Neurocognitive Deficits in Participants at Clinical High-Risk for Psychosis: Relationships to Clinical Symptoms and Functioning

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Abstract

Background: Neurocognitive impairments are a core feature of schizophrenia (ScZ) contributing to ongoing psychopathology and poor psychosocial functioning. These deficits have been consistently observed before illness onset in individuals at clinical high risk for psychosis (CHR) suggesting that they may be an endophenotype of the disorder. Traditional CHR studies have recruited exclusively using clinical pathways however, it has been recently reported that the majority of individuals who present with a first episode of psychosis have not been seen by specialised prodromal services suggesting that these studies only capture a subgroup of CHR individuals (Ajnakina et al., 2017). Few studies have included CHR individuals recruited from community pathways who may differ from those recruited clinically in the degree of neurocognitive impairment and clinical trajectory. Neurocognitive functioning in CHR individuals may also be influenced by the high prevalence of comorbid non-psychotic disorders experienced by the population. So far, few studies have addressed this question which may provide valuable information to improve functional and clinical outcome in those at-risk.

Aim 1: To explore the degree of neurocognitive impairment in CHR-participants recruited from the general population and identify their relationship with positive symptom severity and functioning.

Aim 2: To investigate the influence of comorbid non-psychotic disorders on neurocognitive functioning in CHR-participants by identifying the degree of neurocognitive impairment in a CHR-negative group who scored below the CHR threshold but are characterised by non-psychotic disorders

Aim 3: To explore the association between baseline neurocognitive functioning and clinical outcome at 12 months.

Methods: The Youth Mental Health and Resilience Study (You-R) recruited CHR- and CHR-negative participants from the general population using a unique web-based screening tool. At baseline neuropsychological tests together with functioning assessments were administered to healthy controls (N = 57), CHR-negative participants (N = 43), community recruited CHR- (N = 110) and clinically recruited CHR-participants (N = 12). CHR-participants received follow-up

assessments at 3 or 6 month intervals. At the 12 month assessment participants were categorised as remitters (CHR-R; N = 33), non-remitters (CHR-NR; N = 16) or converters (N = 1) depending on the change of their attenuated psychotic symptom status from the baseline to follow-up assessment.

Results 1: Community recruited CHR-participants presented with small to moderate sized impairments in motor speed, processing speed, emotion recognition (response time) and attention by comparison to healthy controls. Within the community recruited CHR group emotion recognition (RT) predicted positive symptom severity while verbal memory, emotion recognition (RT) and the neurocomposite score significantly predicted functioning.

Results 2: CHR-negative participants were not impaired by comparison to HC in any of the neuropsychology tests and they had a statistically significant better performance in processing speed by comparison to the CHR-positive group.

Results 3: Overall, there was a high number of non-transitions and remissions at 12 months. Comparisons of baseline neurocognitive functioning revealed that non-remitters were statistically significantly more impaired in motor speed and emotion recognition (RT) than remitters. Moreover, remitters but not non-remitters performed similarly to healthy controls in a number of neuropsychological tests at baseline.

Conclusions: Community recruited CHR-participants presented with neurocognitive impairments by comparison to healthy controls in domains highlighted by previous research using clinically recruited populations. These impairments were more pronounced in CHR individuals who had ongoing attenuated psychotic symptoms at 12 months compared to those who remitted. However, the high number of non-transitions and remissions questions if this was a group enriched for psychosis risk. Additionally, although the CHR-negative group presented with preserved neurocognitive functioning they had a lower prevalence of comorbid non-psychotic disorders than the CHR-positive group so the influence of comorbid non-psychotic disorders remains largely unknown.

Statement of Candidate's Contribution to the Study

This study was a large project undertaken by a team that included a full-time research assistant, three PhD candidates, three MSc (Res) candidates (including myself) and visiting collaborators under the supervision of Professor Peter Uhlhaas. My role during the study was primarily to conduct and score neurocognitive assessments and support PhD students and visiting collaborators who carried out the clinical assessments. I independently carried out all the data analysis included in the MSc (Res) thesis.

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Table of Contents

List of Tables

List of Figures

List of Abbreviations

APA = American Psychiatric Association

APS = Attenuated Psychotic Symptoms

ARMS = At-Risk Mental States

BACS = Brief Assessment of Cognition

BLIPS = Brief Limited Intermittent Psychotic Symptoms

BS = Basic symptoms

CAARMS = Comprehensive Assessment of At-risk Mental State

CHR = Clinical High Risk

CI = Confidence Intervals

CMHTs = Community Mental Health Teams

COGDIS/COPER = Cognitive Disturbances/Cognitive-Perceptive Basic Symptoms

COWAT = Controlled Oral Word Association Test

CPT = Continuous Performance Task

CVLT = California Verbal Learning Test

DSM-II-R = Diagnostic and Statistical Manual of the American Psychiatric Association – 3rd edition (Revision)

DSM-IV = Diagnostic and Statistical Manual of the American Psychiatric Association - 4th edition

DSM-5 = Diagnostic and Statistical Manual of the American Psychiatric Association - 5th edition

DSST = Digit Symbol Substitution Test

FEP = First Episode of Psychosis

GP = General practitioner

HC = Healthy controls

ICD-10 = International Statistical Classification of Diseases and Related Health Problems - 10th revision

IQ = Intelligence quotient

M = Mean

NART = National Adult Reading Test

NHS = National Health Service

OR = Odds ratio

PCA = 9-item questionnaire of perceptual and cognitive aberrations

PCMHTs = Primary Care Mental Health Teams

Penn CNB = University of Pennsylvania Neurocognitive Battery

PQ-16 = 16-Item Version of the Prodromal Questionnaire

RAVLT = Rey Auditory Verbal Learning Test

SIPS = Structured Interview for Prodromal Syndromes

SOFAS = Social and Occupational Functioning Assessment Scale

SOPS = Scale of Prodromal Symptoms

SPI-A = Schizophrenia Prediction Instrument – Adult Version

TMT = Trail Making Test

ToL = Tower of London

UHR = Ultra-high risk

Chapter 1

Schizophrenia

Schizophrenia (ScZ) is a severe and complex psychotic disorder that is associated with a number of cognitive, behavioural and affective abnormalities. Despite having a relatively low median population prevalence of 3.3 per 1000 (Saha, Chant, Welham & McGrath, 2005) ScZ was ranked in the top 25 leading causes of disability worldwide in 2013 (Vos et al., 2015). Those diagnosed with ScZ have a lower life expectancy contributed to by higher rates of comorbid illnesses such as coronary heart disease, stroke, type II diabetes, respiratory diseases and some cancers (Laursen, Nordentoft & Mortensen, 2014) and unnatural deaths including suicide (Charlson, Baxter, Dua, Degenhardt, Whiteford & Vos, 2015). This comes at a considerable societal and economic cost. A report by the Schizophrenia Commission found that in England this cost amounted to £11.8 billion per year (Andrews, Knapp, McCrone, Parsonage & Trachtenberg, 2012). This is because ScZ is a chronic and long-lasting condition with less than 14% recovering within the first 5 years of their first psychotic episode (Robinson, Woerner, McMeniman, Mendelowitz & Bilder, 2004) and only an additional 16% making a late phase recovery (Harrison et al., 2001). It is also common for individuals to have periods of stability and relapse due to environmental adversity or poor response to treatment (National Collaborating Centre for Mental Health UK, 2014). Although symptomatology and functioning varies considerably between individuals, the effects of the illness are often highly detrimental with only 5% to 15% of people with ScZ being employed (Schizophrenia Commission, 2012).

