typically affected include verbal memory, working memory, attention and processing speed and executive functions whereas emotion recognition (the ability to perceive and recognise facial emotion expressions), theory of mind (the ability to infer others' beliefs and emotions), social perception and knowledge (the ability to detect and comprehend social cues with respect to social context) and attributional style (attribution of causes of events to the self, others, or the environment) are the social cognitive domains most affected (Paquin, Lecomte, & Potvin, 2017). Whether cognitive impairment in schizophrenia constitutes a specific deficit to domains or a generalised deficit across

domains is a debated issue, although it is likely that cognitive impairments in specific domains are superimposed on a more general cognitive deficit (Cassetta & Goghari, 2016).

Interest in the cognitive impairments of schizophrenia is growing, driven largely by findings suggesting that these impairments are better predictors of functional outcome than positive or negative symptoms (Green, 1996; Harvey et al., 1998). Specifically, cognitive deficits have been linked to worse functional outcomes such as poor self-care, decreased ability to live independently, poor social skills, inability to maintain successful employment and poor compliance with medication regimens (Lepage, Bodnar, & Bowie, 2014). Effect sizes for the associations between cognitive impairments and functional deficits are typically in the medium range for specific domains although larger effect sizes are possible for summary scores (Green, Kern, Braff, & Mintz, 2000).

A meta-analysis by Fett et al. (2011) found that social cognition explained 16% of the variance in community functioning while neurocognition explained only 6%. Community functioning was most strongly associated with theory of mind (r = 0.48) followed by social perception and knowledge (r = 0.41), verbal fluency (r = 0.32) and emotion perception and processing (r = 0.31). Also, Schmidt, Mueller, and Roder (2011) conducted a review of 15 studies and concluded that social cognition acts as a mediator between neurocognition and functional outcomes. Specifically, social knowledge (mean effect size of 0.28) and social perception (mean effect size of 0.21) produced the largest effect sizes for explaining this mediation effect.

1.8 The clinical high-risk state for psychosis.

Over the last few decades, the concept of a clinical high-risk (CHR) state for psychosis (also known as the "at-risk mental state" (ARMS), "prodromal" and "ultra-high risk" (UHR) state) has evolved to capture the prodromal phase of schizophrenia (Fusar-Poli et al., 2013). Alongside APS, the CHR state is characterised by a constellation of other clinical signs including negative symptoms, mood symptoms, cognitive deficits and functional decline (Tandon et al., 2009).

Studies of CHR individuals have been increasingly common, in part due to the potential benefits of early intervention and the opportunity to study the "near-psychotic" state

without the confounding effects of long-term medication use and chronicity. This is evidenced by the recent inclusion of "Attenuated Psychosis Syndrome" in the appendix (Section 3) of the DSM-5 as a condition for further study (Sisti & Calkins, 2016).

Two broad sets of CHR criteria currently prevail: the UHR and BS criteria. Whereas the UHR criteria detect psychosis risk in the late prodromal phase when functioning is somewhat compromised, the BS criteria detect early psychosis risk, ideally before functional impairments arise.

UHR criteria were developed and validated within the Personal Assessment and Crisis Evaluation (PACE) Clinic by Yung et al. (1996) in Melbourne, Australia to identify help-seeking individuals at imminent risk of psychosis, i.e., individuals at risk for developing a first-episode within the next 12 months. Inclusion requires the presence of one or more of the following: APS; brief limited intermittent psychotic symptoms (BLIPS); and trait vulnerability plus a marked decline in psychosocial functioning (Genetic Risk and Deterioration syndrome: GRD), with the former constituting the most common UHR group. Several studies have since validated the UHR criteria, finding that those who meet the criteria have a high risk of developing psychosis over 1–2.5 years, with rates in the range of 8% to 54% (Miller et al., 2002; Morrison et al., 2012). Specifically, Fusar-Poli et al. (2016) found that transition risk in the BLIPS subgroup was higher than in the APS subgroup while there was no prognostic difference between the GRD subgroup and individuals not at CHR for psychosis, raising concerns about the validity of the GRD subgroup.

Different measures have been created to assess UHR criteria: the Comprehensive Assessment of At-Risk Mental States (CAARMS); the Structured Interview for Prodromal Syndromes (SIPS) and the companion Scale of Prodromal Symptoms (SOPS); the Basel Screening Instrument for Psychosis (BSIP); the Early Recognition Inventory for the Retrospective Assessment of the Onset of Schizophrenia (ERIraos); and a self-rating prodromal screening questionnaire (Loewy, Bearden, Johnson, Raine, & Cannon, 2005). Developed by Yung et al. (2005) at the PACE clinic, the CAARMS is widely used in Australia, Asia and Europe whereas the SIPS/SOPS, developed by Miller et al. (2003), is commonly used in North America and Europe. The ERIroas, now largely used in German and Italian studies, was developed by Häfner et al. (1992) to assess schizophrenia onset

retrospectively and later, Riecher-Rössler et al. (2007) created the BSIP in the Early Detection of Psychosis Clinic in Basel.

In contrast, BS are defined as subtle, subclinical, self-experienced disturbances in drive, stress tolerance, affect, attention, memory, thinking, speech, perception and motor action (Schultze-Lutter & Theodoridou, 2017). These symptoms, often noticed years before the onset of psychosis, are thought to be the earliest perceivable signs of the neurobiological disturbance underlying the development of psychosis, hence the term "basic" (Huber & Gross, 1989). Unlike UHR criteria, BS are not necessarily observable by others; are independent of unusual thought content and reality testing; and individuals have full insight into the symptoms' psychopathological nature.

Initially, BS were assessed using the Bonn Scale for the Assessment of Basic Symptoms (BSABS; Huber & Gross, 1989). Shorter versions of the scale were later developed – the Schizophrenia Proneness Instrument, Adult version (SPI-A; Schultze-Lutter, Addington, Ruhrmann, & Klosterkötter, 2007) for adults and the Schizophrenia Proneness Instrument, Child and Youth version (SPI-CY; Schultze-Lutter, Marshall, & Koch, 2012) for children and adolescents. While the BSABS only allows a rating of presence, the SPI-A and the SPI-CY also allow a frequency-based severity rating based on the past 3 months. Out of the BS evaluated on the SPI-A and the SPI-CY, which are both characteristic and uncharacteristic of psychosis, there can be derived 2 scales to evaluate specifically the characteristic BS: the Cognitive Disturbances scale (COGDIS) and the Cognitive-Perceptive Basic Symptoms scale (COPER).

Specifically, the COGDIS subset of BS seems to indicate a more imminent risk of psychosis compared to the COPER subset, with 25.3% of participants meeting COGDIS criteria transitioning to psychosis at 1 year following baseline assessment compared to 14.4% of those meeting COPER criteria (Schultze-Lutter et al., 2015).

Informed by such findings, the European Psychiatric Association issued guidelines supporting the use of BS criteria, in particular COGDIS, along with APS and BLIPS UHR criteria, for early detection of psychosis.

1.9 Outcomes in the CHR group.

Transition to psychosis in CHRs has markedly declined in recent years. The 2 year risk of transition to psychosis from an initial CHR state has shifted from an early 30% (Fusar-Poli et al., 2012a) to the current 20% (Fusar-Poli et al., 2016). This phenomenon may be explained by effective early intervention, earlier referral or inclusion of false positives (Lee et al., 2014). In addition, Simon et al. (2013) carried out a meta-analysis of remission rates and reported that 73% of 773 CHR subjects did not transition to psychosis during a 2-year follow-up. Of these, 46% fully remitted from their APS, corresponding to clinical remission in 35%. Thus, CHR nonconverters are a heterogeneous group comprising individuals who later remit from an initial CHR state and those who do not remit and continue to experience APS.

Lin et al. (2011) found that, among CHRs with the poorest functional outcome, only 49% converted to psychosis. Since such a large proportion of nonconverters continue to report disability in multiple fields, it is evident that intervention should not be limited only to those with emerging psychosis. Although CHR studies have widely focused on transition to psychosis as the main outcome of interest, this arbitrary threshold, based entirely on positive symptoms, may be suboptimal for identifying individuals truly at risk of poor long-term outcome. Increasingly, evidence suggests that neurocognitive and social cognitive performance, functioning and a variety of clinical symptoms at baseline are of critical importance when predicting long-term functional outcome.

1.9.1 Cognition.

Cognitive deficits generally manifest in the premorbid phase of schizophrenia, increase in severity from the prodrome to the first psychotic episode and remain relatively stable thereafter (Corigliano et al., 2014). Indeed, Giuliano et al. (2012) revealed that CHRs had small-to-medium impairments (effect sizes from -0.26 to - 0.67) across nine cognitive domains, intermediate in magnitude between healthy control (HC) and first episode psychosis (FEP) samples. More recently, Seidman et al. (2016) found that CHR participants engaged in the North American Prodrome Longitudinal Study (NAPLS 2) performed significantly worse than HCs on 19 neuropsychological tests assessing four factors derived from factor analysis: executive and visuospatial abilities, verbal abilities,

attention and working memory abilities and declarative memory abilities. Certainly, deficits in a diffuse range of cognitive domains have been reported in CHR samples, the most pronounced of which are described in detail below.

1.9.1.1 Working memory.

Working memory refers to the cognitive function to retain and mentally manipulate information over a short period of time. In a meta-analysis by Fusar-Poli et al. (2012b), CHR participants were reportedly impaired on working memory relative to HCs, with an effect size of 0.36. This impairment became even more marked in those CHRs who subsequently transitioned to psychosis. Utilising the Self Ordered Pointing Task (SOPT) - a test of working memory – and BS criteria, Frommann et al. (2011) found that deficits in working memory were more pronounced in the late prodromal phase compared to the early prodromal phase. Other established measures of working memory include n-back and digit sequencing tests.

Goghari et al. (2014) observed an association between impaired spatial working memory performance and lower global functioning as measured by the Global Assessment of Functioning (GAF) scale. Furthermore, Liu et al. (2018) observed that, within the salience network, working memory demand related resting-state functional connectivity (FC) between the right insula and thalamus varied among controls, remitters and non-remitters. Controls had low FC at low demand and high FC at high demand; remitters had high FC at low demand and low FC at high demand; and non-remitters had high FC in both demands. Overall, the CHR state was associated with functional dysconnectivity.

1.9.1.2 Processing speed.

Processing speed refers to the pace at which individuals are able to perceive information, make sense of that information and then respond. Reduced processing speed is reported to be the most sensitive discriminator of CHR individuals from controls. Consistent with previous studies, Bang et al. (2015) found that processing speed in CHRs was decreased to the level of those with FES. Furthermore, Kelleher, Clarke, Rawdon, Murphy, and Cannon (2013a) found that non-help-seeking community-based young adolescents who met criteria for prodromal syndromes performed significantly more poorly than HCs on three measures

of processing speed: the Trail Making Test-A (TMT-A), the Trail Making Test-B (TMT-B) and the Brief Assessment of Cognition in Schizophrenia Symbol Coding task (BACS-SC).

Michel, Ruhrmann, Schimmelmann, Klosterkötter, and Schultze-Lutter (2014) investigated potential predictors of psychosis in CHRs over 24 months and found that psychosis transition risk was highest in the presence of APS criteria, COGDIS criteria and a processing speed deficit. Among CHRs, processing speed deficits at baseline predict poor social outcome over a follow-up period of 3 to 5 years (Carrión et al., 2013) and correlate strongly with self-perceived impairments in stress tolerance cross-sectionally (Schultze-Lutter et al., 2007).

Specifically, processing speed deficits may point to aberrant integration of whole brain connectivity, rather than indexing impairment in discrete neural networks (Kelleher et al., 2013a)

1.9.1.3 Attention.

Attention refers to a state of awareness in which the senses are focused exclusively and selectively on particular aspects of the environment. Hou et al. (2016) found that performance on the Stroop Colour and Word Test (SCWT) measure of attention gradually decreased from the HC, first degree relatives of patients not fulfilling UHR criteria (FDR), FES to CHR groups. However, following a meta-analysis of 32 studies, Hauser et al. (2017) noted that, while a second measure of attention - the Continuous Performance Test (CPT) - differentiated between CHR and HCs in the domain of attention/vigilance, the SCWT did not. Utilising the CPT – Identical Pairs (CPT-IP), Torgalsbøen, Mohn, Czajkowski, and Rund (2015), found that attention/vigilance at baseline was a significant predictor of social functioning 2 years later, while Lam et al. (2018) stated that changes in attention accounted for longitudinal changes in social and occupational functioning over a 24-month follow-up period.

Rapid orienting of attention to events that are unexpected and contextually deviant is commonly associated with the event related potential (ERP) component P3a or novelty P3. This component, peaking around 300 milliseconds after stimulus onset at fronto-central scalp electrodes, is reduced in amplitude in CHRs (del Re et al., 2015).

1.9.1.4 Motor speed.

A number of motor abnormalities have been proposed as core features of psychosis risk, including Parkinsonism, spontaneous dyskinesia, psychomotor slowing and neurological soft signs (Walther & Mittal, 2017).

Gschwandtner et al. (2006) used a fine motor function test battery comprising five different subdomains: steadiness, precision steadiness, aiming, tapping and inserting long and short pins. CHR individuals performed below HCs in all subdomains, predominantly in dexterity and velocity. Similarly, Lencz et al. (2006) measured motor speed with the TMT-A, the Finger Tapping Test and the Grooved Pegboard Test and reported a z-score deficit > 1 relative to the HC group mean. Although the TMT-A is categorised as a measure of processing speed, it can also serve as an index of motor speed due to its low cognitive load.

Giuliano et al. (2012), on the other hand, did not find reliable deficits in fine motor speed. The relevant studies in this review only contributed data on the Finger Tapping Test, leading to the conclusion that a more comprehensive battery is likely to reveal abnormalities. Moreover, on examination of gross motor behaviour using innovative video analysis software during a standard clinical interview, Dean, Samson, Newberry, and Mittal (2017) did not find evidence of psychomotor slowing. Rather, the CHR group showed greater speed of body movements compared to HCs, suggesting that psychomotor slowing is subtle during the CHR period. For example, Dean and Mittal (2015) found that CHR individuals were significantly impaired relative to HCs in the ability to scale velocity using pen movements on a digital tablet, possibly reflecting some rigidity or Parkinsonism.

Over a follow-up period of 3-5 years, motor disturbances at baseline are reportedly predictive of later role outcome, independent of conversion to psychosis (Carrión et al., 2013). Furthermore, Fryer et al. (2018) collected functional MRI data during Go/NoGo task performance from CHR youth, individuals with early illness schizophrenia (ESZ) and HCs. Compared to HCs, CHR and ESZ groups had slower and more variable reaction times on Go trials and reduced NoGo activation in right inferior frontal gyrus (RIFG) and anterior cingulate cortex (ACC) - regions associated with response conflict and response inhibition.

1.9.1.5 Verbal learning and memory.

Verbal learning is the process of actively memorising new material while verbal memory refers to the temporary maintenance and manipulation of verbal information. Standard word lists (California/Auditory/Rey/Hopkins Verbal Learning Test) and subscales of the Wechsler Memory Scale (WMS) have been used to investigate verbal learning and memory. Non-remitters present with significantly worse immediate/delayed verbal memory, as measured by the California Verbal Learning Test (CVLT), when compared to HCs (Lee et al., 2014). Interestingly, when remitters and non-remitters comprised one group of nonconverters, this difference disappeared for delayed verbal memory but remained for immediate verbal memory. In contrast to FEP studies, the low CVLT scores reported in previous CHR studies appear to be driven primarily by impairments in the rate of learning rather than by attentional processes. Egloff et al. (2018) indicated that, while FEP patients were impaired in both initial recall and learning rate, ARMS patients were only impaired in learning rate on the CVLT.

Niendam et al. (2006) detected pronounced verbal learning and memory deficits in CHR individuals using child and adult versions of the CVLT-II and the WMS-III. Furthermore, these deficits were predictive of current social functioning, irrespective of negative or positive symptom severity. Similarly, Cornblatt et al. (2015) suggested that, for CHR individuals, verbal memory along with disorganised communication, suspiciousness and a decline in social functioning were the best predictors of later transition to psychosis. They claimed that this model increased the risk of positive prediction from 30% with the CHR criteria alone to 81.8%.

Specifically, deficits in verbal learning and memory may be related to a reduced connectivity between the hippocampus and PFC secondary to a reduction of hippocampal volume (Antoniades et al., 2018). However, it is currently unclear how hippocampal volume reductions impact on, and therefore precede, these connectivity alterations.

1.9.1.6 Verbal fluency.

Verbal fluency is the ability to retrieve and express words compatible with required criteria. It can be measured by semantic (category) and phonological (letter) fluency tasks. Deficits

in this domain reportedly precede psychosis onset by up to 30 months (Lencz et al., 2006). In schizophrenia, semantic fluency seems to be impaired to a greater extent than phonological fluency – a finding replicated in CHRs. Magaud et al. (2010) found that CHR individuals had a lower mean total semantic fluency score than help-seeking controls. This effect remained significant when each semantic category (animals and fruits) was considered separately. By contrast, no differences were observed between CHRs and help-seeking controls in total phonological fluency scores or when each letter (P and R) was considered separately. Additionally, although Lee et al. (2014) did not detect differences at baseline between remitters and non-remitters for performance on a semantic fluency task, the performance of remitters improved whereas the performance of non-remitters declined over the 2-year follow up period.

Lower scores on the Controlled Word Association Test (COWAT) measure of verbal fluency at baseline have been found to predict both poor functioning and lower scores on the Scale of Assessment for Negative Symptoms (SANS) at follow-up an average 7.26 years later (Lin et al., 2011). During verbal fluency performance, CHRs display reduced activation in prefrontal brain regions and reduced prefrontal-temporal functional connectivity, which may, in turn, be driven by changes in subcortical glutamate function (Allen et al., 2015; Holper et al., 2015).

1.9.1.7 Executive function.

Executive functions are complex, higher order processes involved in the planning, organisation, regulation and monitoring of goal-directed behaviour. Deficits in executive control functioning are already present in the early prodrome of psychosis relative to HCs (Frommann et al., 2011). Moreover, this deficit is greater than - and independent from - impairments in other cognitive domains. Simon et al. (2012) administered a comprehensive neuropsychological test battery to CHRs and found that executive functions showed the largest impairments, although they did not predict later conversion.

Riecher-Rössler et al. (2009) were the first to identify a risk profile for transition to psychosis including not only clinical symptomatology but also a neurocognitive variable: suspiciousness, anhedonia/asociality and performance on a measure of executive functioning. With this combination, transition to psychosis could be predicted with a

sensitivity of 83.3% and a specificity of 79.3%. In other words, 15 of 18 converters and 23 of 29 nonconverters could be correctly predicted. Further research has also shown that executive functioning deficits at baseline significantly predict both role and social functioning at 1-year follow-up (Eslami, Jahshan, & Cadenhead, 2011).

Utilising the TMT-B to measure executive function, Koutsouleris et al. (2010) observed impaired performance in CHRs versus HCs. As well as relating this impairment to a volumetric pattern covering mainly prefrontal, premotor, occipital and cerebellar brain regions, they linked it to an attenuated structural connectivity between the prefrontal and limbic–paralimbic cortices.

1.9.2 Social cognition.

Fusar-Poli et al. (2012b), in the first comprehensive meta-analysis of cognitive functioning in CHR subjects, found significant deficits in social cognition compared to HCs despite the different measures used across studies. Furthermore, the magnitude of this deficit exceeded any of the examined neurocognitive domains. In a later meta-analysis (van Donkersgoed, Wunderink, Nieboer, Aleman, & Pijnenborg, 2015), CHRs presented with moderate deficits in affect recognition and affect discrimination in faces as well as in voices and in verbal theory of mind compared to HCs. Although a moderate effect was also found for visual theory of mind, this was not significant.

Additionally, Corcoran et al. (2015) found evidence of emotion recognition deficits, as measured by the Penn Emotion Recognition task (ER40), in CHR individuals who later transitioned to schizophrenia. Specifically, these deficits were driven by a decrease in discrimination of negative expressions portraying fear and anger from neutral expressions. Mean emotion recognition scores obtained by these CHR individuals were at or below those observed in normally developing 10-year-olds whereas CHRs without transition and HCs showed age-appropriate performance levels. Moreover, face emotion processing in combination with negative symptoms produced the best classification model for schizophrenia onset, with an accuracy of 96%. Kohler et al. (2014) also used the ER40, revealing comparable impairments in recognition of happy, angry and fearful expressions

for CHRs and schizophrenia subjects. Participants with genetic risk for schizophrenia were less impaired, showing reduced recognition of fearful expressions.

Conversely, while findings from baseline measures of the NAPLS 2 cohort suggested that CHRs were significantly impaired in theory of mind and emotion recognition, the emotion recognition deficits did not remain statistically significant when controlling for age and IQ (Barbato et al., 2015). Also, Glenthøj et al. (2018) reported no significant group differences in response latency on any of the six emotion recognition tasks from the CANTAB Battery (CANTAB ERT) or the total score between CHRs and HCs, suggesting that both groups use a similar level of automatic processing.

Contrary to previous findings in individuals with schizophrenia, social cognition does not seem to mediate the pathway from neurocognition to functional outcome in those at CHR for psychosis (Barbato et al., 2013). The association of social cognitive abilities with functioning and social skills was examined by Glenthøj et al. (2016). CHRs demonstrated decrements in both theory of mind and emotion recognition tasks. In particular, CHRs were selectively impaired at recognising the negative emotions of disgust, anger and fear. While theory of mind ability was associated with self-reported functioning, aspects of emotion recognition were associated with role functioning and social skill performance. In comparison, although Cotter et al. (2017) showed that poorer performance on a visual theory of mind task was associated with poorer overall functioning in CHRs, no association was evident between emotion recognition and functioning. However, their measure of emotion recognition incorporated a narrow range of expressions, possibly lowering sensitivity.

When inferring other's beliefs and emotions, CHR and schizophrenia subjects exhibit hyperactivity in the superior temporal sulcus (STS) and hypoactivity in the inferior frontal gyrus (IFG). While the schizophrenia group display higher activity in the left STS compared to both HCs and CHRs when inferring other's beliefs, the CHR group show higher activity in this region when inferring other's emotions (Takano et al., 2017). Hyperactivity in the STS is also evident during emotion recognition in CHRs in addition to hyperactivity in the amygdala and posterior cingulate (Haut et al., 2017).

1.9.3 Clinical and functional characteristics.

In terms of clinical characteristics, evidence suggests that negative, positive and disorganised symptoms (Brandizzi et al., 2015; Eslami et al., 2011; Salokangas et al., 2014; Schlosser et al., 2012) at baseline predict CHR participants' functional outcome at follow-up. Brandizzi et al. (2015) found that the suicidality and self-harm CAARMS subscale emerged as the strongest predictor of good, versus poor, functional outcome in univariate analyses while CAARMS total score significantly contributed to the final prediction model. Although Salokangas et al. (2014) found that positive, negative and disorganised symptoms associated strongly with poor functioning at baseline, only negative symptoms were retained in the model predicting functioning from 9-18 months.

Functioning prior to disorder onset is considered one of the strongest predictors of later functional outcome in subjects with chronic schizophrenia (Barajas et al., 2013), FEP (Chang et al., 2013) and those at CHR for psychosis. Brandizzi et al. (2015) found that GAF scores and employment status at baseline contributed to the prediction of functional outcome in CHR subjects at 6 years. As expected, better functioning at baseline predicted good functional outcome. Similarly, impaired social and role (academic/occupational) functioning at baseline, as measured with the Global Functioning: Social (GF: Social) and Global Functioning: Role (GF: Role) scales, have previously been shown to predict poor functioning over a follow-up period of 3-5 years (Carrión et al., 2013). Carrión et al. (2013) also noted that CHRs with good social outcome showed a modest improvement in social functioning compared to those with poor social outcome (23.6% vs -5.0%) and CHRs with good role outcome showed a modest improvement in role functioning compared to those with poor role outcome (61.4% vs -9.1%).

Additionally, poor premorbid psychosocial adjustment, as measured by the Premorbid Adjustment Scale (PAS), has been shown to predict low GAF scores over a follow-up period of 18 months (Salokangas et al., 2014). Adolescence adjustment (12-18 years) - especially subscales relating to social and sociosexual development and school adaptation - was found to have stronger associations with functioning than childhood adjustment (up to 11 years). On the other hand, no differences in association were apparent between early (12-15 years) and late (16-18 years) adolescence adjustment and functioning.

Conversely, Lin et al. (2011) did not find an association between baseline GAF scores and later poor outcome as defined by low scores on the Quality of Life Scale (QLS) and the Social and Occupational Functioning Assessment Scale (SOFAS).

Notably, the GAF score is based on both symptomatic severity and functional impairment, whichever is more severe. Therefore, under certain circumstances, functional impairment may contribute minimal information. In contrast, the GF: Social and GF: Role scales refer only to functioning, preventing conflation with symptom severity.

1.10 Aims of this thesis.

Current understanding of the CHR state for psychosis has been based almost entirely on studies of help-seeking participants. However, little-to-nothing is known about members of the general population who meet CHR criteria but do not contact specialised early detection services, meaning that current data collected on the CHR state is unrepresentative of the total population.

Mills, Fusar-Poli, Morgan, Azis, and McGuire (2017) collected cross-sectional data from a general population sample (N = 208) and found that 18 participants (8.7%) met UHR criteria, 16 (7.7%) met BS criteria and four met both. Community CHR individuals were similar to help-seeking individuals in age, gender, ethnicity, employment status, years of education, history of childhood trauma and current cannabis use, but were more likely to be first-generation migrants. Also, positive symptoms, negative symptoms and general psychopathology were less severe in the community, versus help-seeking, CHR sample while levels of social and occupational functioning were higher. However, they had poorer functioning than non-CHR subjects. Importantly, approximately half of the community CHR sample had sought help for a psychological or emotional problem in the past year from a non-specialised agency, counteracting the view that these individuals are “non-help-seeking”.

Clearly, the general population comprises an important target group in CHR research. Improved identification of CHRs in the general population would ensure that these individuals have better access to specialised mental health interventions. Although an online screening approach would provide an efficient, accessible and cost-effective method

to detect CHR-participants at the population-level, the utility of such an approach is largely unexplored.

Moreover, in light of declining transition rates and the heterogeneity of CHR samples, it is becoming increasingly important to focus on outcomes other than psychosis transition, such as functional status. Despite over 2 decades of preventative research, an understanding of the complex factors associated with good and poor functional outcomes in CHR individuals remains elusive.

Utilising an online screening approach, to ensure the majority of the CHR sample were recruited from the general population, the aim of this thesis is to address the following questions:

(1) Can functional and cognitive variables discriminate between CHR individuals and HCs at baseline?

(2) What is the relationship between cognitive performance, clinical symptoms and functioning in CHR individuals at baseline?

(3) What is the functional outcome of CHR individuals at 6- and 12-month follow-up?

(4) Does functioning remain stable or change over 6- and 12-months?

(5) Can clinical, functional and cognitive variables at baseline discriminate between CHR individuals with good functional outcome (GFO) and poor functional outcome (PFO) at 6- and 12-months?

(6) What are the baseline predictors of PFO in CHR individuals at 6- and 12-months?

It was hypothesised that: (1) functional and cognitive variables would discriminate between CHR individuals and HCs at baseline; (2) cognitive performance would be related to clinical symptoms and functioning at baseline; (3) a substantial proportion of CHR individuals would have PFO at 6- and 12-months; (4) levels of functioning would remain

stable in the PFO group and improve in the GFO group over 6- and 12-months; (5) baseline clinical, functional and cognitive variables would discriminate between CHR individuals with GFO and PFO at 6- and 12-months; and (6) a combination of baseline clinical, functional and cognitive variables would provide the best prediction of functional outcome at 6- and 12-months.

2.0 Methods

2.1 Recruitment and participants.

Data were collected as a part of a Medical Research Council (MRC) funded, longitudinal, multisite study entitled "Youth Mental Health Risk and Resilience Study" (YouR-Study; Uhlhaas et al., 2017) which aims to identify neurobiological and psychological mechanisms and predictors of psychosis-risk. The study was approved by the ethical committees of the NHS Research Ethical Committee Glasgow and Greater Clyde and is being carried out according to the Research Governance Framework for Health and Community Care (Second edition, 2006). The specific YouR-Study protocol utilised in the current study is displayed in Figure 1.

In the baseline analyses, 129 CHR individuals (97 females, 32 males) were included. At 6-month follow-up, data was available for 86 CHR individuals (65 females, 21 males) whilst, at 12-month follow-up, data was available for 69 CHR individuals (53 females, 16 males). Although these CHR samples were primarily recruited from the general population, eight individuals in the baseline analyses, five in the 6-month follow-up analyses and two in the 12-month follow-up analyses were referred to the study. Also, of note, five individuals in the baseline and 6-month follow-up analyses and three individuals in the 12-month follow-up analyses transitioned to psychosis.

In addition to CHR-participants, 46 CHR-negative (CHR-N) participants who did not meet CHR criteria at first baseline clinical assessment and 55 HCs without an Axis I diagnoses and/or family history of psychotic disorders were recruited. Follow-up data was available for 40 CHR-N participants. The CHR-N group was included to control for psychiatric comorbidities associated with the CHR state.

Email invitations, flyers and public transport advertisements were used to direct potential CHR and CHR-N participants from the general population to our website (www.your-study.org.uk). Specifically, email invitations were sent out to colleges and Universities in Glasgow and Edinburgh. For potential referrals, NHS-patient services in NHS Greater Glasgow and Clyde and NHS Lothian and student counselling services were approached. Informed consent for potential referrals was either obtained on-site or participants were

asked to register online for the study. HCs were recruited from a participant database held by the University of Glasgow's Centre for Cognitive Neuroimaging (CCNi).

General inclusion and exclusion criteria applicable to all groups is shown in Table 1. CHR-Ns and HCs were also excluded if they had a first degree relative with a diagnosis of schizophrenia.

Table 1

General Inclusion and Exclusion Criteria

Inclusion Criteria	**Exclusion Criteria**
Written informed consent	An existing neurological disorder
Male or non-pregnant female ≥ 16 years of age	> 35 years of age
Normal to corrected vision	Metal implants in body parts
	Pregnancy
	Suicidal intent

Informed consent for the web screening was provided online, followed by two questionnaires to assess psychosis risk: 1) the 16-item version of the prodromal questionnaire (PQ-16; Ising et al., 2012) which was developed from the 92-item PQ (Loewy et al., 2005) and 2) a 9 item-scale for the assessment of perceptual-cognitive anomalies (PCA) generated from existing patient descriptions of cognitive and perceptual experiences and the SPI-A. Participants were asked to provide ratings based on experience in the last 12 months. In order to qualify for the second part of the study, participants were required to positively endorse 6 or more items on the PQ and/or 3 or more items on the PCA.

2.2 Baseline clinical assessments.

Participants who met PQ and/or PCA criteria were invited, via email, to participate in the second part of the study which involved baseline clinical assessments to ascertain CHR status and a baseline cognitive assessment.

2.2.1 Demographic and treatment information.

At the beginning of the first baseline clinical assessment, informed consent was obtained. Demographic information was collected including gender, age, years of education, citizenship and family history. Participants were also asked to discuss any episode of physical or mental health illness they had experienced in the last 12 months and whether they had received treatment, medication or been admitted to a psychiatric ward for such an episode in their lifetime. Suicide risk was assessed and if current suicidality was reported, appropriate referrals were made and the participant did not continue in the study.

2.2.2 Assessment of CHR symptoms and criteria.

Two semi-structured interviews – the positive scale of the Comprehensive Assessment of At-Risk Mental States (CAARMS; Yung et al., 2005) and 14 items of the Schizophrenia Proneness Instrument, Adult version (SPI-A; Schultze-Lutter et al., 2007) - were administered by trained research assistants and MSc/PhD level researchers during the initial screening to assess psychosis risk. These instruments have shown excellent overall inter-rater reliability: 0.85 for the CAARMS and 0.91 for the SPI-A (Fusar-Poli et al., 2015).

The CAARMS is the dominant method of determining whether participants meet the criteria for an at-risk mental state (ARMS). ARMS refer to the cluster of symptoms and signs detected by the operationalised ultra-high risk (UHR) criteria. Specifically, participants were administered the positive scale of the CAARMS which is designed to assess four symptom subscales – unusual thought content, non-bizarre ideas, perceptual abnormalities and disorganised speech. Each of these are rated on a 0-6 scale for intensity and frequency. In addition, participants rated how distressed they were by these symptoms using a scale from 0 (not at all distressed) to 100 (extremely distressed). A positive symptom severity score was calculated as the summed scores of the product of intensity (0–6) and frequency (0–6) scores of the four subscales.

In order to meet UHR Criteria and be classified into the CHR group, participants must have experienced either: (1) a 30% or greater drop in Global Assessment of Functioning (GAF) score from a premorbid level, sustained for one month and occurring within the past

12 months or (2) chronically low GAF (score of ≤ 50) for the past 12 months or longer. In addition, participants must also meet criteria for at least one of the following groups:

- **Group 1: Vulnerability Group -** Family history of psychosis in first degree relative or Schizotypal Personality Disorder identified in the participant.
- **Group 2: Attenuated Psychosis Group -** Individuals who have experienced sub-threshold (intensity or frequency) positive psychotic symptoms in the past year.
- **Group 3: Brief Limited Intermittent Psychosis Syndrome (BLIPS) Group -** Those who have experienced short episodes of frank psychotic symptoms within the past year that have not lasted longer than a week and have resolved without treatment.

Participants were classified into the FEP group if symptom intensity was scored as a 6 on either unusual thought content, non-bizarre ideas, or disorganised speech, or 5-6 on perceptual abnormalities, with an associated frequency score of 4-6 (at least "3 to 6 times a week - more than an hour per occasion") and with these experiences lasting longer than one week.

Two partially overlapping items from the SPI-A were administered: COGDIS which assesses nine basic symptoms (BS) of cognitive disturbance and COPER which assesses 10 cognitive-perceptive BS. Participants were asked to rate the maximum frequency of occurrence of these BS within the past 3 months on a 0-9 point scale with scores between 3 and 6 indicating symptom presence. A score of 7 was given if the symptom had always been present at the same severity whereas scores of 8 and 9 indicated that, although the symptom was present, there was not sufficient information to give a rating between 0 and 6. If applicable, the participant was also asked to rate how distressing the BS were on a scale from 0 to 100.