1.1 Diagnosing Schizophrenia

There are two competing taxonomies of mental disorders; the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM- 5; APA, 2000) and the International Statistical Classification of Diseases and Related Health Problems 10th Edition (ICD-10; WHO, 1992). A summary comparing the criteria required for a ScZ diagnosis for each assessment is reported in Table 1. The imminent release of the 11th edition of the ICD will see notable changes in some criteria with the aim of being more congruous with the DSM-5. However, differences regarding the length of

symptom duration and functional impairment will remain (Tandon et al., 2013) continuing to cause inconsistencies in diagnosis between clinicians

Table 1: DSM-5 and ICD-10 criteria for ScZ

	Required clinical symptoms	Length of symptoms	Functioning	Prodromal phase	Exclusion criteria
DSM-5	*At least two of*: hallucinations, delusions, disorganised speech (eg., frequent derailment or incoherence), grossly disorganised or catatonic behaviour, negative symptoms (i.e., diminished emotional expression or avolition)	More than 6 months	Reduction in premorbid functioning in one (or more) major areas; work, interpersonal relations or self-care	At least 6 months	Drug intoxication or withdrawal, concurrent major depressive or manic episodes, schizoaffective, bipolar or depressive disorder with psychotic features, overt brain disease
ICD-10	*At least one of*: thought echo, thought insertion/withdrawal/broadcast, passivity, delusional perception, third person auditory hallucination, running commentary, persistent bizarre delusions *or two or more of:* persistent hallucinations, thought disorder, catatonic behaviour, negative symptoms, significant behaviour change	More than 1 month	N.A.	N.A.	Drug intoxication or withdrawal, mood disorders, schizoaffective disorder, overt brain disease

1.2 Pathogenesis of Schizophrenia

1.2.1 Neurodegenerative Hypothesis

Kraepelin (1919) coined the label ‘dementia praecox’ after observing that patients had a progressive decline in their behavioural functioning which he attributed to ongoing deterioration of the brain anatomy (Jablensky, 2007). This led to the conceptualisation that ScZ was a neurodegenerative disorder. Some neuroimaging studies report findings of progressive changes in brain structures in those with ScZ (Andreasen, et al., 2011; Van Haren et al., 2008; Olabi, Ellison-

Wright, McIntosh). However, there are many difficulties in differentiating abnormal from normal ageing as numerous factors can alter the structure of the brain such as cannabis abuse (Martín-Santos et al., 2010; Yücel et al., 2008;) and lifestyle factors such as the regularity of exercise (Colcombe et al., 2006; Pajonk et al., 2010) and antipsychotic medications (Ho, Andreasen, Ziebell, Pierson & Magnotta, 2011). Thus, it cannot be determined if psychosis results in an ongoing deterioration of brain structures.

1.2.2 Neurodevelopmental Hypothesis

Although not mutually exclusive, the neurodevelopmental hypothesis of ScZ is seen to be a competing theory of ScZ pathogenesis. It was first proposed by Scottish psychiatrist Thomas Clouston (1891) but was largely dismissed in favour of the neurodegenerative approach until its revival 30 years ago.

Originally, it proposed that ScZ was the result of abnormal development caused by pre- or perinatal complications. Structural brain abnormalities in ventricle size and gyrification patterns observed in those diagnosed with ScZ were proposed to be caused by problems during foetal development like periventricular bleeding or hypoxia (Lewis & Murray, 1987; van Os & Kapur, 2009; Reveley, Clifford, Reveley & Murray, 1982). An insult to early development is supported as individuals with ScZ in adulthood have been found to have speech difficulties, delayed motor development, lower test performances and a solitary play preference during childhood compared to age-matched controls (Jones, Murray, Rodgers & Marmot, 1994). It has been proposed that pre- and perinatal risks alone cannot be used to predict the development of ScZ in adulthood and may indicate a more general susceptibility to future mental illness (Jones et al., 1994). However, some specificity has been reported as neurodevelopmental features and educational attainment were associated with psychosis but not affective or neurotic symptoms, which were found to be better predicted by social factors (Jones et al., 1994; Rodgers, 1990).

Heritability rates of ScZ have been estimated as being around 80% (Cardno & Gottesman, 2000; Sullivan, Kendler & Neale, 2003) suggesting the importance of genetics in the development of the disorder. In line with the neurodevelopmental hypothesis it is proposed that these abnormalities

initiate a cascade of neural events disrupting early brain development leading to the emergence of psychotic symptoms in late adolescence and early adulthood (Birnbaum & Weinberger, 2017; Owen, O'Donovan, Thapar & Craddock, 2011). This has been supported by post-mortem studies that have reported abnormal brain changes mediated by brain gene expression which occur early in development and not at overt illness onset (Hill & Bray, 2012; Tao et al., 2014). Various candidate genes have been associated with the ScZ phenotype (Fatemi & Folsom, 2009) in addition to several large, rare copy number variants (CNVs; Owen, et al., 2011). However, CNVs specific to a severe psychosis phenotype have not been identified (Owen et al., 2011). Moreover, CNVs associated with ScZ overlap with neurodevelopmental disorders like autism, ADHD and learning disabilities suggesting a neurodevelopmental continuum of risk that results in distinct disorders when genetics converge with epigenetic and environmental risk factors (Birnbaum & Weinberger, 2017).

1.2.3 Environmental Risk Factors

A number of environmental risk factors have been identified that influence the development of ScZ. A meta-analysis found that those with psychosis were 2.7 times (95% CI = 1.90-3.88) more likely to have experienced childhood adversity than controls (Varese et al., 2012). This association was found to be related to all types of adversity investigated (abuse, neglect, parental death and bullying) and was dependent upon the extent and number of traumatic experiences. Varese and colleagues (2012) propose that the elimination of childhood adversities that they examined (assuming causality) could reduce the number of individuals diagnosed with psychosis by 33%.

Further support for the impact of adversity comes from research illustrating the high prevalence of ScZ among immigrant populations who face persecution, social exclusion, poverty and social upheaval (Li, Law & Andermann, 2012). It has been observed that school children from a different ethnic background than the majority of students were more at risk of developing a psychotic disorder than their peers (van Nierop et al., 2014). Additionally, psychosis has also been found to be more prevalent in urban populations (van Os, 2004). Zammit and colleagues (2010) suggest that this finding may be explained by the characteristics of the people living in these areas (compositional effects) rather than the places themselves (contextual effects) as there were differences in the frequency of psychosis between smaller neighbourhoods within the same cities.

The authors report that psychosis risk in certain neighbourhoods may be caused by the degree of social fragmentation. Together these findings tie in with the idea that social defeat is a core risk factor for psychosis (Selten & Cantor-Graae, 2005). Specifically, it is proposed that paranoia could develop due to persistent social adversity (Garety, Kuipers, Fowler, Freeman & Bebbington, 2001).

Moreover, cannabis use has been linked to adverse effects on adolescent psychosocial development and mental health. The main component of cannabis, delta-9-tetrahydrocannabinol (THC) elicits temporary psychotic symptoms and impairs cognition in healthy volunteers (Morrison et al., 2009). The use of cannabinoids in adolescence has been found to increase the risk of developing psychosis in adulthood in a dose-related interaction (Radhakrishnan, Wilkinson & D'Souza, 2014), especially when it is of high potency and in synthetic forms (Murray, Quigley, Quattrone, Englund & Di Forti, 2016). It has been reported that individuals with a history of cannabis use in adolescence develop psychosis up to 2.7 years before individuals who do not use cannabis (Donoghue et al., 2014). Another study proposed that 8% to 24% of cases of first episode psychosis could have been prevented without the impact of cannabis (Di Forti et al., 2015).

1.2.4 Pathophysiological Theories

A prominent hypothesis of the underlying cause of ScZ symptomology centres on the role of dopamine which came into focus following observations that positive symptoms in ScZ improved following the administration of drugs that blocked the reuptake of dopamine. This led to the prediction that there was excess transmission at dopamine receptors, in particular D2 receptors (Creese, Burt & Snyder, 1976; Seeman & Lee, 1975). However, this notion was not supported by later evidence that found no differences in the number of dopamine metabolites in the cerebrospinal fluid in those with ScZ by comparison to healthy controls (Widerlöv, 1988). Additionally, patients who were unresponsive to other antipsychotics responded well to clozapine despite its low affinity for D2 receptors (Peroutka & Synder, 1980; Richelson, 1984; Seeman, Lee & Chau Wong, 1976).