Participants were also recruited into the CHR group if they met either COPER or COGDIS criteria (see Table 2). To meet COPER criteria, the participant had to report at least one of 10 cognitive perceptive BS as having first occurred more than 12 months ago with a frequency score of 3-6 (at least "several times in a month or weekly") within the past 3 months. To meet COGDIS criteria, the participant must have experienced at least two of

nine cognitive disturbance BS – five of which are also included in COPER - with a frequency score of 3-6 within the past 3 months.

Table 2

COGDIS and COPER Criteria

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

2.2.3 Assessment of functioning.

At the first baseline clinical assessment, overall (global) functioning over the past month was assessed using the modified version of the GAF scale included in the Structured Interview for Psychosis-Risk Syndromes (SIPS; McGlashan, Walsh, & Woods, 2010). The GAF is scored by considering impairments in psychological, social and role functioning. The scale is divided into 10 equal 10-point intervals that have clear anchor points with scores ranging from 1 to 100 (with 100 indicating superior functioning and 1 representing extreme dysfunction).

At the second baseline clinical assessment, Global Functioning: Social (GF: Social) and Global Functioning: Role (GF: Role) scales (Cornblatt et al., 2007), broadly derived from the traditional GAF scale, were used to measure social and role functioning. These complementary scales generate three scores: lowest level of functioning in the past month (current functioning), lowest level of functioning over the past year and highest level of

functioning over the past year. For both scales, scores range from 1 to 10 where 1 indicates extreme dysfunction and 10 represents superior functioning. A score of 6 typically characterises UHR participants. The GF: Social scale assesses the quality and quantity of the participant's social contact/interactions with friends and family including conflict, intimate relationships and involvement. On the other hand, the GF: Role scale considers performance and level of support required in school, university, work or housekeeping, depending on the participant's age. As well as preventing psychiatric symptoms from confounding functioning, these scales have shown excellent inter-rater reliability in both CHRs and FEPs with an intraclass correlation coefficient for current functioning of 0.85 for the GF: Social scale and 0.93 for the GF: Role scale (Cornblatt et al., 2007).

2.2.4 Assessment of psychiatric disorders.

Participants were administered the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al. 1998) during the second baseline clinical assessment to identify psychiatric comorbidity. The MINI is a short, structured diagnostic interview used to assess the 17 major psychiatric disorders (27 past and current disorders) in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM–IV; APA, 1994) and the *International Classification of Diseases*, 10th Revision (ICD-10, WHO, 1992). Diagnoses assessed by the MINI in the current study were the following: anxiety disorders (panic attack disorder, agoraphobia, social phobia, generalised anxiety disorder); mood disorders (episodes of major depression, hypomania and mania*);* eating disorders *(*anorexia nervosa and bulimia nervosa); suicidality; alcohol dependence/abuse; and substance dependence/abuse.

The MINI is organised in diagnostic modules with branching tree logic and based on yes and no answers. There are one or two screening questions per disorder which are used to rule out the diagnosis when answered negatively. However, if answered positively, additional symptom questions are asked, possibly resulting in the diagnosis of a psychiatric disorder.

Concurrent validity of the MINI with more extensive structured interviews is good as demonstrated by median kappas of 0.67 and 0.63 with the Structured Clinical Interview for DSM diagnoses, Patient Version (SCID-P; Sheehan et al., 1997) and the Composite International Diagnostic Interview (CIDI; Lecrubier et al., 1997), respectively (Sheehan et

al., 1998). The MINI also demonstrates excellent inter-rater reliability (median kappa = 0.92) and good test-retest reliability (median kappa = 0.78).

2.3 Baseline cognitive assessment.

2.3.1 Brief Assessment of Cognition in Schizophrenia.

Participants were administered a standard cognitive battery: The Brief Assessment of Cognition in Schizophrenia (BACS; Keefe et al., 2004). This measure is simple to use, requiring only paper, pencils and a stopwatch and takes approximately 35 minutes to complete. The BACS assesses multiple domains of cognitive function (see Table 3) thought to be effected by schizophrenia and which appear to have clear functional relevance (Keefe, 2012). Indeed, Keefe, Poe, Walker, and Harvey (2006) found that the BACS composite score was strongly correlated to functioning measures including independent living skills ($r = 0.45$), performance-based assessment of functioning ($r = 0.56$) and interview-based assessments of cognition in patients with schizophrenia ($r = 0.48$). Also, the BACS exhibits similar sensitivity to the cognitive deficits of schizophrenia as a standard 2.5-hour battery (Keefe et al., 2004).

The BACS composite score displays high test-retest reliability in schizophrenia patients and HCs (intraclass correlation coefficients > 80) and has a high correlation ($r = 0.84$, $p < 0.001$) with the composite score derived from the CATIE Neurocognitive Test Battery (Keefe et al., 2007a, 2007b; Hill et al., 2008).

Table 3

Neurocognitive Domains Assessed by the 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 no particular order. Procedure repeated five times.	Number of words recalled per trial	0-75

Working Memory	Digit Sequencing Task	Participants are read randomly ordered clusters of numbers which steadily increase in trial length. They are asked to report 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 given 60 seconds to place as many as possible in a container, two at a time with each hand simultaneously.	Number of tokens correctly placed in the container	0-100
Verbal Fluency	Semantic Fluency	Participants are asked to name as many animals as possible in 60 seconds	Number of animals named	0 - infinity
	Letter Fluency	In two separate trials, participants are given 60 seconds to produce as many words as possible beginning with a given letter, here F and S.	Number of words generated per trial	0 - infinity
Attention and Processing Speed	Symbol Coding	Participants are given 90 seconds to write numerals 1-9 as matches to non-meaningful symbols on a response sheet, as based on a key provided to them.	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 different-coloured balls arranged on three pegs. They then estimate the number of times the balls in picture A have to be moved in order to match the arrangement in picture B. If participants respond correctly to all 20 trials, two additional, harder trials are administered.	Number of correct responses	0-22

2.3.2 The Penn Computerized Neurocognitive Battery.

The following three tasks from the Penn Computerized Neurocognitive Battery (CNB; Moore, Reise, Gur, Hakonarson, & Gur, 2015) were included in the cognitive assessment:

1) Continuous Performance Task; 2) Letter N-Back Test; and 3) Emotion Recognition Task. The CNB demonstrates good test-retest reliability and sensitivity to diagnosis (R. E. Gur et al., 2007) as well as favourable correlations with traditional paper-pencil batteries in those with schizophrenia (R. C. Gur et al., 2001).

The Penn Continuous Performance Test (PCPT; Kurtz, Ragland, Bilker, Gur, & Gur, 2001) is a measure of visual attention and vigilance. In this task, a series of red vertical and horizontal lines composed of 7-segments flash at a rate of one second each. Specifically, the stimulus flashes for 300 milliseconds and a blank page is then displayed for 700 milliseconds. During this response window, the participant has to press the spacebar when the lines form a complete number (initial 3 minutes) or a complete letter (next 3 minutes). The total number of true positive responses is recorded as the accuracy score and the median response time for true positive responses is selected as a measure of response time (RT).

The Penn Letter-N-Back Test (LNB2; Ragland et al., 2002) is a measure of working memory. In this task, a continual series of letters flash on screen for 500 milliseconds (one at a time) and the participant has an additional 2000 milliseconds to respond by pressing the spacebar according to three different rules - known as 0-back, 1-back and 2-back. During the 0-back condition, the participant has to press the spacebar whenever the letter "X" appears on the screen. During the 1-back condition, the participant is tasked with pressing the spacebar whenever the letter on the screen is the same as the previous letter (i.e. in the series, "R", "M", "M", the spacebar should be pressed upon appearance of the second "M"). During the 2-back condition, a spacebar press is required when the letter onscreen matches the letter before the previous letter (i.e. in the series "R", "M", "R", the spacebar should be pressed upon appearance of the second "R"). The total number of true positive responses is recorded as the accuracy score and the median response time for true positive responses is selected as a measure of RT.

The Penn Emotion Recognition Task (ER40; R. C. Gur et al., 2002) is a measure of emotion recognition – a key component of social cognition. Participants are presented with 40 faces (one at a time) and must decide, by a multiple-choice format, whether the actor's face expresses happiness, sadness, anger, fear or no emotion (neutral). There are 4 female and 4 male faces for each emotion covering a wide age range and four races (Caucasian,

African-American, Asian and Hispanic). The total number of correct responses is used as the accuracy score and median response time for correct responses serves as a measure of RT.

2.4 Outcome assessment.

Follow-up interviews were conducted approximately 6- and 12-months post-baseline for CHR and CHR-N participants. During these two visits, participants were administered the positive scale of the CAARMS as well as the GF: Social and GF: Role scales.

CHR participants were divided into two functional outcome groups at 6- and 12-month follow-up using the GAF scale: (1) a good functional outcome (GFO) group (GAF score ≥ 65) and (2) a poor functional outcome (PFO) group (GAF score ≤ 64). The group split at the GAF score of 65 was chosen because the 60-70 range corresponds to the presence of "some persistent difficultly in social, occupational or school functioning but [the person] has some meaningful interpersonal relationships". GAF scores below 60 indicate moderate to severe impairment, whilst scores above 70 signify slight impairment to good function.

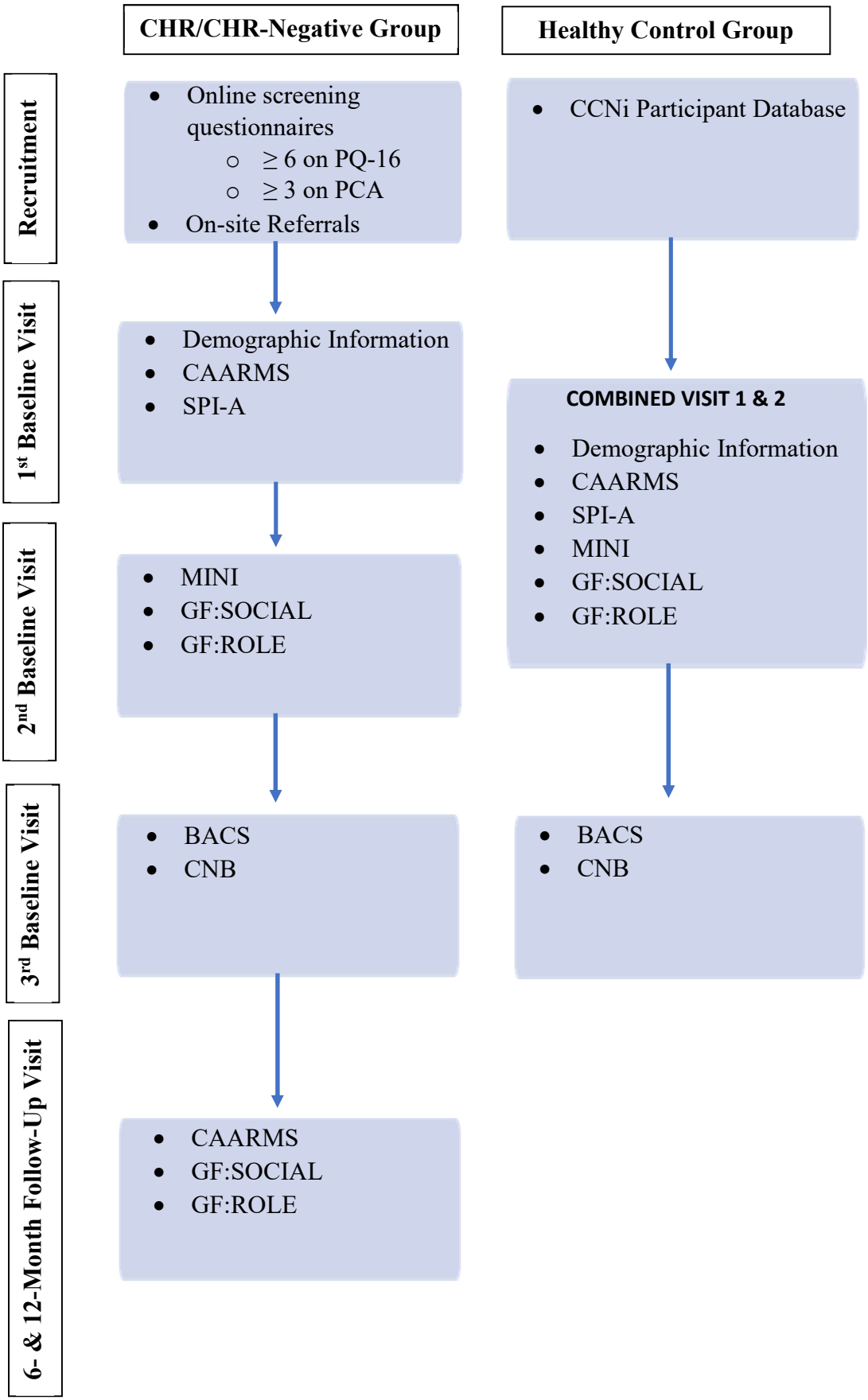

Figure 1. Flow diagram of the current study protocol

2.5 Statistical analyses.

All statistical analyses were performed using SPSS Version 25 and the level of significance was set at 0.05 (two-tailed).

BACS and CNB raw scores for each cognitive domain were separated by gender and converted into standardized z-scores using the means and standard deviations of gender-specific HCs. This gender correction was applied in order to address statistically significant gender differences in BACS cognitive domain scores previously reported in normative data from healthy controls (Keefe et al., 2008). The BACS composite score for each participant was calculated by averaging all six z-scores obtained from the primary measures and then re-standardising the averaged score in the same way mentioned above (Keefe et al., 2004).

Descriptive statistics included mean and standard deviation for continuous variables; median and range for ordinal variables; and absolute and relative frequencies for categorical variables. Differences in baseline demographic, clinical, functional and cognitive characteristics between groups were analysed using one-way ANOVAs for continuous variables; non-parametric Kruskal-Wallis H tests for ordinal variables; and chi-square tests for categorical variables. When the homogeneity of variances assumption was violated in one-way ANOVA analyses, Welch's F was reported. Since the one-way ANOVA is considered a robust test against the normality assumption, no alternative tests were applied. Wilcoxon signed rank tests were also conducted to ascertain whether functioning significantly changed over time within the same CHR subjects.

For cognition analyses, Hochberg's GT2 test and the Games-Howell test were used as post hoc tests for ANOVA analyses and Welch analyses, respectively. Effect sizes for each cognitive domain were calculated using Cohen's d (Cohen, 1988).

All cognitive domains, except BACS composite, were entered into stepwise multiple linear regressions in order to assess the relationship between cognitive performance, clinical symptoms and functioning at baseline in the CHR group. Multivariable logistic regression models were constructed to predict CHR participants' functional outcome at 6-and 12-months since the outcome variable was dichotomous (GFO was coded as 0 and PFO was

coded as 1). Potential clinical, functional and cognitive variables were initially computed individually in univariable logistic regression analyses. Next, two multivariable logistic regressions using stepwise backward selection (likelihood ratio) were employed because these analyses were primarily exploratory. Cognitive variables that reached a borderline significance ($p < 0.10$) in univariable analyses were entered in the first model. In the second model, cognitive variables included in the first model were entered alongside clinical and functional variables that reached a significance level of $p < 0.10$ in univariable analyses. Although the logistic regression analyses violated the widely advocated ten events per variable (EPV) rule, Vittinghoff and McCulloch (2007) have argued that an EPV of 10 as a minimal guideline criterion is too conservative, showing that severe problems mainly occur in models with 2-4 EPV.

The overall variance explained by the models obtained through stepwise linear and logistic regressions was measured by the R^2 statistic and Nagelkerke pseudo R^2 statistic (R^2_N), respectively. Diagnostic accuracy of the logistic regression models was determined with area under the receiver operating characteristic (ROC) curves (AUC).

3.0 Results

3.1 Baseline.

Baseline demographic, clinical and functional characteristics of CHR individuals, HCs and CHR-Ns are summarised in Table 4.

Table 4

Baseline Characteristics of CHR Individuals, HCs and CHR-Ns

Characteristic	**CHRs (n = 129)**	**HCs (n = 55)**	**CHR-N (n = 46)**	**df**	**F/ X^2/H**	**p**	**Post Hoc Contrasts ***
Age (years), M ± SD	21.64 ± 4.28	22.31 ± 3.38	23.00 ± 4.84	2, 102	F = 1.64	0.199	
Gender, N female (%)	97 (75)	37 (67)	29 (63)	2	X^2 = 2.88	0.237	
Years of education, M ± SD	15.29 ± 3.17	16.38 ± 2.84	16.46 ± 3.48	2, 227	F = 3.57	< 0.05	
UK Citizen, N (%)	90 (70)	26 (47)	23 (50)	2	X^2 = 10.78	< 0.01	
GAF, median (range)	58 (21-95)	88 (67-97)	70 (43-94)	2	H = 116.83	< 0.001	1 vs 2,3 & 2 vs 3
CAARMS Positive Items, median (range)							
Unusual Thought Content	1 (0-5)	0 (0-1)	0 (0-5)	2	H = 47.97	< 0.001	1 vs 2,3 & 2 vs 3
Non-Bizarre Ideas	3 (0-6)	0 (0-2)	0 (0-5)	2	H = 97.88	< 0.001	1 vs 2,3
Perceptual Abnormalities	3 (0-6)	0 (0-3)	0 (0-4)	2	H = 101.36	< 0.001	1 vs 2,3 & 2 vs 3
Disorganised Speech	1 (0-4)	0 (0-1)	0 (0-3)	2	H = 55.88	< 0.001	1 vs 2,3 & 2 vs 3
Total Positive Severity	28 (0-72)	0 (0-12)	5 (0-24)	2	H = 143.43	< 0.001	1 vs 2,3 & 2 vs 3
CHR Criteria Subgroup, N (%)							
UHR	41 (32)	0 (0)	0 (0)				
BS	32 (25)	0 (0)	0 (0)				

UHR/BS	54 (42)	0 (0)	0 (0)				
GF: Social, median (range)	8 (5-10)	9 (8-10)	8 (6-9)	2	H = 73.10	< 0.001	1 vs 2,3 & 2 vs 3
GF: Role, median (range)	8 (4-9)	9 (5-9)	8 (5-9)	2	H = 57.16	< 0.001	1 vs 2,3 & 2 vs 3
Medication, N (%)				10	$X^2 = 41.96$	< 0.001	
Anti-psychotic	2 (2)	0 (0)	1 (2)				
Mood stabiliser	1 (1)	0 (0)	0 (0)				
Anti-depressant	29 (22)	0 (0)	10 (22)				
Other	15 (12)	1 (2)	6 (13)				
Multiple	17 (13)	0 (0)	2 (4)				
Diagnosis, N (%)				2	$X^2 = 125.89$	< 0.001	
Anxiety disorders	92 (71)	0 (0)	21 (46)				
Mood disorders	82 (64)	0 (0)	13 (28)				
Eating disorders	11 (9)	0 (0)	1 (2)				
Suicide Risk	67 (52)	1 (2)	10 (22)				
Alcohol Dependence/Abuse	40 (31)	2 (4)	10 (22)				
Substance Dependence/Abuse	19 (15)	0 (0)	2 (4)				

Note. Abbreviations: CHR, clinical high-risk; HC, healthy control; CHR-N, clinical high-risk-negative. * 1 = CHRs, 2= HCs, 3 = CHR-Ns.

CHR individuals had significantly poorer global, social and role functioning as well as significantly higher intensity scores on all CAARMS positive items compared to HCs and CHR-Ns. Except for the non-bizarre ideas CAARMS positive item, CHR-Ns were also significantly impaired on these measures compared to HCs. Significant group differences were found for years of education, citizenship, medication use and MINI diagnoses. That said, no significant post hoc differences were observed for years of education.

Table 5 displays the baseline neurocognitive and social cognitive performance for CHR individuals, CHR-Ns and HCs. Due to incorrect task

performance, one CHR participant was removed from the CNB working memory analyses while two CHR-N participants and two CHRs with PFO were removed from the CNB attention analyses.

Table 5

Baseline Cognitive Performance of CHR Individuals, HCs and CHR-Ns

Domain	CHR (n = 129)		HCs (n = 55)		CHR-N (n = 46)		df	F	p	Cohen's d	Post Hoc Contrasts *
	M	SD	M	SD	M	SD					
BACS											
Verbal Memory	-0.14	1.20	0	1	0.14	1.04	2, 227	1.39	0.252	0.17	
Motor Speed	-0.68	1.15	0	1	-0.32	0.92	2, 227	8.52	< 0.001	0.58	1 vs 2
Attention & Processing Speed	-0.41	1.08	0	1	0.12	1.14	2, 227	5.50	< 0.01	0.36	1 vs 3
Verbal Fluency	-0.15	0.97	0	1	-0.23	0.86	2, 227	0.72	0.454	0.14	
Executive Function	-0.07	1.24	0	1	0.01	1.15	2, 227	0.08	0.921	0	
Working Memory	-0.02	1.44	0	1	0.26	1.13	2, 114	0.97	0.381	0	
BACS Composite Score	-0.54	1.62	0	1	-0.01	1.28	2, 115	4.81	< 0.05	0.36	1 vs 2
CNB											
Emotion Recognition Accuracy	-0.12	1.09	0	1	-0.10	0.92	2, 227	0.26	0.773	0.11	
Emotion Recognition RT	0.62	1.62	0	1	0.18	1.34	2, 113	5.09	< 0.01	0.39	1 vs 2
Attention Accuracy	-0.48	1.87	0	1	0.09	1.14	2, 120	3.39	< 0.05	0.26	
Attention RT	-0.10	0.87	0	1	-0.28	0.98	2, 223	1.17	0.312	0.11	
Working Memory Accuracy	-0.31	1.40	0	1	-0.16	1.24	2, 110	1.40	0.251	0.22	
Working Memory RT	-0.03	0.82	0	1	-0.12	0.99	2, 226	0.20	0.822	0	

Note. RT (response time). Effect sizes between CHR and HC groups, measured by Cohen's d, are classified as small (0.2), medium (0.5) and large (0.8). * 1 = CHRs, 2 = HCs, 3 = CHR-Ns

Significant group differences were demonstrated for motor speed ($F(2, 227) = 8.52$, $p < 0.001$), attention and processing speed ($F(2, 227) = 5.50$, $p < 0.01$), BACS composite score ($F(2, 115) = 4.81$, $p < 0.05$), emotion recognition RT ($F(2, 113) = 5.09$, $p < 0.01$) and attention accuracy ($F(2, 120) = 3.39$, $p < 0.05$). Specifically, CHR individuals had slower motor speed, poorer BACS composite scores and increased emotion recognition RTs compared to HCs and reduced attention and processing speed compared to CHR-Ns. No significant post hoc differences were observed for attention accuracy although the difference between CHRs and both CHR-Ns ($p = 0.052$) and HCs ($p = 0.071$) approached significance.

Effect sizes (Cohen's d) between CHR and HC groups for each cognitive domain are illustrated in Figure 2.

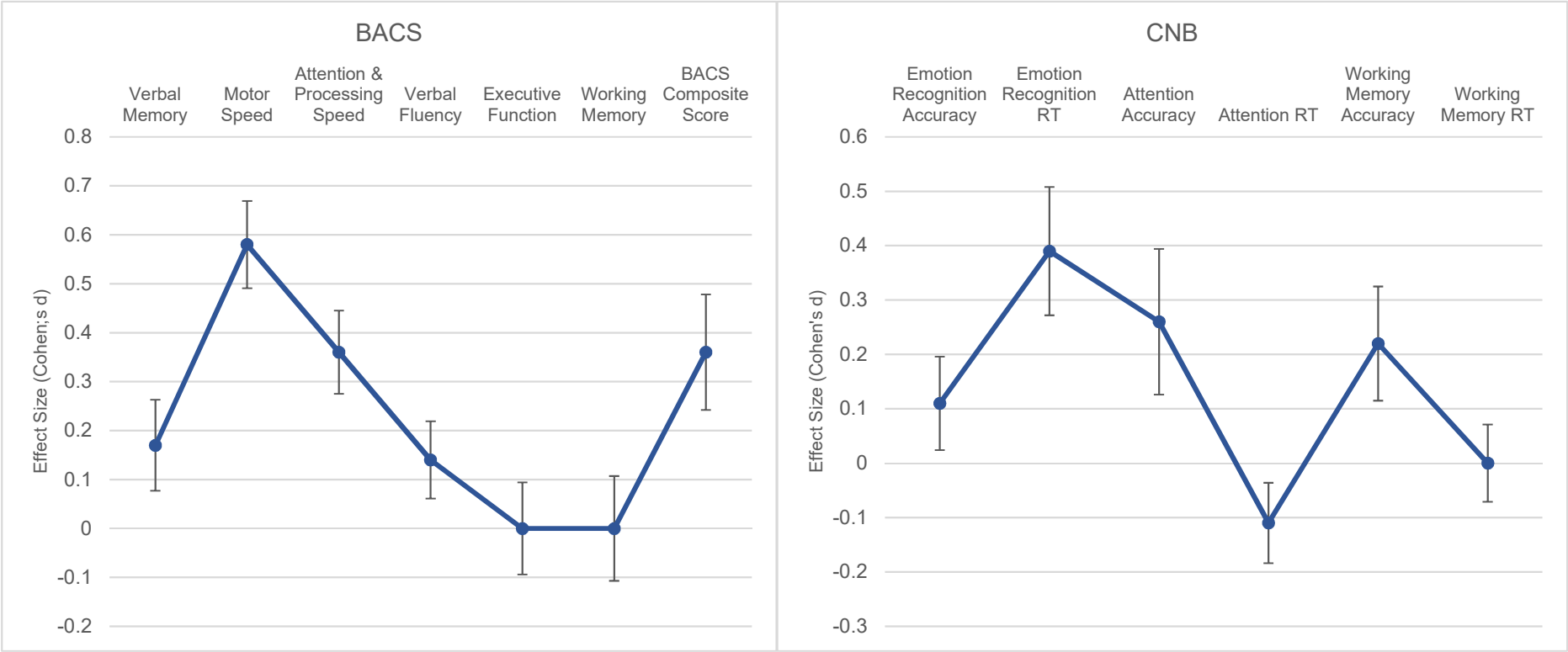

Figure 2. Effect sizes for BACS and CNB domains, as measured by Cohen's d, between CHRs and HCs at baseline: classified as small (0.2), medium (0.5) and large (0.8). Error bars indicate standard errors of the mean. Positive values indicate worse performance while negative values indicate better performance compared to HCs.

When comparing CHR individuals to HCs, a medium effect size was found for motor speed (d = 0.58).

All BACS and CNB cognitive domains, except BACS composite, were entered into stepwise multiple linear regressions in order to assess the relationship between cognitive performance, clinical symptoms and functioning at baseline in the CHR group (Table 6).

Table 6

Linear Regression for the Effects of Cognitive Performance on Clinical Symptoms and Functioning at Baseline in CHR participants

Variable	B	SE	β	R^2	F	p
GAF						
Emotion Recognition RT	-2.10	0.90	-0.17	0.03	5.47	< 0.05
CAARMS-Positive Severity						
Emotion Recognition RT	3.23	0.95	0.25	0.08	7.48	< 0.01
Attention RT	-3.05	1.48	-0.15			
Social Functioning						
Emotion Recognition RT	-0.20	0.05	-0.27	0.14	9.88	< 0.001
Emotion Recognition Accuracy	0.21	0.07	0.20			
Verbal Memory	0.14	0.07	0.15			
Role Functioning						
Emotion Recognition RT	-0.17	0.06	-0.21	0.09	8.55	< 0.001
Attention & Processing Speed	0.16	0.08	0.15			

RT (response time).

Emotion recognition RT significantly predicted global functioning, accounting for 3% of the variance. Emotion recognition RT and attention RT combined to significantly predict CAARMS positive severity scores, accounting for 8% of the variance. Emotion recognition RT also combined with emotion recognition accuracy and verbal memory to significantly predict social functioning, explaining 14% of the variance while emotion recognition RT together with attention and processing speed significantly predicted role functioning, explaining 9% of the variance.

3.2 6-month follow-up.

Baseline demographic, clinical and functional characteristics of CHR individuals with GFO and PFO at 6-month follow-up, HCs and CHR-Ns are summarised in Table 7.

Table 7

Baseline Characteristics of CHR Individuals Grouped by Functional Outcome at 6 Months, HCs and CHR-Ns

Characteristic	**CHRs**		**HCs**	**CHR-N**	**df**	**F/ X^2/H**	**p**		**Post Hoc Contrasts ***
			(n = 55)	**(n = 40)**					
	GFO (n = 34)	**PFO (n = 52)**					**Overall**	**GFO vs PFO**	
Age (years), M ± SD	21.21 ± 3.17	21.42 ± 4.26	22.31 ± 3.39	23.00 ± 4.79	3, 92	F = 1.71	0.171	0.993	
Gender, N female (%)	28 (82)	37 (71)	37 (67)	28 (70)	3	X^2 = 2.50	0.475	0.237	
Years of education, M ± SD	15.32 ± 2.68	15.31 ± 3.50	16.38 ± 2.84	16.35 ± 3.51	3, 177	F = 1.67	0.176	1.000	
UK Citizen, N (%)	20 (59)	36 (69)	26 (47)	18 (45)	3	X^2 = 7.40	0.060	0.361	
GAF, median (range)	68 (21-91)	57 (43-80)	88 (67-97)	69.50 (43-94)	3	H = 109.55	< 0.001	< 0.01	3 vs 1, 2, 4 & 2 vs 1, 4
CAARMS Positive Items, median (range)									
Unusual Thought Content	0 (0-5)	2 (0-5)	0 (0-1)	0 (0-5)	3	H = 41.31	< 0.001	0.744	3 vs 1, 2, 4 & 2, 4
Non-Bizarre Ideas	3 (0-5)	3 (0-6)	0 (0-2)	0 (0-5)	3	H = 80.70	< 0.001	1.000	3, 4 vs 1, 2
Perceptual Abnormalities	3 (0-5)	3 (0-5)	0 (0-3)	0 (0-4)	3	H = 88.04	< 0.001	1.000	3, 4 vs 1, 2
Disorganised Speech	1 (0-4)	0 (0-4)	0 (0-1)	0 (0-3)	3	H = 39.05	< 0.001	1.000	3 vs 1, 2, 4
Total Positive Severity	23.50 (4-72)	28.50 (0-58)	0 (0-12)	5 (0-24)	3	H = 122.13	< 0.001	1.000	3 vs 1, 2, 4 & 4 vs 1, 2
CHR Criteria Subgroup, N (%)					9	X^2 = 186.78	< 0.001	0.254	
UHR	13 (38)	16 (31)	0 (0)	0 (0)					

BS	10 (29)	10 (19)	0 (0)	0 (0)					
UHR/BS	11 (32)	26 (50)	0 (0)	0 (0)					
GF: Social, median (range)	8 (6-10)	7 (5-9)	9 (8-10)	8 (6-9)	3	H = 60.49	< 0.001	< 0.01	2 vs 1, 3, 4 & 3 vs 1, 4
GF: Role, median (range)	8 (6-9)	7 (4-9)	9 (5-9)	8 (5-9)	3	H = 76.90	< 0.001	< 0.001	2 vs 1, 3, 4
Medication, N (%)					15	$X^2 = 54.88$	< 0.001	0.283	
Anti-psychotic	1(3)	0 (0)	0 (0)	1 (3)					
Mood stabiliser	1 (3)	0 (0)	0 (0)	0 (0)					
Anti-depressant	4 (12)	12 (23)	0 (0)	10 (25)					
Other	5 (15)	6 (12)	1 (2)	6 (15)					
Multiple	4 (12)	11 (21)	0 (0)	2 (5)					
Diagnosis, N (%)					3	$X^2 = 99.80$	< 0.001	0.146	
Anxiety disorders	19 (56)	43 (83)	0 (0)	20 (50)					
Mood disorders	15 (44)	34 (65)	0 (0)	13 (33)					
Eating disorders	5 (15)	4 (8)	0 (0)	1 (3)					
Suicide Risk	10 (29)	34 (65)	1 (2)	10 (25)					
Alcohol Dependence/Abuse	11 (32)	17 (33)	2 (4)	10 (25)					
Substance Dependence/Abuse	3 (9)	11 (21)	0 (0)	2 (5)					

Note. Abbreviations: CHR, clinical high-risk; HC, healthy control; CHR-N, clinical high-risk-negative. * 1 = CHRs with GFO, 2 = CHRs with PFO, 3 = HCs, 4 = CHR-Ns.

Of the 86 CHR participants, 52 (60%) had a PFO whereas 34 (40%) had a GFO at 6-month follow-up. Groups did not differ significantly on age, gender, years of education or citizenship.

CHR individuals with PFO exhibited the following significant differences: poorer global functioning compared to those with GFO and CHR-Ns; higher intensity scores on unusual though content than CHR-Ns; and reduced role and social functioning compared to all three groups. CHR

individuals with GFO and PFO had significantly higher intensity scores on two CAARMS-positive items – non-bizarre ideas and perceptual abnormalities – compared to HCs and CHR-Ns as well as significantly higher CAARMS total positive severity than CHR-Ns. HCs had significantly better global functioning as well as lower scores for three CAARMS-positive items - unusual thought content, disorganised speech and total positive severity - than all other groups. They also displayed significantly better social functioning compared to CHR individuals with GFO and CHR-Ns.

Significant differences between groups were also found for CHR criteria subgroup met, medication use and MINI diagnoses. However, these significant differences disappeared when solely comparing CHR individuals with GFO and PFO.

Changes in functioning over the 6- and 12-month follow-up period were explored using three measures – GAF, GF: Role and GF: Social – for CHR individuals with GFO and PFO at 6-months (Table 8). Only CHR participants who had been retested twice since baseline - first at 6 months and then again at 12 months - were included in the analysis.

Table 8

Changes in Functioning for CHR Groups with GFO and PFO at 6 Months

	Baseline		**6 Months**		**12 Months**		**Baseline vs 6 months**		**Baseline vs 12 Months**	
	Median	**Range**	**Median**	**Range**	**Median**	**Range**	**Z**	**p**	**Z**	**p**
GFO Group (N = 26)										
GAF	68	40-91	70.50	67-94	78	47-88	-1.77	0.077	-1.94	0.053
GF: Role	8	6-9	8	7-9	8	5-9	-0.29	0.771	-0.49	0.623
GF: Social	8	6-10	8	6-9	8	6-9	-0.39	0.695	-0.74	0.463
PFO Group (N = 37)										
GAF	58	43-80	58	21-64	58	21-80	-1.52	0.128	-0.34	0.735
GF: Role	7	4-9	8	2-9	8	4-9	-1.05	0.294	-1.12	0.263
GF: Social	7	6-9	7	5-9	8	5-10	-1.39	0.165	-0.10	0.919

CHR individuals with GFO and PFO at 6 months showed relatively stable global, role and social functioning between baseline and both 6- and 12-months. Notably, in the GFO group, global functioning improvements approached significance between both baseline and 6 months ($Z = -1.77$, $p = 0.077$) and baseline and 12 months ($Z = -1.94$, $p = 0.053$).