Following these findings, technological advances in neurochemical imaging allowed for a more accurate measurement of dopamine levels. Studies reported an increased striatal dopamine synthesis capacity in those with ScZ (Meyer-Lindenberg et al., 2002; McGowan et al., 2004). This

abnormality is also present in first degree relatives of those with ScZ (Huttunen et al., 2008) and those in the prodromal phase of the illness (Howes, et al., 2009). This is proposed to be associated with adverse events in early life which make the dopamine system hyper-responsive to stressors later on. For example, those who report adverse childhood experiences including low maternal care, parental loss or separation, physical or sexual abuse during their childhood have an elevated striatal dopamine release in response to stress (Egerton et al., 2016; Pruessner, Champagne, Meaney & Dagher,2004). Adverse environmental conditions paired with a dysregulated dopamine system is proposed to create a vicious cycle where dopamine release is extended to non-threatening stimuli that promote psychotic beliefs (Howes & Murray, 2014).

Impairments in dopaminergic functioning induce mainly positive psychotic symptoms as evidenced by studies that administered dopaminergic agonists such as amphetamine (Krystal et al., 2005). Following the administration of ketamine, an N-methyl-D-aspartate (NMDA) agonist, positive, negative and cognitive symptoms were elicited suggesting an overarching role of glutamate in the manifestation of psychotic symptoms (Morgan, Mofeez, Brandner, Bromley & Curran, 2004; Stone et al., 2012). Furthermore, NMDA receptors are located at brain circuits that regulate the release of dopamine suggesting that malfunctions in dopamine are mediated by an underlying glutamatergic dysfunction (Javitt, 2010).

There are two primary neurotransmitters that account for 90% of all signal transmission; GABA which is inhibitory and glutamate which is excitatory. Impairments in both systems have been recorded via post-mortem and *in vivo* studies. NMDA, a subtype of glutamate receptor has been reported to hypofunction in those diagnosed with ScZ as evidenced by higher levels of its endogenous antagonist kynurenic acid in the cerebrospinal fluid and post-mortem brain in those with ScZ. (Linderholm et al., 2010). Evidence for dysfunctions in the GABA system are rooted in observations of deficits in parvalbumin containing GABA neurons (Lewis, Curley, Glausier & Volk, 2012) and the decreased expression of GAD67 which plays a central role in the synthesis of GABA in those with ScZ (Curley et al., 2011; Ray, Weickert, Wyatt & Webster, 2011). Additionally, FEP participants have been found to have lower concentrations of GABA in the cerebrospinal fluid which was associated in a dose-response relationship with positive and negative

symptom severity and attentional deficits (Orhan, Fatouros-Bergman, Goiny, Malmqvist & Piehl, 2018).

Observations of glutamate and GABA dysfunction complement the dysconnectivity hypothesis of ScZ which posits that impairments in the functional integration of the brain underlie symptomology (Friston & Frith, 1995; Friston, 1998; Friston, Brown, Siemerkus & Stephan, 2016). Functional integration within and between brain regions is controlled by neural oscillations that coordinate neural activity (Buzsaki, 2006). GABAergic neurons are integral to the initiation of high frequency oscillations and their synchronisation while glutamatergic connections mediate their strength, duration and long-range synchronisation (Traub et al., 2004; Wang & Buzsaki, 1996). Aberrant neural oscillations have been recorded in individuals with ScZ and have been found to be associated with positive symptoms, disorganised and negative symptoms and cognitive dysfunction (Lee, Williams, Haig & Gordon, 2003; Spencer et al., 2004; Uhlhaas et al., 2006). Furthermore, in support of the neurodevelopmental hypothesis, there is suggested to be a critical developmental period where neuronal interactions have to be temporally precise and spatially focused enough to be supported by maturing cortical circuits. Pre- or postnatal insults may prevent this developmental process leading to dysregulated coordinated neural activity that result in the emergence of psychotic symptoms and cognitive impairment in late adolescence and early adulthood (Uhlhaas, Roux Rodriguez, Rotarska-Jagiela & Singer 2009).

Chapter 2

The Psychosis Prodrome

The neurodevelopmental hypothesis of psychosis predicts that deviations in cognitive, emotion and behavioural processes will be apparent before the onset of frank psychosis. Although these early symptoms of psychotic disorders have been observed for a long time the aspirations of effective early intervention have only emerged in the last 20 years. In 1932 the term prodromal was introduced by Mayer-Gross. 'Prodrome' means forerunner to an event and in medical terms the period before the onset of an illness (Yung & McGorry, 1996). Early anecdotal reports from studies of patients before the onset of frank psychosis reported that the most commonly described symptoms were; decreased concentration and attention, decreased drive and motivation, depressed mood, sleeping problems, anxiety, social withdrawal, suspiciousness, deterioration in role functioning and irritability (Yung et al., 1996). Other studies have also identified similar non-specific features of the prodromal phase such as reduced motivation, deterioration in role functioning and social withdrawal (Lencz, Smith, Auther, Correll & Cornblatt, 2004). Negative symptoms of depression and anxiety are common and likely to be the reason those at risk seek help in the first instance (Falkenberg et al., 2015; Fusar-Poli et al., 2012).

Studies have reported that psychotic symptoms have been recorded in 8% to 14% of children aged 11 - 13 years old (Kelleher & Cannon., 2011; Poulton, Caspi, Moffitt, Cannon, Murray & Harrington, 2000), a much higher prevalence than psychotic disorders reported in adulthood. The presence of psychotic symptoms should not always be treated as a precursor of psychotic disorders as it has been reported that 75-90% of psychotic experiences are transitory (van Os, Linscott, Myin-Germeys, Delespaul & Krabbendam, 2009) and do not interfere with functioning (Kelleher & Cannon, 2011).

2.1 Identifying Individuals in the Prodromal Phase of Psychosis

There are a number of different criteria that have been developed in order to detect symptoms of early psychosis. A recent review reported 22 measures for psychosis risk (Daneault & Stip, 2013). These instruments are often combined in research studies making it more challenging to define a

universal risk threshold (Yung, Nelson, Thompson & Wood, 2010). The most commonly used methods are the ultra-high-risk (UHR) and Basic Symptoms (BS) approaches which will be discussed in the following.

In order to more effectively study the early symptoms of frank psychosis a 'close-in' strategy was developed by Yung & McGorry (1996). As it is unknown if these individuals will develop frank psychosis they are referred to as being 'at-risk' and not in the prodromal phase. Individuals are required to be between 15 - 30 years of age as this is the most common period for psychosis to emerge and be clinically help seeking. Depending on the frequency, duration and intensity of psychotic-like symptoms (ideas of reference, unusual perceptual experiences including body-related illusions, paranoid ideation/mistrust, magical thinking and odd speech) presented participants would then be categorised into a suitable group (see Table 2). Using this criteria Yung and colleagues (2007) reported transition rates to psychosis of 34% within 6 months of referral and between 35% to 40% within twelve months. A more recent meta-analysis found that transition rates were found to be 36% during a 3-year follow-up (Fusar-Poli et al., 2012). The UHR criteria focuses on the onset of frank psychotic symptoms and not the development of a specific psychotic disorder like ScZ as using a non-specific outcome will identify more individuals at risk of future disability (Yung et. al., 2003).

Another approach in detecting those who are at-risk is based on the work by Huber and Gross (1989). They identified the presence of Basic Symptoms (BS), which are subjectively experienced alterations of individual cognitive domains, such as: thought interference, preservation, pressure or blockages, disturbance of receptive language, decreased ability to discriminate between ideas and perception, unstable ideas of reference, derealisation, and visual or acoustic perceptual disturbances (Klosterkötter, Hellmich, Steinmeyer & Schultze-Lutter, 2001). These are distinct from psychotic symptoms as they are independent from abnormal thought content, reality testing and the individual is aware of their pathologic nature (Schultze-Lutter, 2009). Research has indicated that based on BS alone transition rates in CHR individuals can be as high as 54.9% within 4 years (Schmidt et al., 2015). The individual can meet either the Cognitive Perceptive Basic Symptoms (COPER) or Cognitive Disturbances (COGDIS) criteria (see Table 2).