Table 9 displays the baseline neurocognitive and social cognitive performance for CHR individuals with GFO and PFO at 6-month follow-up, CHR-Ns and HCs. Due to incorrect task performance, one CHR participant was removed from the CNB working memory analyses while two CHR-N participants and two CHRs with PFO were removed from the CNB attention analyses.

Table 9

Baseline Cognitive Performance of CHR Individuals Grouped by Functional Outcome at 6 Months, HCs and CHR-Ns

Domain	CHR				HCs (n = 55)		CHR-N (n = 40)		df	F	p	Post Hoc Contrasts *	GFO vs PFO	
	GFO (n= 34)		PFO (n = 52)											
	M	SD	M	SD	M	SD	M	SD					p	Cohen's d
BACS														
Verbal Memory	0.21	1.12	-0.40	1.12	0	1	0.20	1.08	3, 177	3.33	< 0.05		0.064	0.54
Motor Speed	-0.53	1.10	-1.05	1.20	0	1	-0.43	0.93	3, 177	9.02	< 0.001	2 vs 3, 4	0.153	0.44
Attention & Processing Speed	0.13	1.13	-0.85	1.01	0	1	0	1.23	3, 177	8.47	< 0.001	2 vs 1, 3, 4	< 0.001	0.92
Verbal Fluency	-0.05	0.91	-0.30	0.91	0	1	-0.22	0.87	3, 177	1.14	0.336		0.772	0.28
Executive Function	0.30	0.95	-0.17	1.20	0	1	-0.06	1.20	3, 177	1.32	0.271		0.275	0.42
Working Memory	0.45	1.42	-0.51	1.41	0	1	0.19	1.15	3, 177	4.79	< 0.01	2 vs 1, 4	< 0.01	0.68
BACS Composite Score	0.17	1.51	-1.20	1.43	0	1	-0.12	1.34	3, 177	10.89	< 0.001	2 vs 1, 3, 4	< 0.001	0.92
CNB														
Emotion Recognition Accuracy	0.21	0.90	-0.27	1.09	0	1	-0.15	0.94	3, 177	1.74	0.161		0.175	0.46
Emotion Recognition RT	0.44	1.56	0.79	1.85	0	1	0.23	1.40	3, 87	2.69	0.051	2 vs 3	0.781	0.20
Attention Accuracy	-0.23	1.48	-0.51	1.36	0	1	0.12	1.11	3, 173	2.34	0.075		0.885	0.20
Attention RT	-0.13	0.76	0.01	1.00	0	1	-0.31	1.04	3, 173	1.00	0.393		0.986	0.16
Working Memory Accuracy	-0.09	1.47	-0.48	1.49	0	1	-0.29	1.29	3, 176	1.35	0.260		0.689	0.26
Working Memory RT	-0.11	0.69	0	0.81	0	1	-0.15	1.04	3, 176	0.31	0.818		0.994	0.14

Note. RT (response time). Effect sizes between CHR GFO and PFO groups, measured by Cohen's d, are classified as small (0.2), medium (0.5) and large (0.8).

* 1 = CHRs with GFO, 2 = CHRs with PFO, 3 = HCs, 4 = CHR-Ns

Significant group differences were demonstrated for verbal memory ($F(3, 177) = 3.33$, $p > 0.05$), motor speed ($F(3, 177) = 9.02$, $p < 0.001$), attention and processing speed ($F(3, 177) = 8.47$, $p < 0.001$), working memory ($F(3, 177) = 4.79$, $p < 0.01$) and BACS composite score ($F(3, 177) = 10.89$, $p < 0.001$), while a trend was observed for emotion recognition RT ($F(3, 87) = 2.69$, $p = 0.051$).

Specifically, CHR individuals with PFO showed the following significant differences: reduced attention and processing speed and BACS composite score compared to the other three groups; slower motor speed compared to HCs and CHR-Ns; increased emotion recognition RTs compared to HCs; and poorer working memory when compared to CHR individuals with GFO and CHR-Ns. No significant post hoc differences were observed for verbal memory although the difference between CHR individuals with PFO and both CHR-Ns ($p = 0.052$) and CHR individuals with GFO ($p = 0.064$) approached significance.

Effect sizes (Cohen's d) between CHR GFO and PFO groups for each cognitive domain are illustrated in Figure 3.

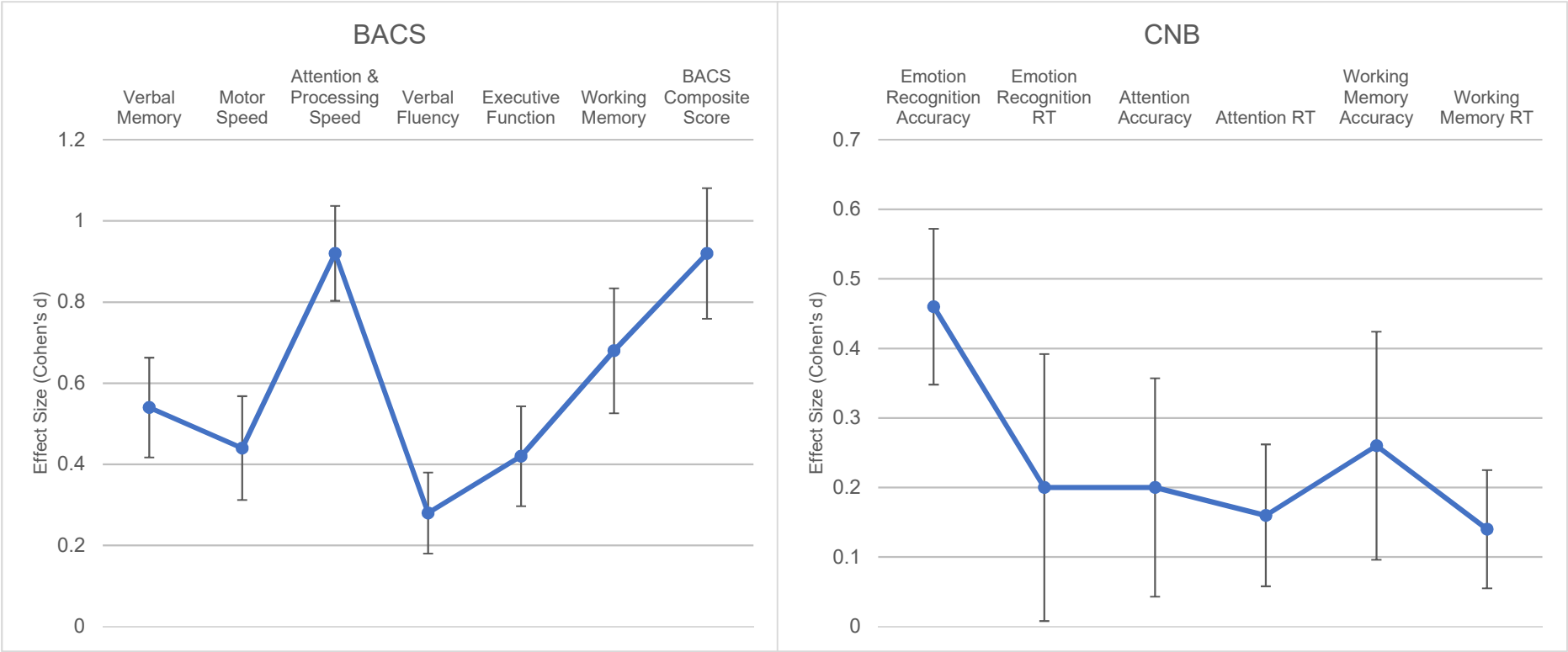

Figure 3. Effect sizes for BACS and CNB domains, as measured by Cohen's d, between CHRs with GFO and PFO at 6 months: classified as small (0.2), medium (0.5) and large (0.8). Error bars indicate standard errors of the mean. Positive values indicate worse performance while negative values indicate better performance compared to CHRs with GFO.

When comparing CHR individuals with PFO and GFO, large effect sizes were found for attention and processing speed (d = 0.92) and BACS composite score (d = 0.92) while medium to large effect sizes were found for working memory (d = 0.68) and verbal memory (d = 0.54).

Clinical, functional and cognitive variables were then tested individually with univariable logistic regressions to examine possible baseline predictors of CHR functional outcome at 6 months (Table 10). To avoid redundancy, CAARMS total positive severity was included instead of single CAARMS positive items and BACS composite was omitted.

Table 10

Univariable Logistic Regression Analyses for Prediction of 6-Month Functional Outcome

Variable	B	SE	Wald	p	OR (95% CI)
Clinical					
CAARMS Total Positive Severity	0.016	0.014	1.337	0.248	1.016 (0.989-1.044)
Functional					
GAF	-0.097	0.026	14.005	< 0.001	0.908 (0.863-0.955)
GF: Role	-1.409	0.348	16.417	< 0.001	0.244 (0.124-0.483)
GF: Social	-0.980	0.286	11.736	< 0.01	0.375 (0.214-0.657)
BACS					
Verbal Memory	-0.508	0.216	5.526	< 0.05	0.602 (0.394-0.919)
Motor Speed	-0.403	0.206	3.821	0.051	0.669 (0.447-1.001)
Attention & Processing Speed	-0.935	0.270	11.994	< 0.01	0.392 (0.231-0.666)
Verbal Fluency	-0.313	0.250	1.562	0.211	0.731 (0.448-1.194)
Executive Function	-0.407	0.220	3.424	0.064	0.666 (0.433-1.024)
Working Memory	-0.528	0.185	8.136	< 0.01	0.590 (0.410-0.848)
CNB					
Emotion Recognition Accuracy	-0.518	0.257	4.079	< 0.05	0.595 (0.360-0.985)
Emotion Recognition RT	0.123	0.135	0.829	0.363	1.131 (0.868-1.474)
Attention Accuracy	-0.149	0.166	0.812	0.367	0.861 (0.622-1.092)
Attention RT	0.177	0.250	0.500	0.480	1.193 (0.731-1.948)
Working Memory Accuracy	-0.207	0.178	1.352	0.245	0.813 (0.574-1.152)
Working Memory RT	0.198	0.298	0.440	0.507	1.219 (0.679-2.186)

Note. RT (response time). Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval

Functional variables that reached a significance level of $p < 0.10$ included global functioning (OR = 0.908, 95% CI = 0.863-0.955, $p < 0.001$); role functioning (OR = 0.244, 95% CI = 0.124-0.483, $p < 0.001$); and social functioning (OR = 0.375, 95% CI = 0.214-0.657, $p < 0.01$).

Cognitive variables that reached a significance level of $p < 0.10$ included verbal memory (OR = 0.602, 95% CI = 0.394-0.919, $p < 0.05$); motor speed (OR = 0.669, 95% CI =

0.447-1.001, p = 0.051); attention and processing speed (OR = 0.392, 95% CI = 0.231-0.666, p < 0.01); executive function (OR = 0.666, 95% CI = 0.433-1.024, p = 0.064); working memory (OR = 0.590, 95% CI = 0.410-0.848, p < 0.01); and emotion recognition accuracy (OR = 0.595, 95% CI = 0.360-0.985. p < 0.05).

Two multivariable logistic regressions using stepwise backward selection (likelihood ratio) were used to determine whether these variables could successfully predict 6-month functional outcome for CHR individuals (Table 11). Cognitive variables that reached a significance level of $p < 0.10$ in univariable analyses were entered in the first model. In the second model, cognitive variables included in the first model were entered alongside clinical and functional variables that reached a significance level of $p < 0.10$ in univariable analyses. No sources of multicollinearity were identified among potential predictor variables (tolerance: 0.634 to 0.789, VIF: 1.268 to 1.578).

Table 11

Multivariable Logistic Regression Models for Prediction of 6-Month Functional Outcome

Variable	B	SE	Wald	p	OR (95% CI)	AUC (SE) [95% CI]	R^2_N	Sensitivity	Specificity
Model 1 – Cognition									
Emotion Recognition Accuracy	-0.589	0.329	3.119	0.074	0.555 (0.291-1.058)	0.816 (0.048) [0.722-0.910]	0.363	82.7	58.8
Attention & Processing Speed	-0.769	0.274	7.885	< 0.01	0.463 (0.271-0.793)				
Working Memory	-0.541	0.207	6.817	< 0.01	0.582 (0.388-0.874)				
Model 2 – Combined									
Attention & Processing Speed	-1.289	0.442	8.490	< 0.01	0.276 (0.116-0.656)	0.911 (0.032) [0.849-0.973]	0.623	0.904	0.765
Working Memory	-0.462	0.229	4.092	< 0.05	0.630 (0.402-0.986)				
GAF	-0.103	0.034	9.388	< 0.01	0.902 (0.845-0.964)				
GF: Role	-1.178	0.431	7.454	< 0.01	0.308 (0.132-0.717)				

Note. AUC values are classified as acceptable (0.7), good (0.8) and excellent (0.9). Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval; AUC, area under the curve; R^2_N, Nagelkerke pseudo R^2 statistic

Model 1 accounted for 36.3% of the variance in CHR participants' 6-month functional outcome ($R^2_N = 0.363$). Baseline attention and processing speed (OR = 0.463, 95% CI = 0.271-0.793, p < 0.01) and working memory (OR = 0.582, 95% CI = 0.388-0.874, p < 0.01) were significant predictors of 6-month functional outcome for CHR individuals while emotion recognition accuracy (OR = 0.555, 95% CI = 0.291-1.058, p = 0.074) did not contribute significantly to the model.

Model 2 accounted for 62.3% of the variance in CHR participants' 6-month functional outcome ($R^2_N = 0.623$). Baseline attention and processing (OR = 0.276, 95% CI = 0.116-0.656, p < 0.01); working memory (OR = 0.630, 95% CI = 0.402-0.986, p < 0.05); global functioning (OR =

0.902, 95% CI = 0.845-0.964, p < 0.01); and role functioning (OR = 0.308, 95% CI = 0.132-0.717, p < 0.01) were significant predictors of 6-month functional outcome for CHR individuals.

The receiver-operating characteristic (ROC) curves for these models are shown below (Figure 4).

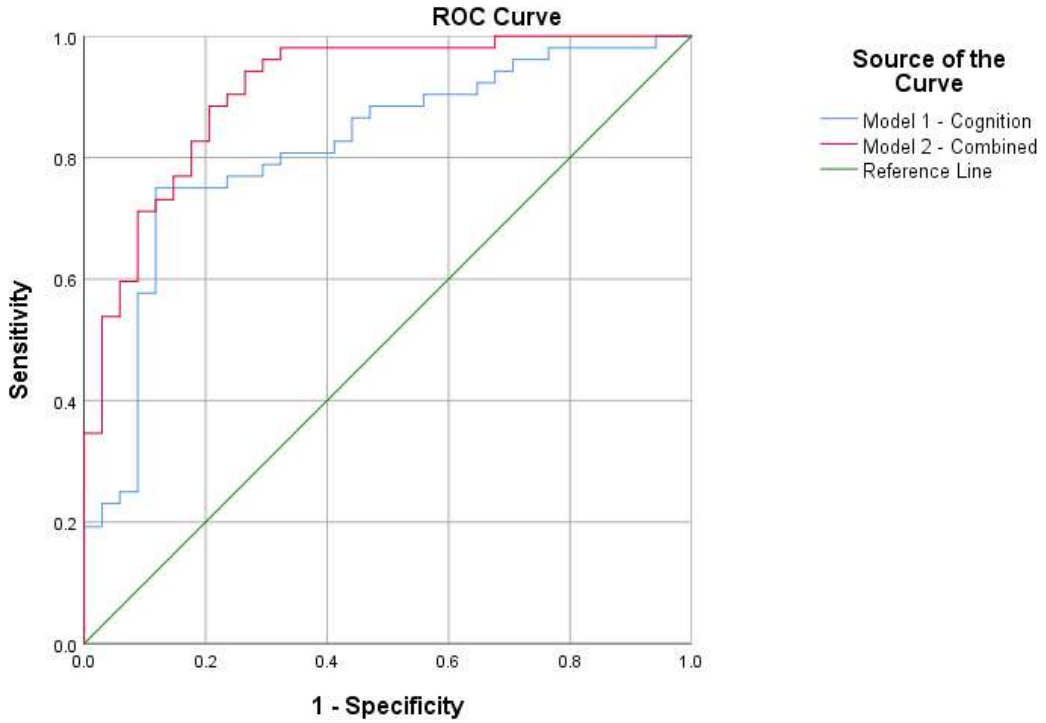

Figure 4. Receiver-operating characteristic (ROC) curves for the multivariable logistic regression models predicting 6-month functional outcome

The area under the curve for model 1 was 0.816 (95% CI = 0.722-0.910, p < 0.001), indicating a good discriminative ability, with a sensitivity of 82.7% and specificity of 58.8%. The area under the curve for model 2 was 0.911 (95% CI = 0.849-0.973, p < 0.001), indicating an excellent discriminative ability, with a sensitivity of 90.4% and specificity of 76.5%.