There is evidence for an initial prodromal state (EIPS) and a late initial prodromal state (LIPS). The sequence of symptom development starts with non-specific complaints and is followed by BS - which defines the EIPS (Ruhrmann, Schultze-Lutter & Klosterkotter, 2003). The LIPS is marked by attenuated psychotic symptoms (APS) and brief limited psychotic symptoms (BLIPS) as described in the UHR criteria. Schultze-Lutter and colleagues (2008) conducted a retrospective study of this symptomatic sequence in a sample of participants with first episode psychosis (FEP). They reported that almost all (98.4%) experienced prodromal symptoms and a third of participants reported BS earlier rather than simultaneously to or later than APS. This sequence was supported partially as most participants' non-specific mental problems follow BS and/or APS before the onset of psychotic symptoms.

Table 2: Summary of UHR and BS assessment criteria

	Psychotic symptoms intensity	Psychotic symptoms frequency	Functioning	Duration	Recency
Ultra High Risk (UHR) Criteria					
Trait group	None or subthreshold	N.A.	30% drop from premorbid levels **OR** GAF score <50	>1 month >12 months	Within last 12 months
APS group (a) subthreshold intensity	Subthreshold	Several times per week	N.A.	12 months or less	Within last 12 months
APS group (b) subthreshold frequency	Threshold	>1 per month but less than several times per week	N.A.	12 months or less	Within last 12 months
BLIPS group	Threshold	Daily	N.A.	<1 week, must have spontaneously resolved	Within last 12 months
Basic Symptoms (BS) Criteria					
Cognitive Perceptive Basic Symptoms (COPER)	At least one basic symptom	Weekly	N.A.	12 months or more	Within the last 3 months
Cognitive Disturbances (COGDIS)	At least two	Weekly	N.A.		Within the last 3 months

2.2 Transition from Subthreshold to Threshold Psychotic Symptoms

Transitioning from attenuated psychotic symptoms to threshold psychotic symptoms is conceptualised by Yung and colleagues (1998) by the presence of at least one fully positive psychotic symptom several times a week for more than one week (Yung et al., 2003). The SIPS/SOPS criteria requires at least one fully positive psychotic symptom several times per week for at least one month or at least one fully positive symptom for at least one day if these symptoms are severely disorganized or dangerous (Miller et al., 2003). The differences between these two sets

of criteria highlight the inconsistencies in the diagnosis of psychosis threshold that depends largely on clinical judgement.

A large number of individuals identified as ‘at-risk’ will never meet these criteria (Fusar-Poli et al., 2013). The rates of transition to psychosis in the research has declined in recent studies. To determine the cause of falling transition rates Yung and colleagues (2007) investigated the available data from the PACE clinic in Australia. They found no significant differences in the functioning and symptom level of UHR participants across studies. They reported that the lower transition rates reported in later studies were partially due to a reduction in the duration of symptoms of patients prior to intervention. This could be a consequence of supportive therapy and a prescription of antidepressants and/or anxiolytics that reduces stress and thus risk of transition. Thus, the non-transitioned sample could reflect a significant number of false-false-positives; individuals who would have transitioned if they had not received support. There may also be a number of false-positives; individuals who were not at real risk of transition. Additionally, Fusar-Poli and colleagues (2013) put forward the possibility of a lead-time bias where those in the prodromal phase are detected earlier than they were in older studies giving the impression that transitions occur later.

It has been argued that psychotic symptoms exist on a continuum and individuals should not be categorised dichotomously as ‘psychotic’ or ‘nonpsychotic’. Evidence to support this approach comes from the high prevalence of psychotic like experiences (5% to 8%) in healthy non-help seeking general population (van Os et. al., 2009). Furthermore, paranoid, schizoid and schizotypal personality disorders have a total prevalence of 1.6% (95% CI = 0.8 - 2.9) in the UK (Coid, Yang, Tyrer, Roberts & Ullrich, 2006) with most of these individuals not developing a psychotic disorder. Studies examining if psychotic symptoms lie on a continuum with psychotic illness have reported that psychotic symptoms group together in similar ways at clinical and subclinical levels, supporting the psychosis continuum hypothesis (Reininghaus, Priebe & Bentall, 2012; Reininghaus et al., 2015; Shevlin, McElroy, Bentall, Reininghause & Murphy, 2016).

With the conceptualisation of ‘transitioning’ to psychosis researchers have looked for an underlying biological basis. A prominent area of interest has been grey matter. The majority of the

literature presents findings of gradual reductions grey matter as psychosis develops (Cannon et al., 2015; McIntosh et al., 2011). However, a recent study reported a similar increase in volume and thickness in ARMS and FEP participants furthermore as the ARMS group is highly heterogeneous, containing individuals that will transition and false-positives it suggests that these abnormalities are a stable endophenotype for psychosis risk (Dukart et al., 2017). It has been proposed that the increase in grey matter observed in ARMS and FEP individuals may reflect cortical reorganisation and in turn resilience to psychosis onset and symptom severity (Palaniyappan, Das & Dempster, 2017). This is supported by other studies that have reported an association between remission from baseline symptoms and an increase in grey matter (Lappin et al., 2014; Schaufelberger et al., 2011). Considering these findings, it suggests that changes in grey matter are associated with the severity of positive psychotic symptoms however cortical reorganisation may be possible in some individuals resulting in a decrease of symptom severity.

Psychotic symptoms appear to lie on a continuum with the presence of transient symptoms in the general population through to the severe manifestation of ScZ at the other end of the spectrum. However, research has indicated that there are measureable biological differences in individuals with a larger degree of symptom severity suggesting that the distinction between ‘psychotic’ and ‘not-psychotic’ is not completely arbitrary.

Chapter 3

Cognitive Functioning in ScZ

3.1 General vs Specific Deficit

It has been proposed that the neurocognitive deficits observed in ScZ are underpinned by a general cognitive impairment (Dickinson et al., 2008; Keefe et al., 2006). Lower IQ scores with moderate to large effect sizes have been reported in those with ScZ by comparison to controls (Reichenberg & Harvey, 2007). However, IQ tests often do not assess all cognitive domains. Factor analysis has generated seven distinct cognitive factors including: verbal learning & memory, visual learning & memory, working memory, attention/vigilance, reasoning/problem solving (executive functioning) speed of processing and social cognition which have been used to develop neurocognitive batteries (Dickinson et al., 2008). Despite evidence that there are discrete neurocognitive domains, it has been reported that 64% of the variability in test performance was mediated by a general cognitive ability factor with individual contributions being made by processing speed and verbal memory (Dickinson et al., 2008). It has been proposed that rather than being mediated by a general cognitive ability factor, general cognitive impairments reflect the contribution of domain specific impairments (Gold, Hahn, Strauss & Waltz, 2009). This is supported as performance in neurocognitive assessments are highly correlated therefore deficits specific domains may mediate performance in other domains (Dickenson et al., 2008). Additionally, performance on some specific cognitive tasks have been reported as being preserved (Gold et al., 2009) adding to evidence that there is not simply a general cognitive impairment in ScZ.

Specific tasks and domains have been reported to be particularly affected in ScZ. Processing speed as measured by the Digit Symbol Substitution Task (DSST) (Dickinson et al., 2008; Dickinson, Ramsey & Gold, 2007; Henry & Crawford, 2005), Stroop Test (Golden, 1978) and Trail Making Test A (Reitan & Wolfson 1985) have illustrated impairments with large effect sizes (Reichenberg et al., 2007). This is supported by neuroimaging studies that have found an association between slowed processing speed and white matter abnormalities in line with the dysconnectivity theory of

ScZ which posits that deficits of the disorder are a result of problems in the communication of brain regions rather than differences in local brain activity (Antonova et al., 2005). The DSST has reported more consistent and larger impairments than other measures of processing speed. However, these deficits have been argued to be overestimated (Knowles et al., 2010) and contributed to by deficits in working memory rather than processing speed (Barch & Ceaser, 2012).