3.3 12-month follow-up.

Baseline demographic, clinical and functional characteristics of CHR individuals with GFO and PFO at 12-month follow-up, HCs and CHR-Ns are summarised in Table 12.

Table 12

Baseline Characteristics of CHR Individuals Grouped by Functional Outcome at 12 months, HCs and CHR-Ns

Characteristic	**CHRs**		**HCs**	**CHR-Ns**	**df**	**F/ X^2/H**	**p**		**Post Hoc Contrasts ***
			(n = 55)	**(n = 40)**					
	GFO	**PFO**					**Overall**	**GFO vs**	
	(n = 34)	**(n = 35)**						**PFO**	
Age (years), M ± SD	22.15 ± 3.74	21.97 ± 5.07	22.31 ± 3.39	23.00 ± 4.79	3, 79	F = 0.34	0.796	0.998	
Gender, N female (%)	26 (76)	27 (77)	37 (67)	28 (70)	3	X^2 = 1.48	0.686	0.947	
Years of education, M ± SD	16.03 ± 3.34	15.54 ± 3.91	16.38 ± 2.84	16.35 ± 3.51	3, 160	F = 0.53	0.665	0.991	
UK Citizen, N (%)	20 (59)	25 (71)	26 (47)	18 (45)	3	X^2 = 6.91	0.075	0.272	
GAF, median (range)	63.50 (40-91)	56 (40-80)	88 (67-97)	69.50 (43-94)	3	H = 94.57	< 0.001	0.122	3 vs 1, 2, 4 & 2 vs 4
CAARMS Positive Items, median (range)									
Unusual Thought Content	0 (0-5)	2 (0-5)	0 (0-1)	0 (0-5)	3	H = 43.84	< 0.001	< 0.05	3 vs 1, 2, 4 & 2 vs 1, 4
Non-Bizarre Ideas	3 (0-5)	3 (0-6)	0 (0-2)	0 (0-5)	3	H = 83.20	< 0.001	1.000	3, 4 vs 1, 2
Perceptual Abnormalities	3 (0-5)	3 (0-6)	0 (0-3)	0 (0-4)	3	H = 87.50	< 0.001	1.000	3, 4 vs 1, 2
Disorganised Speech	0 (0-4)	2 (0-4)	0 (0-1)	0 (0-3)	3	H = 46.15	< 0.001	0.435	3 vs 1, 2, 4 & 2 vs 4
Total Positive Severity	21 (4-72)	37 (9-66)	0 (0-12)	5 (0-24)	3	H = 123.18	< 0.001	0.790	3 vs 1, 2, 4 & 4 vs 1, 2
CHR Criteria Subgroup, N (%)					9	X^2 = 188.97	< 0.001	< 0.01	
UHR	12 (35)	13 (37)	0 (0)	0 (0)					

BS	12 (35)	2 (6)	0 (0)	0 (0)					
UHR/BS	10 (29)	20 (57)	0 (0)	0 (0)					
GF: Social, median (range)	8 (6-10)	7 (5-9)	9 (8-10)	8 (6-9)	3	H = 59.14	< 0.001	0.377	3 vs 1, 2, 4 & 2 vs 4
GF: Role, median (range)	8 (6-9)	7 (4-9)	9 (5-9)	8 (5-9)	3	H = 38.01	< 0.001	0.081	3 vs 1, 2 & 2 vs 4
Medication, N (%)					15	$X^2 = 59.24$	< 0.001	0.661	
Anti-psychotic	0 (0)	0 (0)	0 (0)	1 (3)					
Mood stabiliser	1 (3)	0 (0)	0 (0)	0 (0)					
Anti-depressant	5 (15)	7 (20)	0 (0)	10 (25)					
Other	5 (15)	5 (14)	1 (2)	6 (15)					
Multiple	4 (12)	7 (20)	0 (0)	2 (5)					
Diagnosis, N (%)					3	$X^2 = 90.25$	< 0.001	0.720	
Anxiety disorders	21 (62)	27 (77)	0 (0)	20 (50)					
Mood disorders	18 (53)	19 (56)	0 (0)	13 (33)					
Eating disorders	3 (9)	4 (12)	0 (0)	1 (3)					
Suicide Risk	13 (38)	20 (59)	1 (2)	10 (25)					
Alcohol Dependence/Abuse	8 (24)	10 (29)	2 (4)	10 (25)					
Substance Dependence/Abuse	4 (12)	3 (9)	0 (0)	2 (5)					

Note. Abbreviations: CHR, clinical high-risk; HC, healthy control; CHR-N, clinical high-risk-negative. * 1 = CHRs with GFO, 2 = CHRs with PFO, 3 = HCs, 4 = CHR-Ns.

Of the 69 CHR participants, 35 (51%) had a PFO whereas 34 (49%) had a GFO at 12-months follow-up. Groups did not differ significantly on age, gender, years of education or citizenship.

Intensity scores on unusual thought content were significantly poorer for CHR individuals with PFO, versus GFO. CHR individuals with PFO had significantly lower global, role and social functioning as well as higher intensity scores on unusual thought content and disorganised speech

- compared to CHR-Ns. CHR individuals with GFO and PFO also displayed significantly poorer role functioning relative to HCs; significantly higher CAARMS total positive severity scores compared to CHR-Ns; and significantly higher intensity scores on two CAARMS-positive items – non-bizarre ideas and perceptual abnormalities – compared to both HCs and CHR-Ns. HCs had significantly better global and social functioning as well as lower intensity scores on three CAARMS positive items – unusual thought content, disorganised speech and total positive severity - than all other groups.

Significant differences between groups were also found for CHR criteria subgroup met, medication use and MINI diagnoses. When solely comparing CHR individuals with GFO and PFO, these significant differences disappeared for medication use and MINI diagnoses but remained for CHR criteria subgroup met. Indeed, CHR individuals with PFO were more likely to meet UHR/BS criteria and less likely to meet BS criteria alone than CHR individuals with GFO.

Changes in functioning over the 6- and 12-month follow-up period were explored using three measures – GAF, GF: Role and GF: Social – for CHR individuals with GFO and PFO at 12 months (Table 13). Only CHR participants who had been retested twice since baseline - first at 6 months and then again at 12 months - were included in the analysis.

Table 13

Changes in Functioning for CHR Groups with GFO and PFO at 12 Months

	Baseline		**6 Months**		**12 Months**		**Baseline vs 6 months**		**Baseline vs 12 Months**	
	Median	**Range**	**Median**	**Range**	**Median**	**Range**	**Z**	**p**	**Z**	**p**
GFO Group (N = 31)										
GAF	63	40-91	68	53-94	78	67-88	-2.00	< 0.05	-4.01	< 0.001
GF: Role	8	6-9	8	7-9	8	6-9	-0.55	0.581	-0.17	0.868
GF: Social	8	6-10	8	6-9	8	6-10	-0.17	0.864	-2.17	< 0.05
PFO Group (N = 32)										
GAF	57	43-80	58	21-81	51	21-64	-1.54	0.124	-3.38	< 0.01
GF: Role	7	4-9	8	2-9	8	4-9	-0.38	0.702	-0.77	0.439
GF: Social	7.50	6-9	7	5-9	7	5-9	-1.81	0.070	-1.06	0.291

CHR individuals with GFO and PFO group displayed relatively stable role and social functioning between baseline and both 6- and 12-months. In the GFO group, global functioning improved between baseline and 6 months (Z = -2.00, p < 0.05) while global functioning (Z = -4.01, p = < 0.001) and social functioning (Z = -2.17, p = < 0.05) improved between baseline and 12 months. In the PFO group, global functioning worsened between baseline and 12 months *(*Z = -3.38, p = < 0.01), while declines in social functioning between baseline and 6 months approached significance (Z = -1.81, p = 0.070).

Table 14 displays the baseline neurocognitive and social cognitive performance for CHR individuals with GFO and PFO at 12-month follow-up, CHR-Ns and HCs. Due to incorrect task performance, one CHR participant was removed from the CNB working memory analyses while two CHR-N participants and two CHRs with PFO were removed from the CNB attention analyses.

Table 14

Baseline Cognitive Performance of CHR Individuals Grouped by Functional Outcome at 12 Months, HCs and CHR-Ns

Domain	CHR				HCs (n = 55)		CHR-N (n = 39)		df	F	p	Post Hoc Contrasts *	GFO vs PFO	
	GFO (n= 34)		PFO (n = 35)											
	M	SD	M	SD	M	SD	M	SD					p	Cohen's d
BACS														
Verbal Memory	0	1.21	-0.12	1.23	0	1	0.20	1.08	3, 160	0.53	0.661		0.999	0.09
Motor Speed	-0.79	1.07	-1.11	1.12	0	1	-0.43	0.93	3, 160	9.81	< 0.001	3 vs 1, 2 & 2 vs 4	0.717	0.30
Attention & Processing Speed	-0.18	1.27	-0.69	1.13	0	1	0	1.23	3, 160	3.11	< 0.05	2 vs 3	0.342	0.43
Verbal Fluency	-0.10	0.75	-0.29	0.99	0	1	-0.22	0.87	3, 160	0.85	0.469		0.949	0.22
Executive Function	0.07	1.53	-0.18	0.97	0	1	-0.06	1.20	3, 160	0.24	0.870		0.965	0.18
Working Memory	-0.14	1.35	-0.10	1.65	0	1	0.19	1.15	3, 160	0.52	0.670		1.000	0
BACS Composite Score	-0.44	1.65	-0.92	1.72	0	1	-0.12	1.34	3, 76	3.15	< 0.05	2 vs 3	0.647	0.29
CNB														
Emotion Recognition Accuracy	0.10	0.98	-0.10	0.95	0	1	-0.15	0.94	3, 160	0.47	0.705		0.955	0.20
Emotion Recognition RT	0.41	1.41	1.04	1.87	0	1	0.23	1.40	3, 77	3.28	< 0.05	2 vs 3	0.395	0.39
Attention Accuracy	0.07	1.16	-0.78	1.45	0	1	0.12	1.11	3, 156	4.49	< 0.01	2 vs 1, 3, 4	< 0.05	0.65
Attention RT	-0.08	0.80	-0.13	0.95	0	1	-0.31	1.04	3, 156	0.80	0.494		1.000	0.06
Working Memory Accuracy	-0.39	1.64	-0.56	1.61	0	1	-0.29	1.29	3, 159	1.32	0.269		0.997	0.11
Working Memory RT	-0.11	0.75	0.06	0.82	0	1	-0.15	1.04	3, 159	0.40	0.756		0.975	0.21

Note. RT (response time). Effect sizes between CHR GFO and PFO groups, measured by Cohen's d, are classified as small (0.2), medium (0.5) and large (0.8). * 1 = CHRs with GFO, 2 = CHRs with PFO, 3 = HCs, 4 = CHR-Ns

Significant differences were evident between groups for motor speed ($F(3, 160) = 9.81$, $p < 0.001$), attention and processing speed ($F(3, 160) = 3.11$, $p < 0.05$), BACS composite score ($F(3, 76) = 3.15$, $p < 0.05$) emotion recognition RT ($F(3, 77) = 3.28$, $p < 0.05$) and attention accuracy ($F(3, 156) = 4.49$, $p < 0.01$).

CHR individuals with GFO and PFO had significantly slower motor speed compared to HCs. Those with PFO also showed the following significant differences: slower motor speed than CHR-Ns; slower attention and processing speed, poorer BACS composite score and increased emotion recognition RT compared to HCs; and reduced attention accuracy relative to the other three groups.

Effect sizes (Cohen's d) between CHR GFO and PFO groups for each cognitive domain are illustrated in Figure 5.

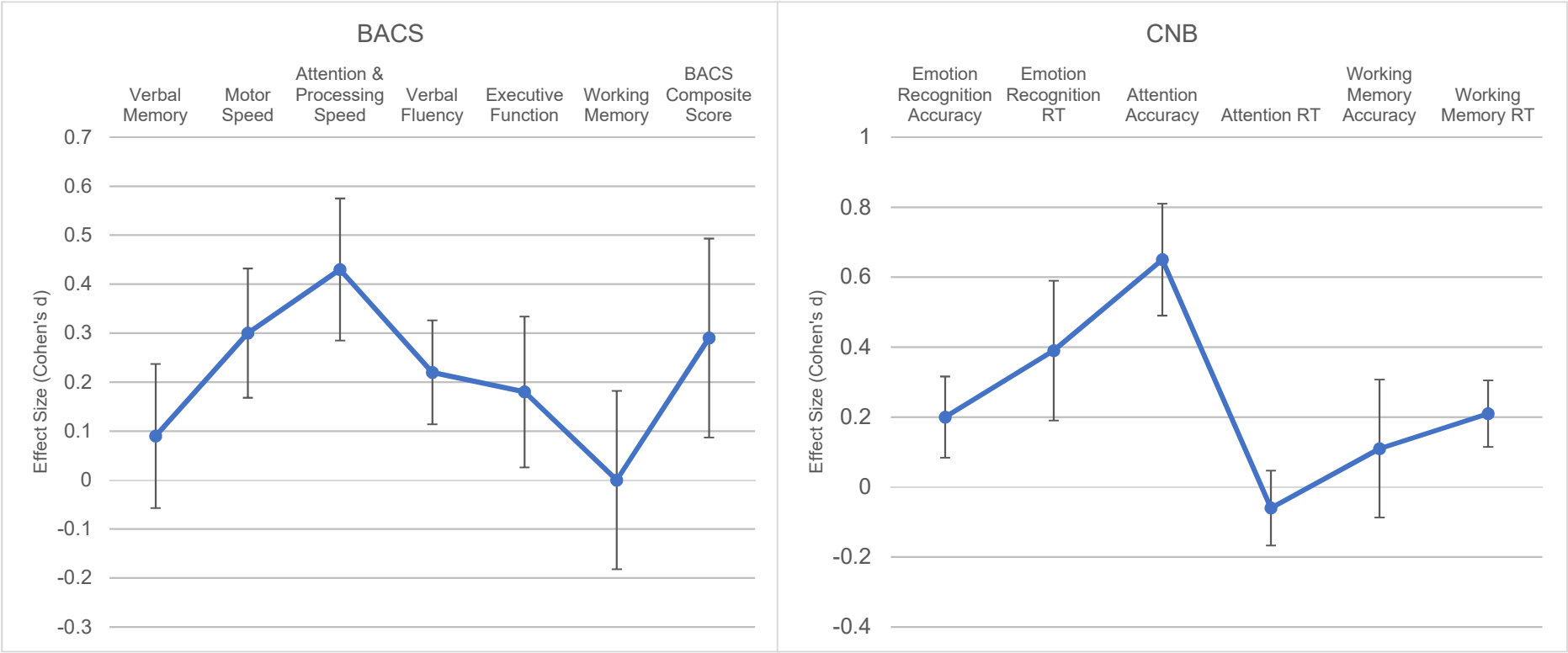

Figure 5. Effect sizes for BACS and CNB domains, as measured by Cohen's d, between CHRs with GFO and PFO at 12 months: classified as small (0.2), medium (0.5) and large (0.8). Error bars indicate standard errors of the mean. Positive values indicate worse performance while negative values indicate better performance compared to CHRs with GFO.

When comparing CHR individuals with PFO and GFO, a medium to large effect size was found for attention accuracy (d = 0.65).

Clinical, functional and cognitive variables were then tested individually with univariable logistic regressions to examine possible baseline predictors of CHR functional outcome at 12 months (Table 15). To avoid redundancy, CAARMS total positive severity was included instead of single CAARMS positive items and BACS composite was omitted.

Table 15

Univariable Logistic Regression Analyses for Prediction of 12-Month Functional Outcome

Variable	B	SE	Wald	p	OR (95% CI)
Clinical					
CAARMS Total Positive Severity	0.043	0.017	6.506	< 0.05	1.044 (1.010-1.080)
Functional					
GAF	-0.076	0.026	8.489	< 0.01	0.927 (0.881-0.975)
GF: Role	0.817	0.290	7.927	< 0.01	0.442 (0.250-0.780)
GF: Social	-0.611	0.276	4.897	< 0.05	0.543 (0.316-0.933)
BACS					
Verbal Memory	-0.079	0.201	0.156	0.693	0.924 (0.623-1.370)
Motor Speed	-0.276	0.228	1.468	0.226	0.759 (0.485-1.186)
Attention & Processing Speed	-0.368	0.218	2.850	0.091	0.692 (0.451-1.061)
Verbal Fluency	-0.255	0.283	0.810	0.368	0.775 (0.445-1.350)
Executive Function	-0.141	0.194	0.524	0.469	0.869 (0.594-1.271)
Working Memory	0.017	0.161	0.012	0.914	1.018 (0.742-1.397)
CNB					
Emotion Recognition Accuracy	-0.219	0.260	0.705	0.401	0.804 (0.483-1.339)
Emotion Recognition RT	0.244	0.160	2.316	0.128	1.276 (0.932-1.746)
Attention Accuracy	-0.531	0.224	5.622	< 0.05	0.588 (0.379-0.912)
Attention RT	-0.068	0.283	0.057	0.811	0.934 (0.536-1.628)
Working Memory Accuracy	-0.064	0.153	0.173	0.678	0.938 (0.695-1.266)
Working Memory RT	0.277	0.318	0.762	0.383	1.319 (0.708-2.459)

Note. RT (response time). Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval

The clinical variable, CAARMS total positive severity, reached a significance level of $p < 0.10$ (OR = 1.044, 95% CI = 1.010-1.080, $p < 0.05$).

Functional variables that reached a significance level of $p < 0.10$ included global functioning (OR = 0.927, 95% CI = 0.881-0.975, $p < 0.01$); role functioning (OR = 0.442, 95% CI = 0.250-0.780, $p < 0.01$); and social functioning (OR = 0.543, 95% CI = 0.316-0.933, $p < 0.05$).

Cognitive variables that reached a significance level of $p < 0.10$ attention and processing speed (OR = 0.692, 95% CI = 0.451-1.061, $p = 0.091$) and attention accuracy (OR = 0.588, 95% CI = 0.379-0.912, $p < 0.05$).

Two multivariable logistic regressions using stepwise backward selection (likelihood ratio) were used to determine whether they these variables could successfully predict 12-month functional outcome for CHR individuals (Table 16). Cognitive variables that reached a significance level of $p < 0.10$ in univariable analyses were entered in the first model. In the second model, cognitive variables included in the first model were entered alongside clinical and functional variables that reached a significance level of $p < 0.10$ in univariable analyses. No sources of multicollinearity were identified among potential predictor variables (tolerance: 0.637 to 0.957, VIF: 1.045 to 1.571).

Table 16

Multivariable Logistic Regression Models for Prediction of 12-Month Functional Outcome

Variable	B	SE	Wald	p	OR (95% CI)	AUC (SE) [95% CI]	R^2_N	Sensitivity	Specificity
Model 1 – Cognition									
Attention Accuracy	-0.531	0.224	5.622	< 0.05	0.588 (0.379-0.912)	0.692 (0.066) [0.563-0.820]	0.131	82.4	51.5
Model 2 – Combined									
Attention Accuracy	-0.634	0.251	6.387	< 0.05	0.531 (0.325-0.867)	0.818 (0.053) [0.713-0.923]	0.351	0.727	0.706
CAARMS Total Positive Severity	0.036	0.021	2.982	0.084	1.036 (0.995-1.079)				
GAF	-0.062	0.031	4.150	< 0.05	0.940 (0.885-0.998)				

Note. AUC values are classified as acceptable (0.7), good (0.8) and excellent (0.9). Abbreviations: SE, standard error; OR, odds ratio; CI, confidence interval; AUC, area under the curve; R^2_N, Nagelkerke pseudo R^2 statistic

Model 1 accounted for 13.1% of the variance in CHR participants' 12-month functional outcome ($R^2_N = 0.131$). Baseline attention accuracy (OR = 0.588, 95% CI = 0.379-0.912, $p < 0.05$) was a significant predictor of 12-month functional outcome for CHR individuals.

Model 2 accounted for 35.1% of the variance in CHR participants' 12-month functional outcome ($R^2_N = 0.351$). Baseline attention accuracy (OR = 0.531, 95% CI = 0.325-0.867, $p < 0.05$) and global functioning (OR = 0.940, 95% CI = 0.885-0.998, $p < 0.05$) were significant predictors of 12-month functional outcome for CHR individuals while CAARMS total positive severity (OR = 1.036, 95% CI = 0.995-1.079, $p = 0.084$) did not contribute significantly to the model.

The ROC curves for these models is shown below (Figure 6).

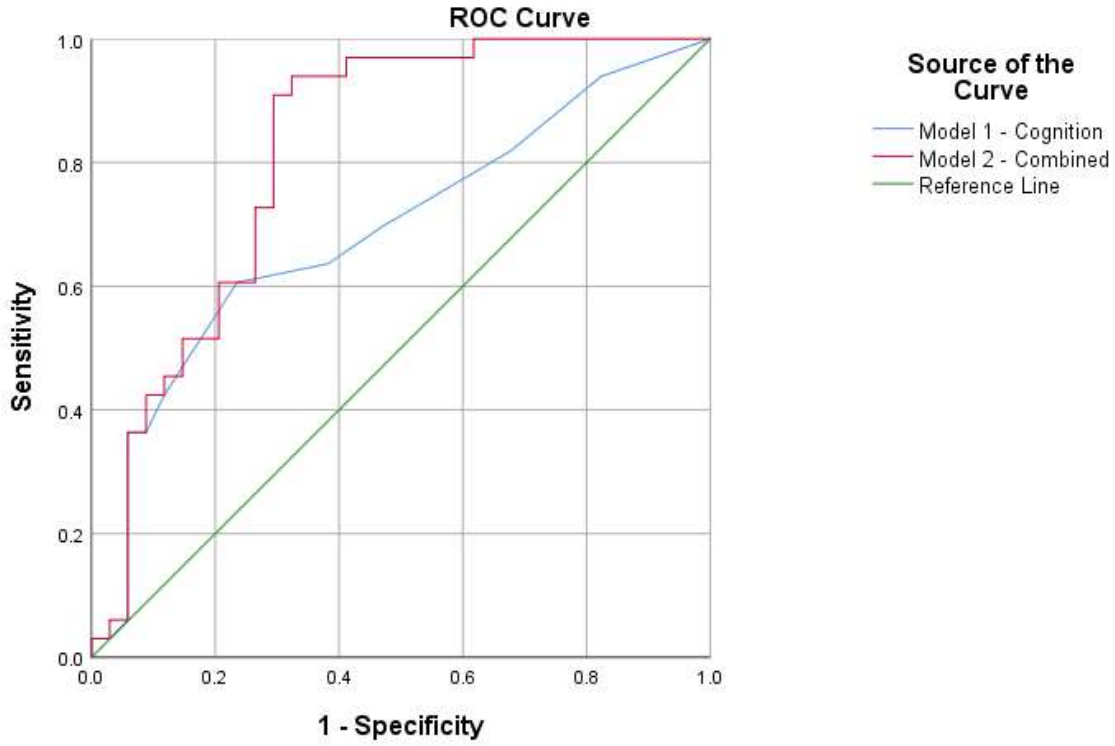

Figure 6. Receiver-operating characteristic (ROC) curve for the multivariable logistic regression model predicting 12-month functional outcome

The area under the curve for model 1 was 0.692 (95% CI = 0.563-0.820, $p < 0.01$), indicating that discriminative ability was nearly acceptable, with a sensitivity of 82.4% and specificity of 51.5%. The area under the curve for model 2 was 0.818 (95% CI = 0.713-0.923, $p < 0.001$), indicating a good discriminative ability, with a sensitivity of 72.7% and specificity of 70.6%.

4.0 Discussion

The present study set out to assess the relationship between cognitive performance, clinical symptoms and functioning at baseline and baseline predictors of functional outcome at 6- and 12-month follow-up in a sample of CHR participants primarily recruited from the general population.

The baseline analyses yielded two main findings. First, functional and cognitive variables discriminated between CHR individuals and HCs at baseline. Second, cognitive performance was related to clinical symptoms and functioning at baseline. Additionally, the 6- and 12-month follow-up analyses yielded four main findings. First, a substantial proportion of CHR individuals had PFO at 6- and 12- months follow-up (60% and 51%, respectively). Second, levels of functioning remained relatively stable for CHR participants over 6- and 12-months. Third, baseline clinical, functional and neurocognitive variables, but not social cognitive variables, discriminated between CHR individuals with GFO and PFO at 6- and/or 12-months. Fourth, a combination of cognitive and functional variables at baseline provided the best prediction of functional outcome at 6- and 12-months.

4.1 Baseline comparison of functioning and cognition.

CHR individuals had significantly poorer global, social and role functioning compared to HCs and CHR-Ns. Similar impairments in global functioning, as measured by the GAF, and social and role functioning, as measured by the GF: Social and GF: Role scales, have been described in help-seeking CHRs, relative to HCs (Allen et al., 2015; Carrión et al., 2011; Schlosser et al., 2012). In comparison to these studies, CHR individuals included in the present investigation displayed considerably better levels of global, social and role functioning, perhaps owing to the large proportion of participants recruited from the general population and attending university in the current sample. Since significant differences were also evident between CHRs and CHR-Ns, these functioning impairments may be exclusively associated with the at-risk state.

In the current study, CHR individuals had slower motor speed, poorer BACS composite scores and increased emotion recognition RTs compared to HCs as well as reduced

attention and processing speed compared to CHR-Ns. The symbol-coding measure of attention and processing speed is, reportedly, the best discriminator of CHRs and schizophrenia participants from HCs (Dickinson et al., 2007; Fusar-Poli et al., 2012b). Kelleher et al. (2013) also reached this conclusion in a CHR sample recruited from the general population. Although CHR participants in the present investigation displayed a similar processing speed deficit, with an associated effect size of d = 0.36, this result did not reach significance. Furthermore, the lack of a significant difference in processing speed when CHR samples are compared to non-CHR psychiatric controls in prior studies raises questions as to the specificity of this deficit, and others, to the at-risk state (Lin et al., 2013). However, in the current study, CHR-individuals did display significant impairments in attention and processing speed, relative to CHR-Ns, implying that this deficit may be specific to the at-risk state, rather than resulting from psychopathological characteristics common to all mental health disorders.

On the other hand, motor speed deficits in heterogeneous CHR samples are reported less frequently with some studies reporting slowed motor speed (Dean & Mittal, 2015; Lencz et al., 2006; Gschwandtner et al., 2006) and others finding no differences (Dean et al., 2017; Giuliano et al., 2012). Interestingly, when comparing CHR individuals with HCs, the largest effect size in this study was obtained for motor speed (d = 0.58). Previous investigations have reported remarkably smaller motor speed effect sizes (Carrion et al., 2011, 2013; Lencz et al., 2006). However, motor system abnormalities in CHR participants are relatively understudied and only recently garnering attention, in contrast to other cognitive domains such as processing speed. Emotion recognition impairments have also been described in CHR samples compared to HCs (Kohler et al., 2014, van Donkersgoed et al., 2015). However, these studies have primarily focused on tests of emotion recognition accuracy rather than emotion recognition RT. One of the few studies investigating emotion recognition RT found no significant differences between CHRs and HCs (Glenthøj et al., 2018), in contrast to results from the current study. Of note, deficits previously detected in verbal memory, verbal fluency, working memory and executive function in CHR individuals, relative to HCs, were not replicated in the current sample (Frommann et al., 2011; Fusar-Poli et al., 2012b). This is potentially a consequence of the recruitment strategy. By primarily targeting individuals from the general population, the current study permitted the investigation of cognitive

deficits earlier than is possible in clinically presenting, help-seeking samples, perhaps before the majority of cognitive deficits emerge.

4.2 Cognitive predictors of clinical symptoms and functioning at baseline.

In agreement with several prior studies, cognitive performance was significantly related to clinical symptoms and functioning at baseline (Carrión et al., 2011; Glenthøj et al., 2016; Niendam et al., 2006). Interestingly, emotion recognition RT, either alone or in combination with other cognitive variables, predicted global, social and role functioning. Notably, emotion recognition accuracy also predicted social functioning. These findings concur with Glenthøj et al. (2016) who reported that the emotion recognition of anger and surprise was associated with social skill performance while the emotion recognition of disgust was associated with role functioning. In contrast, Cotter et al. (2017) did not identify an association between facial emotion recognition and functioning. This is likely a consequence of their extremely small sample size (n = 30) and, therefore, lack of power to detect an association.

Verbal memory also combined with emotion recognition RT and emotion recognition accuracy to predict social functioning. Niendam et al. (2006) similarly demonstrated that deficits in verbal learning and memory were predictive of social functioning at baseline, irrespective of negative or positive symptom severity. On the other hand, attention and processing speed combined with emotion recognition RT to predict role functioning. Partially in line with these findings, Carrión et al. (2011) demonstrated that processing speed could predict 10% and 7% of the variance for social and role functioning, respectively. Notably, attention RT and emotion recognition RT emerged as predictors of CAARMS-positive severity scores. This novel finding suggests that attention RT and emotion recognition RT could potentially aid in the prediction of psychosis transition.

It is important to highlight that, although cognitive variables were important for predicting both clinical symptoms and functioning, the amount of variance accounted for was relatively low. It is plausible to suggest that the inclusion of additional variables, such as negative symptoms, would increase the total amount of explained variance. For example, Glenthøj et al. (2016) found that emotion recognition RT in

combination with negative symptoms best predicted role functioning, accounting for 35.7% of the variance.

4.3 Outcome at 6- and 12-month follow-up.

Consistent with previous findings in help-seeking samples (Addington et al., 2011; Carrión et al., 2013; de Wit et al., 2014), initial CHR categorisation was associated with persistent functional impairment. Nevertheless, fewer CHR participants presented with PFO at 12 months than 6 months, in line with previous findings of functional improvement over time in nonconverters (Addington et al., 2011). At the 6-month follow-up, 60% of the CHR sample had PFO whilst, at the 12-month follow-up, 51% had PFO. Several studies have found similar rates of PFO, from the higher rate of 64% in a 3-5 year study by Carrión et al. (2013) to the lower rates of 46% and 44% in studies spanning 6 years (Brandizzi et al., 2015) and 2 years (Schlosser et al., 2012), respectively. In contrast, even lower rates have been reported by Velthorst et al. (2013) after 3-6 years follow-up (36%) and by Salokangas et al. (2014) after 18-months follow-up (37%).

Moreover, of the 86 CHR individuals included in the 6-month follow-up analyses, five (6%) transitioned to psychosis while three (4%) of the 69 CHR individuals included in the 12-month follow-up analyses transitioned. Therefore, classification of CHR individuals into the PFO group was not entirely dependent on psychosis conversion, suggesting that functional outcome represents a more clinically relevant outcome than transition to psychosis.

4.4 Changes in functioning over time.

Across the study period, functioning levels remained largely stable for CHR participants with the following exceptions at 12-month follow-up: (1) global functioning scores increased between baseline and both 6- and 12-months for those in the GFO group; (2) social functioning improved between baseline and 12 months for those in the GFO group; and (3) global functioning scores worsened between baseline and 12 months for those in the PFO group. Carrión et al. (2013) found modest improvements in functioning for CHR individuals with good role and social outcomes while those with

poor role and social outcomes displayed impairments in functioning that were stable over time. Moreover, previous studies utilising heterogeneous CHR samples have shown that functioning is stable over time (Cornblatt et al., 2012), whereas others have found improvements, particularly in the year following CHR status identification (Addington et al., 2011). Recently, Addington et al. (2018) divided CHR nonconverters into three groups based on 2-year symptom ratings – remission, symptomatic and prodromal progression. Although the groups did not differ at baseline on either role or social functioning nor at 24 months on role functioning, significant improvements in social functioning were evident in the remission group at 24 months. Overall, current results closely concur with the aforementioned studies given that the majority of functioning parameters improved or remained stable over time. In order to characterise the functioning trajectory for CHR individuals with PFO, further research is required as existing findings are scarce and partially contradictory.

4.5 Baseline clinical characteristics and functional outcome.

Generally, CAARMS positive items measured at baseline did not discriminate between CHR individuals with PFO and GFO at 6- and 12-months, in accordance with past investigations (Brandizzi et al., 2015; Koutsouleris et al., 2018). In fact, more severe APS at baseline have been associated with psychosis conversion, rather than role or social functioning over an average follow-up of 3 years (Carrión et al., 2016a). Therefore, although positive symptoms may be distressing and attract attention clinically, they do not strongly associate with functional outcome. That said, one exception existed whereby CHR individuals with PFO at 12 months displayed significantly poorer intensity scores on unusual thought content compared to CHR individuals with GFO. However, this is likely a consequence of the smaller sample size included at 12 months compared to 6 months.

4.6 Baseline functioning and functional outcome.

Global, social and role functioning at baseline significantly discriminated between CHR individuals with GFO and PFO at 6 months. Specifically, the PFO group showed significantly poorer global, social and role functioning at baseline compared with the GFO group. Therefore, early detection and intervention is particularly critical for CHR

individuals with PFO, especially given that social and role skills are consolidated during late adolescence and early adulthood. At 12 months, no such group differences were found, possibly attributable to the smaller number of CHR individuals with PFO studied at this time point.

Supporting results from the present study, Carrión et al. (2013) found that CHR individuals with poor role outcome, versus good role outcome, at follow-up had poorer role functioning at baseline and individuals with poor social outcome, versus good social outcome, at follow-up had poorer social functioning at baseline. Meanwhile, Koutsouleris et al. (2018) reported that CHR participants with impaired functioning at follow-up, regardless of whether this impairment related to social or role outcome, evidenced reduced role and social functioning at baseline, relative to unimpaired CHRs. Since similar results were detected independent of the measure used to define outcome, GAF is purported to be an effective measure of social and role functioning in the current sample. Nevertheless, it should be noted that social and role functioning levels in the current study greatly exceeded those reported by Carrión et al. (2013) and Koutsouleris et al. (2018). This finding may be particularly characteristic of the current sample recruited primarily from the general population and predominantly consisting of university students.