Psychomotor slowing has also been observed often in those with ScZ however it has not been studied to the same extent as other cognitive processes. Both tests that assess fine motor have found impairments in those with ScZ by comparison to controls (Dickinson et al., 2007; Heinrichs & Zakzanis) and have been found to be associated with dopaminergic striatal activity (Yang, Yu, Yeh, Chiu, Chen & Lee, 2004). These impairments have been associated with a modest effect to depressive or negative symptoms like apathy or motivational problems (Holthausen, Wiersma, Knegtering & Van den Bosch, 1999). Furthermore, they may reflect an underlying deficit in processing speed although factor analysis has identified two distinct symptom domains in those with ScZ (Bilder et al., 2002; Hobart, Goldberg, Barko & Gold, 1999; Morrens et al unpublished data in Morrens et al., 2006). More research is required to be able to identify the underlying causes of psychomotor slowing in those with ScZ.

Assessments of attention and vigilance have also been observed to be impaired in ScZ patients with large effect sizes (Reichenberg et al., 2007). In particular, involuntary attention (Sereno & Holzman, 1996) and attentional control impairments are altered in ScZ participants (Fuller et al., 2006). The specificity of these deficits to ScZ symptomology has been questioned as a similar pattern has been observed in affective disorders so this may not be a strong marker for the disorder (Sereno et al., 1995). Additionally, these problems are thought to be rooted in executive functioning (Kalkstein et al., 2010). Executive functions are higher-order cognitive abilities that direct decision making and skills like volition, motivation, self-awareness, planning, initiating purposeful behaviour, inhibiting inappropriate responses, abstract reasoning and mental flexibility. These abilities are linked to the frontal lobes, in particular the prefrontal cortex (Lezak, 2004) which has been reported to show dysfunctional activation during tasks of executive function in individual's diagnoses with ScZ (Minzenberg, Laird, Thelen, Carter & Glahn, 2009). ScZ patients

present with a number of clinical symptoms that are suggestive of executive functioning impairments such as reduced spontaneity, avolition, mental rigidity and impaired social judgement. Tasks used to assess specific aspects of executive functioning such as rule learning and cognitive flexibility in the Wisconsin Card Sorting Test (WCST; Heaton, 1981), selective attention and the ability to inhibit habitual responses in the Stroop Test and visual attention and task-switching in the Trail Making Task B (Reitan et al., 1985) have all been found to be impaired with large effect sizes in those with ScZ by comparison to controls (Reichenberg et al., 2007). Those with ScZ have additionally been found to be significantly more impaired than other psychiatric groups (Johnson-Selfridge & Zalewski, 2001) suggesting the importance of neurocognitive impairments in the symptomology of ScZ.

Verbal learning and memory deficits are impairments in the ability to encode and retain verbally presented information which are typically assessed using list learning tasks such as the California Verbal Learning Test (CVLT). Large deficits for immediate and delayed recall have been observed in those with ScZ who perform approximately one standard deviation or more below healthy controls (Dickinson et al., 2007). Visual learning and memory have also demonstrated impairments but not to the same extent (Aleman, Hijman, de Haan & Kahn, 1999). Impairments in working memory are also present with large effect sizes in particular when information has to be manipulated rather than only maintained (Aleman et al., 1999; Dickinson et al., 2008; Lee & Park, 2005). Similar findings of specific skills within domains having more pronounced impairments have been recorded in assessments of verbal fluency. Here, impairments in letter fluency but not semantic fluency has been observed in those with ScZ (Dickinson et al., 2007; Henry et al., 2005; Bokat and Goldberg, 2003).

The majority of those with ScZ will experience cognitive impairment but not everyone. Palmer and colleagues (1997) reported that 27% of ScZ patients and 85% of healthy controls were assessed as being not impaired in a clinical neurocognitive assessment. Similarly, Dickinson and colleagues (2007) reported that 27% of those with ScZ had a normal performance in the DSST. In these studies, more information is required to determine whether neurocognition reduced from premorbid levels. This gap has been addressed Kravariti and colleagues (2009) who report of three cognitive

profiles that emerged from their sample. A 'high-functioning' group (22%) who scored within the normal range on global IQ and neurocognitive assessments but still retained deficits of a small effect in verbal memory, working memory and executive functioning and a moderate effect in processing speed. A deteriorating group (37%) who had below average intellectual functioning that declined from their premorbid ability and the stable group (19%) who had below average intellectual ability before symptom onset which maintained. These findings suggest different trajectories in the development of ScZ not all of which are associated with impairments in neurocognition.

3.2 Social Cognition

Social cognition is an underlying mechanism used to navigate the social world (Penn, Sanna & Roberts, 2008). Emotional experience has been reported as being largely intact in ScZ (Cohen & Minor, 2010; Taylor et al., 2012). However, emotion regulation is thought to be disrupted as it has been reported that negative emotions increase in response to neutral and pleasant stimuli (Cohen et al., 2010). A proposed explanation of such findings is that cognitive reappraisal strategies are being used less frequently in those with ScZ (Henry, Rendell, Green, McDonald & O'Donnell, 2008; Horan, Hajcak, Wynn & Green, 2013).

The perception of social cues has also been reported to be impaired: individuals with ScZ have deficits in affective facial processing (Delvecchio. Sugranyes & Grangou, 2013; Taylor, et al., 2012) and emotional prosody (Kantrowitz et al., 2011; Leitman et al., 2007) but not non-affective face processing (Bortolon, Capdevielle & Raffard, 2015) and non-emotional prosody (Murphy & Cutting, 1990; Pijnenborg et al., 2007).These impairments in the interpretation of social information have been proposed to exacerbate delusional symptoms, lead to social withdrawal and impair functioning (Fett, Viechtbaur, Penn, van Os & Krabbendam, 2011; Green, Hellemann, Horan, Lee & Wynn, 2012).

Theory of mind (ToM) deficits have also been consistently recorded in ScZ (Bora, Yucel & Pantelis, 2009; Sprong, Schothorst, Vos, Hox & van Engeland, 2007) and have been reported to be associated with hypoactivation in the ventromedial PFC (vmPFC) and orbitofrontal cortex when

engaged in tasks which required participants to consider another person's perspective to correctly identify objects (Eack, Wojtalik, Newhill, Keshavan & Phillips, 2013) and in the medial prefrontal cortex (mPFC) and bilateral temporoparietal junction (TPJ) when reasoning with another person's beliefs (de Achával et al., 2012; Dodell-Feder, Tully, Lincoln & Hooker, 2014). Hyperactivation of the same areas has been found in ScZ patients who have preserved ToM abilities (de Achával et al., 2012; Brune et al., 2008) suggesting that they are able to engage compensatory mechanisms (Green et al., 2015). However, the hyperactivation of these systems has been associated with the development of paranoid symptoms where individuals 'over-mentalise' causing them to ascribe the incorrect intentions of others (Blakemore et al., 2003; Frith, 2004).

Chapter 4

Cognition in those 'At-Risk' of Psychosis

The neurodevelopmental model of ScZ predicts that impairments in cognition will be present before the onset of frank psychotic symptoms. A better understanding of the pattern and onset of impairment together with its relationship to symptomatology could lead to a more accurate identification of individuals at true risk of transition. The following will review methods and results from previous research that have investigated the extent of neurocognitive deficits in those at-risk.

4.1 Genetic Risk

As ScZ is highly heritable, neurocognition has been examined in the unaffected relatives of ScZ patients via cross-sectional and longitudinal studies to determine if deficits are an endophenotype of the illness. Impairments by comparison to healthy controls in the domains of verbal memory recall, executive function, attention (Sitskoorn et al., 2004), working memory, episodic memory (Delawalla et al., 2006), perceptual motor speed, verbal ability and language (Byrne et al., 2003) have been observed in a dose-response relationship with genetic risk (Johnstone, Lawrie & Cosway, 2002). However, the size of these impairments may be overestimated as participants included were at an age where transitions could still occur although, a study that included older, unaffected parents of individuals with ScZ reported significant neurocognitive impairments by comparison to control couples (Appels et al., 2003). Furthermore, despite not presenting positive psychotic symptomatology unaffected relatives may meet the criteria for schizotypal traits and negative symptoms (Delawalla et al., 2006; Chen et al., 2009) which may contribute to impaired neurocognition.