Poorer global functioning scores have not previously been noted in individuals with PFO, relative to GFO, contradicting results from the current investigation (Brandizzi et al., 2015; Carrión et al., 2013; Lin et al., 2011). However, this inconsistency is relatively minor given that global functioning displays a considerable trend towards significance in these studies with p values of 0.06 and 0.08-0.10 reported by Lin et al. (2011) and Carrión et al. (2013), respectively. Compared to the present study, the baseline global functioning scores reported by Carrión et al. (2013) are around 20 and 12 points lower for both the GFO and PFO group, respectively. The GFO group studied by Lin et al. (2011) also possessed lower baseline global functioning scores, specifically by 6-9 points, while the PFO group had similar scores to those found in the current study, only differing by 1-2 points. Therefore, unlike those with GFO, help-seeking individuals with PFO appear relatively similar to individuals with PFO recruited primarily from the general population.

In the current study, individuals at CHR for psychosis, irrespective of functional outcome group at 6- and 12-months, had significantly impaired global, social and role functioning at baseline, compared to HCs, with one exception. That is, no significant differences in baseline role functioning were observed between individuals with GFO at 6 months and HCs, implying that PFOs are predominantly driven by low levels of role functioning. Therefore, role functioning represents an important target for early interventions focusing on vocational and educational rehabilitation. Indeed, vocational rehabilitation appears to be effective in both individuals with chronic schizophrenia (Bio & Gattaz, 2011) and young people with FEP (Killackey et al., 2018).

Interestingly, CHR individuals with PFO, but not those with GFO, had significantly poorer global, social and role functioning at 6- and 12-months compared to CHR-Ns. Therefore, these functioning deficits appear to be specific to the underlying aetiology of PFO in CHR individuals, rather than resulting from psychopathological characteristics common to all mental health disorders. Similarly, albeit in a heterogeneous sample of help-seeking individuals, Addington et al. (2011) found poorer social and role functioning in CHR nonconverters, relative to a nonpsychiatric comparison group. Heinze et al. (2018) also found substantially lower levels of role functioning in heterogeneous, help-seeking CHR individuals compared to a nonpsychiatric comparison group across four time points –baseline and follow-up at 3-, 6- and 12-months. However, no group differences were observed for social functioning.

4.7 Baseline cognition and functional outcome.

Attention and processing speed, working memory and BACS composite score discriminated between CHR individuals with GFO and PFO at 6 months while attention accuracy discriminated between CHR individuals with GFO and PFO at 12 months. Specifically, the PFO group showed significantly lower scores on these neurocognitive domains than the GFO group. Notably, the BACS and CNB both contain tasks measuring attention and working memory. However, at 6 months, only BACS attention and working memory tasks were significant whereas, at 12 months, only the CNB attention accuracy task was significant. This indicates that working memory and attention cannot easily be conceptualised as simple unitary processes. Also, of note,

more cognitive domains reached significance at 6 months than 12 months, perhaps owing to the smaller sample of CHR individuals with PFO tested at the latter time point.

Studies investigating neurocognitive performance in participants with GFO and PFO are scarce. In agreement with the current study, Carrión et al. (2013) found that CHR participants with poor social outcome had significantly impaired processing speed at baseline compared to those with good social outcome; while participants with poor role outcome had significantly impaired sustained attention at baseline compared to those with good role outcome. While Lin et al. (2011) also detected reduced performance on a task measuring attention and processing speed – the Trails A - for individuals with PFO compared to GFO, two other tasks of attention and processing speed – the symbol-coding and digit span – although exhibiting a trend towards significance, did not differ significantly between the groups. Additionally, the present finding of impaired working memory in CHRs with PFO, versus GFO, at 6 months, contrasts with findings by Carrión et al. (2013) although somewhat concurs with previous evidence of differences in brain functional connectivity between remitters and non-remitters during working memory task performance (Liu et al., 2018).

When comparing CHR individuals with PFO and GFO at 6 months, the largest effects sizes were found for attention and processing speed (d = 0.92) and BACS composite score (d = 0.92) while attention accuracy (d = 0.65) yielded the largest effect size when comparing CHR outcome groups at 12 months. Similarly, Lin et al. (2011) found effect sizes ranging between 0.44 and 0.84 when comparing CHR outcome groups on three different tasks of attention and processing speed. However, compared to the current study, a considerably lower effect size was reported for the symbol-coding task (d = 0.53). This disparity may be due to the help-seeking sample, outcome classification method and/or longer follow-up duration used by Lin et al. (2011). It is worth noting that substantially smaller effect sizes were produced for attention accuracy (d = 0.20) and attention and processing speed (d = 0.43) when comparing the CHR outcome groups at 6- and 12-months, respectively. With a larger sample of CHRs with PFO at 12 months, it is plausible that greater effect sizes would be produced for both attention accuracy and attention and processing speed.

Deficits previously detected in verbal memory, verbal fluency, motor speed and executive function in participants with PFO, versus GFO, were not replicated in the current sample (Carrión et al., 2013; Lin et al., 2011). This inconsistent result is possibly attributable to the general population sampling method, sample size and/or follow-up duration in the current study. Furthermore, there were no significant differences between the CHR outcome groups on the emotion recognition measures of social cognition. This result corroborates with Cotter et al. (2017) who concluded that the ToM measure of social cognition might have stronger associations with functioning than emotion recognition, highlighting the need for future studies to include a broad range of social cognitive measures.

Notably, CHR individuals with PFO at 6- and 12-months had significantly reduced motor speed, attention and processing speed and BACS composite score and increased emotion recognition RT at baseline compared to HCs. At 12 months, reductions in attention accuracy were also evident in those with PFO relative to HCs. Interestingly, no significant differences were identified between CHR individuals with GFO at 6 months and HCs while CHR individuals with GFO at 12 months were only impaired relative to HCs on motor speed. This finding implies that the PFO and GFO group comprise separate and distinct groups with differing cognitive profiles. Indeed, Carrión et al. (2013) showed that performance on eight neurocognitive domains, including motor speed, sustained attention and processing speed, was significantly compromised only in those with PFO compared to HCs.

In this study, CHR participants with PFO, but not GFO, at 6 months had significantly poorer motor speed, attention and processing speed, working memory and BACS composite score at baseline than CHR-Ns, suggesting that these deficits are unique to the 6-month poor outcome group. At 12 months, such group differences were only evident in baseline motor speed and attention accuracy. Notably, there were no significant differences in emotion recognition RT between CHR individuals in the PFO group at 6- and 12-months and CHR-Ns. Therefore, this impairment may not be specific to CHR individuals with PFO and, instead, may be associated with general psychopathology and distress which are common in CHR samples.

4.8 Prediction of functional outcome.

In the current CHR sample, PFO at 6 months was significantly predicted by impairments in attention and processing speed, working memory, global functioning and role functioning at baseline whereas reduced attention accuracy and poor global functioning at baseline significantly predicted PFO at 12 months.

Functioning has also been identified as a key predictor of CHR participants' functional outcome in previous studies (Brandizzi et al., 2015; Koutsouleris et al., 2018). Brandizzi et al. (2015) found that baseline global functioning predicted functional outcome at 6-years follow-up whilst Koutsouleris et al. (2018) reported that poor social functioning in the past year and poor social and role functioning over the lifetime, as measured by the GF: Social and GF: Role scales, were the most useful features for a model predicting social functioning. Although CAARMS total scores also predicted functional outcome in the former study, the positive symptoms total subscale alone did not, in line with the current results. Notably, in the latter study, the authors found less pronounced results for models predicting role functioning, implying that structural neuroimaging and functional data alone could not effectively determine role functioning outcome.

Concurring with the present investigation, attention and processing speed and working memory at baseline have previously been found to predict functioning in CHR samples. Specifically, the symbol-coding measure of attention and processing speed has been found to predict functioning at 12 months, even after accounting for baseline symptoms (Meyer et al., 2014; Sawada et al., 2017). This has also been shown cross-sectionally (Carrión et al., 2011; Meyer et al., 2014) with Carrión et al. (2011) demonstrating that processing speed could predict 10% and 7% of the variance for social and role functioning at baseline, respectively. Additionally, Goghari et al. (2014) showed that spatial working memory measures were predictive of global functioning. In contrast to the final prediction models in the current study, verbal learning and memory, typically measured with the CVLT, has also been shown to predict functioning cross-sectionally and at 12 months (Meyer et al., 2014; Niendam et al., 2006). This inconsistency may relate to the verbal memory measure applied. For example, Sumiyoshi et al. (2017) noted that, while the CVLT (comprising four semantic categories) can discriminate between individuals with bipolar disorder and HCs, the BACS List Learning measure cannot. They suggest that individuals with bipolar disorder only have difficulty recalling

words if word lists are semantically organised which, it is reasonable to assume, may also be the case for individuals at CHR for psychosis.

Only two previous studies (Carrión et al., 2013; Lin et al., 2011) have utilised binary logistic regression models to identify clinical, functional and neurocognitive predictors of functional outcome in individuals at CHR for psychosis. Partially in line with the current study, Carrión et al. (2013) found that poor social outcome was predicted by reduced processing speed, poor social functioning and total disorganised symptoms while poor role outcome was predicted by impaired verbal memory, poor role functioning and motor disturbances. Lin et al. (2011), on the other hand, deemed that neurocognitive and clinical variables most effectively predicted PFO. Specifically, PFO was predicted by impaired verbal learning and memory, verbal fluency and attention and processing speed, mostly in combination with higher negative symptoms. Impairments in verbal memory, verbal fluency and motor speed may have lacked predictive value in the current prediction models due to differences in the specific measures applied across studies. Meanwhile, the use of different recruitment strategies between Lin et al. (2011) and the present investigation potentially explains why functioning significantly predicted PFO only in the latter investigation.

The clinical variables that significantly enhanced prediction of functional outcome in the aforementioned studies (Carrión et al., 2013; Lin et al., 2011) were not under investigation in the current study. Only positive symptoms were assessed and, in agreement with Lin et al. (2011), these did not significantly predict PFO. It is plausible to suggest that, in order to enhance prediction models, future studies should include a broader repertoire of clinical measurements. Indeed, the odds of poor social outcome are nearly 5 times greater in participants with a SOPS total disorganisation subscale score more than 4 at baseline (Carrión et al., 2013).

In the present study, higher levels of accuracy, sensitivity, specificity and explained variance were achieved by integrating neurocognitive variables with functional variables. Moreover, the 6-month predictive model performed considerably better than both social and role outcome models in Carrión et al. (2013) while the 12-month predictive model performed slightly better than the role outcome model and slightly worse than the social outcome model. The exceptional performance of the 6-month

predictive model is possibly attributable to the number of functional variables included in the final model. Indeed, two functional variables – global functioning and role functioning - were included, in contrast to the models in Carrión et al. (2013) which both incorporated only one (either social functioning or role functioning). This further explains why the 12-month predictive model, featuring one functional variable (global functioning), is more similar to both Carrión et al. (2013) models in terms of accuracy, sensitivity, specificity and explained variance.

The utility of combining neurocognitive measures with clinical and/or functional variables is further supported by psychosis conversion predictive models. In a risk calculator algorithm for psychosis conversion, T. D. Cannon et al. (2016) found that verbal learning and memory scores and speed of processing scores added modest, yet significant, independent predictive power above the following significant clinical and functional measures: unusual thought content, suspiciousness and social functioning. This individualised risk calculator has been further validated in an independent external dataset (Carrión et al., 2016a). That said, two previous studies concluded that neurocognitive data did not improve predictive power for psychosis conversion beyond multivariate clinical prediction models (Seidman et al., 2010; Ziermans et al., 2014). Overall, however, it is plausible to suggest that the accuracy of models predicting PFO and/or psychosis conversion will be strengthened by the addition of neurocognitive variables.

4.9 Clinical and research implications.

The online screening process utilised in this study provided a novel method of identifying young people with serious mental health problems, highlighting the usefulness of e-mental health applications for early diagnosis and potentially, early intervention. Indeed, such applications provide convenient access with regards to time and location; allow anonymity to counteract stigma; increase cost-effectiveness; and reduce the demand on clinicians. As evidenced in the present study, this approach is especially useful for investigating prodromal syndromes in the general population. Future studies should consider utilising general population samples in order to increase the generalisability of findings and to further explore clinical, functional and cognitive

characteristics in the very early stages of the prodrome; earlier than is possible in clinically presenting, help-seeking cases.

Additionally, the current findings suggest that cognitive impairments negatively impact on multiple domains of real-world functioning. Deficits in attention and processing speed, working memory, attention accuracy and verbal memory, in particular, may hamper efforts to select and maintain conversational topics and/or focus on school- or course-work, household tasks and job responsibilities. Meanwhile, deficits in emotion recognition may result in socially inappropriate responses or ideas of persecution which are detrimental in both social and occupational settings. Early interventions targeting cognition, such as cognitive remediation, could potentially alleviate cognitive deficits and consequently improve functional outcome in clinical and research settings. A recent systematic review of six studies (Glenthøj, Hjorthøj, Kristensen, Davidson, & Nordentoft, 2017) provided preliminary evidence that cognitive remediation in the CHR population could improve cognition in the domains of verbal memory, attention and processing speed and functional outcome in the domains of social functioning and social adjustment. Future research, utilising a more rigorous methodological approach, is required to investigate the effectiveness of cognitive remediation alone and in conjunction with other interventions (e.g., vocational and educational rehabilitation).

Continued refinement of functional outcome prediction models, with the aim of improving levels of accuracy, sensitivity, specificity and explained variance, is essential. This may be achieved by combining current models with neuroimaging, genetic, neurophysiological and neurochemical data. For example, there is recent evidence that functional outcome is predicted by neuregulin 1 (NRG1) gene expression (Jagannath et al., 2018) as well as thalamic glutamate levels and prefrontal-striatal activation (Allen et al., 2015). Furthermore, Koutsouleris et al. (2018) stated that, in uncertain cases, the addition of neuroimaging machine learning to clinical machine learning provides a 1.9-fold prognostic gain for CHR individuals.

Although research, to date, has largely focused on the questionable outcome of "transition", the current results suggest that outcomes other than transition should become the mainstream target for intervention. As well as finding support for the notion of declining transition rates, the present study found that nonconverters, traditionally

viewed as “false positives”, demonstrated impairments in cognition and social and role functioning that would likely benefit from treatment. Specifically, functional outcome appears to represent a more clinically relevant outcome. CHR individuals with GFO may represent a subgroup of false positive cases, suggesting that some refinement of the current CHR criteria is warranted. Certainly, subjecting these individuals to intense interventions may produce unintended consequences such as anxiety, stigma, discrimination and unnecessary treatment. Individuals with PFO, on the other hand, should be offered similar levels of support to those who convert to psychosis in order to help them cope with persistent cognitive as well as social and educational/occupational difficulties.

4.10 Limitations.

With regard to the gender composition of the current sample, a disproportionate number were female. Although the reason for this is not completely clear, it could reflect a greater willingness of female participants to engage in research studies and perhaps increased psychological knowledge and acceptance of mental health issues. If the latter is correct, different strategies must be employed to engage male participants in early intervention.

In terms of the measurement procedure, functional outcome was based on the GAF scale – a measure which has been criticised for confounding symptoms and functioning, possibly leading to low scores even when social and role functioning are relatively spared. However, the GAF is frequently used to measure functioning and, consequently, offers a good and reliable possibility for comparisons with other studies. Separate functional measures that are not conflated with symptom severity, such as the GF: Social and GF: Role scales might increase construct validity. Additionally, negative symptoms, typically presenting many years before positive symptoms, were not thoroughly assessed in the current study although they reportedly play a prominent role in the impaired functioning of individuals at CHR for psychosis (Glenthøj et al., 2016; Salokangas et al., 2014; Schlosser et al., 2012). Indeed, Carrión et al. (2016b) found that longer negative symptom duration predicted poor social functioning. In contrast, neither positive symptom duration nor severity predicted role or social functioning.

Transition rates in the current study are relatively low given that several recent studies have reported rates of 13-20% (T. D. Cannon et al., 2016; Fusar-Poli et al., 2016; Seidman et al., 2016). Morrison et al. (2012) also noted that the prevalence of transition was lower than expected (8%). However, UHR status was defined on the basis of two baseline CAARMS assessments over 2-4 weeks to avoid under-reporting which led to the exclusion of 29 individuals who met CHR criteria at the first baseline visit. The inclusion of these 29 would have produced an overall transition rate of 18%, in line with the aforementioned studies. The low transition rate in the current study is likely reflective of the incomplete follow-up data collection at this time as well as the sampling method, whereby the majority of CHR participants were recruited from the general population. It also prevented further analysis of the characteristics of those who transitioned.

4.11 Conclusions.

The current study provides important new insights with regard to early detection and intervention in individuals at CHR for psychosis primarily recruited from the general population. Given that such a large proportion of CHR individuals presented with PFO at 6- and 12-months follow-up, the at-risk state appears to represent an appropriate intervention target, regardless of eventual conversion to psychosis. At baseline, neurocognitive and social cognitive performance were associated with clinical symptoms and functioning. Furthermore, CHR individuals with PFO, versus GFO, at 6- and 12-months follow-up were lower functioning and more cognitively impaired at baseline. These findings highlight the importance of such factors for detecting false positives as well as the potential benefits of interventions incorporating vocational and educational rehabilitation and cognitive remediation. Informed by the current findings, it is recommended that clinical early detection teams extend their services into the community in order to improve access to specialised interventions. Although replication in larger samples, over longer follow-up periods, is required to determine generalisability, it is clearly essential that clinicians and researchers alike focus on a broader outcome of interest in individuals at CHR for psychosis and not only on preventing transition to psychosis.

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