Longitudinal studies in genetically high risk individuals have observed that some neurocognitive impairments appear to be stable and related to genetic vulnerability (O'Connor, Harris, McIntosh, Owns, Lawrie & Johnstone, 2009) while some emerge concurrently with the development of psychotic symptoms (Cosway et al., 2000) or are more severe when the individual also has schizotypal traits (Keshavan et al., 2005). These findings complement neuroimaging studies that reported small prefrontal lobes and thalami in asymptomatic unaffected relatives and further

reductions in the temporal lobe in individuals who developed psychotic symptoms (Johnstone et al., 2002). Additionally, performance in executive functioning and verbal learning and memory tasks in unaffected relatives has been reported to be mediated by IQ scores, which was not observed in healthy controls (Byrne et al., 1999) highlighting its utility at a protective factor.

Overall, studies have observed neurocognitive impairment in relatives of individuals with ScZ suggesting that neurocognitive impairment is an endophenotype to the illness. However, as the impairments observed here are not to the same degree as those presented by individuals with ScZ it suggests an association with symptomatology.

4.2 Clinical Risk

Although studies of individuals with genetic risk have highlighted the presence of neurocognitive impairment in the absence of positive symptomatology, longitudinal studies using only this criterion are limited because of their long length and low transition rates (5 - 10%) (Pukrop & Klosterkötter, 2010). Studies that require participants to present with below threshold psychotic symptoms and impaired functioning may highlight a subgroup that is at a higher risk of transition. In a recent meta-analysis Hauser and colleagues (2017) highlighted mild to moderate impairments in attention/vigilance, speed of processing, verbal learning, social cognition and working memory that were intermediary between healthy controls and FEP participants. Impairments in processing speed were the most consistent between studies whilst performance on measures of attention, verbal memory and learning and verbal fluency were mixed. Additionally, spatial working memory, visual memory and general intellectual functioning were found to be generally preserved in high risk samples although there are some exceptions. These findings generally support the results from previous analyses (Bora et al., 2014; Giuliano et al., 2012). Any inconsistences between studies may stem from differences in the categorisation of neurocognitive assessments into domains, for instance verbal fluency in some studies has been considered a neurocognitive domain in its own right while in other studies it has been grouped under executive functions, executive and attention, executive functions and working memory or processing speed (Pukrop et al., 2010).

Analyses have also been conducted at the test level which are more easily comparable between studies. The most robust impairments are in the DSST (Bora et al., 2014; Fusar-Poli et al., 2012; Hauser et al., 2017), consistent with the ScZ literature (e.g. Dickenson, Mary, Ramsey & Gold, 2007). Impairments were also consistently observed in CPT and the WCST (preservation errors) (Bora et al., 2014; Fusar-Poli et al., 2012; Hauser et al., 2017) and preserved ability in the Finger Tapping Tests (Fusar-Poli et al., 2012; Hauser et al., 2017). However, mixed findings were detected in other tasks for example deficits in both the TMT A and TMT B were reported by two meta-analyses (Bora et al., 2014; Hauser et al., 2017) but another observed impairments in only TMT A (Fusar-Poli et al., 2012). Similarly, deficits in both the immediate and delayed recall have been observed in the CVLT in one meta-analysis (Hauser et al., 2017) but impairments in only the immediate recall have been observed in another (Fusar-Poli et al., 2012).

Inconsistencies between studies may be accounted for by differences in ages (Glahn et al., 2013), gender (Walder et al., 2013), years of education (Keefe et al., 2004), comorbid disorders and number of false positives in high risk groups. Furthermore, differences between groups may occur through the choice of assessment criteria. A number of tools have been utilised, the most common assessments are the BS and UHR however other studies have used the DSM-IV criteria for schizotypal personality disorder (Walder, Mittal, Trotman, McMillan & Walker, 2008), negative symptoms (Eastvold, Heaton & Cadenhead, 2007; Smith, Park & Cornblatt, 2006) and DSM prodromal criteria (Gschwandtner et al., 2003) to identify clinically at-risk individuals. This could result in the inclusions of distinct groups of participants with different clinical profiles and perhaps neurocognitive impairment as a result. For example, those identified using the UHR criteria have been reported to have more pronounced impairments in attention (Pukrop et al., 2006) working memory, verbal learning and memory (Fromman et al., 2010) by comparison to those with BS. In addition to highlighting a possible explanation of the inconsistencies between studies, these findings additionally address important questions regarding the etiology of ScZ as they imply an association between the increasing severity of positive symptoms and neurocognitive deterioration suggesting the use of neurocognition as a marker of impending psychosis onset.

4.3 The Role of Cognition in Transition to Psychosis

Longitudinal studies have compared baseline neurocognitive performance between converters and non-converters to frank psychosis. In a recent meta-analysis, converters at baseline have been reported to have poorer performances by comparison to non-converters in the domains for attention/vigilance, speed of processing and verbal and visual learning but not executive functioning or working memory (Bora et al., 2014; De Herdt et al., 2013; Fusar-Poli et al., 2013; Hauser et al., 2017). At test level, Hauser and colleagues (2017) report that the tests with the highest discriminatory power were the Rey-Osterrieth Complex Figure Test (ROCFT), Controlled Oral Word Association Test (COWAT) and the CVLT. Significant differences found in the COWAT have been supported (Giuliano et al., 2011) but the impairment reported in the Letter Number Sequencing Test was not replicated in a previous study (Bora et al., 2014). Although statistically significant differences have been reported there is still a considerable overlap in the neurocognitive ability of converters and non-converters (Bora et al., 2014; Hauser et al., 2017) which may be accounted for by the ongoing risk of psychosis in non-converters suggesting the need for longer follow-up periods.

Furthermore, although there is evidence of baseline differences in neurocognitive performance between converters and non-converters, it has not been determined if they are reliable in predicting transition to psychosis. Studies have reported that including neurocognitive variables like IQ, processing speed, verbal learning, memory or verbal fluency together with clinical variables increased the predictive power of the model (Addington et al., 2016; Cannon et al., 2016; Corblatt et al., 2015, Michel et al., 2014; Metzler et al., 2016; Ziermans et al., 2013) but did not independently predict transition to psychosis. Additionally, it has been proposed that neurocognitive predictors may be better at specifically predicting ScZ than other psychotic illnesses because those diagnosed tend to have more severe neurocognitive impairment (Bora et al., 2014). However, one study reported no differences in those at-risk who went on to develop ScZ and affective psychosis (Olvet et al., 2010).

4.4 Beyond Transitional Outcomes

Transition rates have been the main outcome parameter in at-risk studies however two-thirds of at-risk individuals will not meet the threshold for psychosis (Fusar-Poli et al., 2012). These individuals may continue to have persistent attenuated psychotic symptoms and/or non-psychotic disorders (Lin et al., 2015; Simon et al., 2013) that could continue to negatively impact functioning. This is supported by the observation that 51% of at-risk individuals with the poorest functional outcome at 7 years did not develop a psychotic disorder (Lin et al., 2011). It has been considered that the at-risk criteria may highlight individuals who are also at risk for other non-psychotic, long lasting mental health problems that require intervention (Lin et al., 2015). Thus, research should additionally consider what factors contribute to poor functional outcomes as well as what predicts transition.

4.5 The Role of Cognition and Functional Outcome

Functional outcomes are typically measured by the ability to live independently, the degree of social and family burden, employment status, interpersonal and social functioning and quality of life (Shrivastava, Johnston, Shah & Bureau, 2010). The association of neurocognition and functional outcome has been studied considerably less in at risk populations although poor functioning and neurocognitive impairments have both been consistently observed independently (Brewer et al., 2006). Studying this potential association in at-risk groups is advantageous because functioning in chronic ScZ is confounded by the effects of medication treatment, hospitalisations, relapse and multiple episodes. Furthermore, a greater understanding of this potential interaction in at-risk groups could also improve targets for early intervention.

A long term follow-up using functioning outcomes revealed larger neurocognitive deficits in those with poor functioning, assessed using the SOFAS and Quality of Life Scale, regardless of transitional status (Lin et al., 2011). Specifically these impairments were observed in verbal learning and memory, verbal fluency, basic attention and processing speed but not global cognition. However, only logical memory was able to successfully predict a poor functioning outcome. Another study, reported that baseline performance in the DSST could predict functional outcome

assessed using the SOFAS, after controlling for IQ and baseline functioning (Allot et al., 2018). When social and role functioning were assessed independently role functioning was predicted by global cognition, verbal memory (Carrión et al., 2013; Meyer et al., 2014), motor disturbances (Carrión et al., 2013) and social functioning by processing speed (Carrión et al., 2013) and executive functioning (Eslami, Jashan & Cadenhead, 2011).

Furthermore, it has been reported that negative symptoms may mediate the association between neurocognition and role functioning (Glenthøj et al., 2018; Meyer et al., 2014). This suggests that both neurocognitive deficits and negative symptoms may both be suitable targets for intervention in at-risk groups in order to improve functional outcome. Functional outcome may additionally be affected by the prevalence of comorbid non-psychotic disorder (Lin et al., 2015), although elsewhere it has been proposed that anxiety and depressive symptoms do not influence functioning in at-risk groups (Cotter et al., 2014) suggesting the need for further research.

Chapter 5

Rationale, Aims and Hypotheses for the Current Study

Cognitive impairments are frequently reported in CHR populations by comparison to healthy controls (Bora et al., 2014; Giuliano et al., 2012; Hauser et al., 2017) however, the majority of studies have recruited exclusively from clinical pathways. It was recently observed that the majority of individuals who present with a first episode of psychosis have not been seen by specialised prodromal services (Ajnakina et al., 2017) suggesting that clinically recruited CHR-participants only capture a subgroup of at-risk individuals. The limited research conducted with community recruited CHR-participants has yielded mixed findings with one study suggesting they are similarly symptomatic (Platz et al., 2006) and another reporting higher levels of functioning and lower levels of positive symptom severity (Mills et al., 2017). To the best of our knowledge neurocognitive functioning has not been investigated in community recruited CHR-participants.

Aim 1: To explore the degree of neurocognitive impairment CHR-participants recruited from the general population and identify their relationship with positive symptom severity and functioning.

Hypothesis 1: CHR-participants recruited from the general population will have cognitive impairments by comparison to healthy controls.

Hypothesis 2: Cognitive functioning in community recruited CHR-participants will not be significantly associated with positive symptom severity.

Hypothesis 3: Cognitive functioning in community recruited CHR-participants will be positively associated with psychosocial functioning.

CHR individuals in addition to experiencing positive and negative symptomatology are typically diagnosed with comorbid psychiatric disorders, primarily anxiety, depression and substance abuse that are proposed to influence ongoing psychopathology and functioning (Fusar-Poli, Nelson, Valmaggia, Yung & McGuire, 2012). However, the influence of non-psychotic symptomatology on cognitive functioning in CHR individuals is largely unexplored. A recent study using a 'help-

seeking control group' recruited from clinical pathways reported deficits in processing speed (Carrion et al., 2018), suggesting subthreshold CHR individuals may also experience cognitive deficits by comparison to healthy controls.

Aim 2: To investigate the influence of comorbid non-psychotic disorders on neurocognitive functioning in CHR-participants by identifying the degree of neurocognitive impairment in a CHR-negative group who scored below the CHR threshold but are characterised by non-psychotic disorders

Hypothesis 4: The CHR-negative group will experience cognitive impairments, specifically in processing speed, by comparison to healthy controls but not to the same extent as CHR-participants who met the positive symptom threshold.

Neurocognitive functioning at baseline has been reported to significantly predict clinical outcome alongside clinical variables in CHR populations. To the best of our knowledge, a longitudinal study has not been conducted with CHR-participants recruited from the community so the prevalence of clinical trajectories and their association with baseline neurocognitive functioning in this group is unknown. Typically, the categorisation of clinical outcome of CHR-participants has been limited to converters and non-converters to psychosis. However, non-converter groups remain heterogeneous including both remitters and non-remitters of attenuated psychotic symptoms. In their study with clinically recruited CHR individuals, Lee and colleagues (2014) reported that remitters but not non-remitters performed similarly to healthy controls in baseline neurocognitive assessments suggesting their potential utility in predicting remission.

Aim 3: To explore the association between baseline neurocognitive functioning and clinical outcome at 12 months.

Hypothesis 5: Non-remitters at 12 months will have more pronounced cognitive impairments at baseline compared to remitters who will perform similarly to healthy controls.

Chapter 6

Methodology

6.1 Setting

The data used for the current study was derived from the Youth Mental Health and Resilience (YouR) study (Uhlhaas, Gajwani, Gross, Gumley, Lawrie & Schwannauer, 2017) and is funded by the Medical Research Council (MRC). Recruitment for this study began in October 2014 and is scheduled to finish in Spring 2019.

6.2 Participants

Three groups of participants aged 16 - 35 years old will be used in this analysis; a clinical high risk group (CHR-positive; N = 122) who met the UHR and/or COGDIS/COPER criteria, a clinical high risk negative (CHR-negative; N = 43) group who scored below threshold for UHR and SPI-A criteria but were characterised by psychiatric comorbidity and heathy controls (HC; N = 57) who do not have any DSM-IV disorder, current substance abuse and first degree relative with psychosis. Additional exclusion criteria for all participants included having an existing neurological disorder, metal implants in the body, pregnancy or a current suicide plan.

Participants were recruited through a web-based screening tool (see http://www.your-study.org.uk) which they were invited to via e-mail, flyers, posters and general practioner (GP) letters. Specifically, email invitations were sent to colleges and universities in Glasgow and Edinburgh, posters and flyers were available from NHS clinics and public transportation and letters were sent to potentially suitable participants identified on GP databases. Informed consent for the web screening was provided online, followed by 2 questionnaires: (a) the 16-item version of the Prodromal Questionnaire (PQ-16) and (b) a 9-item questionnaire of perceptual and cognitive aberrations (PCA) that was developed to assess BS. The PQ-16 was developed by Ising and colleagues (2012) from the 92-item prodromal questionnaire (PQ) (Loewy, Bearden, Johnson, Raine & Cannon, 2005) and has a high sensitivity (87%) and specificity (87%) with the CAARMS. Items for the PCA were derived from existing patient descriptions of cognitive and perceptual

experiences (Uhlhaas & Mishara, 2007) and items from the SPI-A (Schultze-Lutter, Addington, Ruhrmann & Klosterkötter, 2007). Participants were asked to provide ratings based on their experiences in the last 12 months. Potential CHR-positive participants had to meet the cut off criteria of 6 or more positively answered questions on the PQ (Isling et al., 2012) and 3 or more on the PCA to be invited for further clinical assessment.

Clinically recruited CHR-positive participants were gathered via NHS patient's services in NHS Greater Glasgow and Clyde and NHS Lothian, NHS First Episode Psychosis Services, Community Mental Health Teams (CMHTs), Primary Care Mental Health Teams (PCMHTs), Clinical Psychology Services, Community Adolescent Mental Health Services (CAMHS) and Non-Governmental Mental Health Organisation's. In total there are 12 (10%) CHR-positive recruited from a clinical route and 85 (78%) from the general population..

All participants were informed that they were free to withdraw from the study at any point and that this will not affect the care or treatment that they receive. For completion of the initial online screening questionnaire, participants were entered into a prize draw to win an iPad. Following consent to take part in the study they were paid £6 per hour.

6.3 Procedure

6.3.1 Screening Interview

Demographic information was obtained verbally including age, gender, years of education, family history of mental illness and suicidality. To establish CHR criteria the positive scale of the CAARMS (Yung et al., 2005) and COGDIS/COPER items from the SPI-A (Schlutze-Lutter et al., 2007) were administered through trained research assistants and MSc/PhD level researchers. Inter-rater reliability meetings were held monthly to ensure consistency in the interpretation and scoring of symptoms between researchers. Participants were recruited into the CHR-positive group if they met a) SPI-A COGDIS/COPER-criteria b) ARMS attenuated psychosis group (subthreshold psychotic syndrome present in the last year without a decline in functioning) c) ARMS vulnerability group (family history of psychosis plus a 30 % drop in GAF) or d) ARMS BLIPs-group (brief limited intermittent psychotic symptoms).

The M.I.N.I. International Neuropsychiatric Interview (M.I.N.I 6.0) (Hergueta et al., 1998), Global Assessment of Functioning Scale (GAF; American Psychiatric Association, 1994) and Social and Role Functioning Scales (Cornblatt et al., 2007) were also administered.

6.3.2 Neurocognitive Assessment

Neurocognitive assessments included the Brief Assessment of Cognition in ScZ Battery (BACS; Keefe et al., 2004) as well as specific tasks from the University of Pennsylvania computerized neurocognitive testing battery (PennCNB; Moore et al., 2015). Additionally, premorbid IQ was estimated using the National Adult Reading Test (NART; Nelson & Willison, 1991) and a visual acuity test were administered.

6.3.3 Follow-up Assessments

CHR-positive participants had a follow-up assessment over the phone or in person every 3 - 6 months for 36 months to administer the positive scale of the CAARMS in addition to the Social and Role Functioning Scale at the 6, 12 and 24-month assessment.

6.4 Measures

6.4.1 Psychopathology and Symptom Measures

Comprehensive Assessment of At-Risk Mental States (CAARMS; Yung et al., 2005): Semi-structured interview used to assess the presence and level of psychotic symptoms (see Chapter 2).

Schizophrenia Proneness Instrument Adult Version (SPI-A; Schlutze-Lutter et al., 2007): Specialised instrument to assess the presence of BS (see Chapter 2).

Mini-International Neuropsychiatric Interview (M.I.N.I 6.0; Hergueta et al., 1998)**: S**tructured psychiatric interview, used primarily in a research setting to diagnose DSM-IV and ICD-10 disorders. Validated to the Structured Clinical Interview for DSM-III-R, Patient Version and the Composite International Diagnostic Interview.

6.4.2 Neurocognitive Measures

Brief Assessment of Cognition (BACS; Keefe et al., 2004): A 30-minute pen-and-paper battery that assesses the following domains: verbal memory and learning, working memory, motor speed, verbal fluency (semantic and letter), processing speed and executive functioning. A composite score is calculated by averaging all of the six tasks and then calculating a z-score. The following tests are described in the following in order of their presentation.

Verbal Memory, List-learning Task: A list of 15 words was read aloud and participants had to recall as many as possible. This procedure was repeated for 5 trials.

Working Memory, Digit Sequencing Task: A sequence of numbers which gradually increase in length every 4 trials was read aloud, the participants had to repeat the sequence back in order from the lowest to highest number.

Motor Speed, Token Motor Task: Participants were presented with 100 tokens that they had to pick up two at a time and put back into the empty container in 60 seconds.

Semantic Fluency, Category Instances Task: In 60 seconds participants had to produce as many different words as possible within the category of animals.

Letter Fluency, Controlled Oral Word Association Task: In 60 seconds participants had to say as many words as possible that began with the letter 'F' and in the second trial, 'S'.

Processing Speed, Digit Symbol Substitution Test (DSST): Participants were presented with a key that matched unique but non-meaningful set of symbols that were each assigned to a number from 1 – 9. They had to fill in a blank response sheet below using the key in 90 seconds.

Executive Functioning, Tower of London (A) Task: Participants were presented with two images of different coloured balls arranged on three pegs of different sizes. They were asked to respond how many moves it would take in the fewest possible moves to make the arrangement in image 'A' look like the arrangement in image 'B'.

University of Pennsylvania Computerised Neurocognitive Testing Battery (PennCNB; Moore et al., 2014): A computerised neurocognitive testing battery to assess the following domains: attention/vigilance, working memory and emotional recognition. Performance was assessed in each test using an accuracy score and the response time (RT). The following describes the tests used to assess each domain in the order of presentation.

Attention/Vigilance, Penn Continuous Performance Test (PCPT): Vertical and horizontal lines flashed onto the screen. Participants had to respond by pressing the spacebar when the lines were arranged in the shape of a complete number and in the second half, a complete letter.

Working Memory, Penn Letter N-Back Test (PLNB): A series of letters individually flashed onto the computer screen. There were 3 conditions, in the first (0-back) participants had to press the spacebar when presented with the assigned target letter. In the second (1-back) and third (2-back) conditions they had to respond when the letter presented was the same as the previous letter or was the same as the two previous letters, respectively.

Emotion Recognition, Emotion Recognition Test (ERT): Faces flashed onto the computer screen and the participants had to assign the correct emotion from a choice of five (happy, sad, anger, fear or no expression).

National Adult Reading Tests (NART; Nelson et al., 1991): A single word, oral reading test of 50 items used to assess premorbid intelligence. Scores are converted to estimate performance, verbal and full IQ using the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981).

6.4.3 Functioning Measures

Global Assessment of Functioning (GAF; American Psychiatric Association, 1994): Assesses functioning in the psychological, social and occupational domains. Scores are rated from 1 – 100, with 1-10 signifying persistent danger and 91-100 superior functioning.

Global Assessment of Functioning Scale, GF: Social and GF: Role. (Cornblatt et al., 2007): The two scales range from 1 to 10, with 10 being superior functioning and 1 extreme dysfunction. Scores reflect the highest and lowest level of functioning in the past year and lowest in the past

month. Both these scales are useful and distinct from GAF scores as they assess social and role functioning independently from each other and psychotic symptoms.

The Global Functioning: Social examines the quantity and quality of peer relationships, age-appropriate intimate relationships, family relationships and assesses if there is any conflict. There is a focus on assessing age-appropriate interactions outside of the family. When social contact is only coming from family members this will set a limit on how high the individual can score (1 to 3). For example, a score of 7 which signifies mild impairments in social functioning would be assigned to a 16 to 18-year-old who had both close and casual friends, is dating but have some problems resolving peer conflict. An individual who would be classified as having a major impairment and a score 4 would have no close friends, significant peer conflict and infrequent family contact.

The Global Functioning: Role assesses performance at school, work or as a homemaker, depending on age. Scores are given with consideration to the demands of the role, level of independence or how much support they require. Again someone would be given a score of 7 if they achieved pass grades (‘D’) in school unsupported or ‘C’ grades with support for example extra time in exams. Someone of a similar age would be given a 4 score if they are failing all classes in mainstream school or passing with major support in place.

Chapter 7

Statistical Analysis

7.1 Baseline Analysis

All statistical analyses were performed using SPSS version 24. When there were more than 2 groups, continuous variables were analysed using a one-way ANOVA or Kruskal–Wallis test. If the homogeneity of variances assumption was violated following a one-way ANOVA, Welch's F was reported. The Hochberg's GT2 test was used post hoc for ANOVA analyses because of large differences in sample sizes. The Games-Howell was used for Welch. Hedge's g effect sizes were calculated for both. Following a statistically significant result from the Kruskal-Wallis test significant pair-wise comparisons were identified using the adjusted p-values to reduce the risk of Type I error.

When there were two groups, continuous variables that met the assumption of normality were analysed using an independent t-test or Mann-Whitney U test if this was violated. Categorical variables were analysed using a chi-square if all the assumptions were met and Fisher's exact test if they were not. A Hedge's g effect size was calculated following an independent t-test. An effect size for a significant Mann-Whitney U test was calculated by using the following equation (Rosenthal, 1991, p. 19).

$$r = \frac{z}{\sqrt{N}}$$

Where z is the z-score generated by SPSS and N is the total number of participants.

7.2 Demographic Characteristics

At baseline there was a sample of 57 healthy controls (HC), 43 clinically at-risk negative (CHR-negative) and 122 clinically at-risk positive participants (CHR-positive). All groups were matched with respect to age and sex. See Table 3 for a full report of the demographic statistical comparisons. Briefly, a statistically significant difference, using the Hochberg's GT2 test, existed between HC and CHR-positive groups as well as the CHR-negative and CHR positive groups in

the number of years of education with CHR-positive participants reporting less years than both groups.

A Fisher's exact test also revealed statistically significant differences between groups in the number of participants on mediation with 46.5% of CHR-negative and 51% of CHR-positive reporting that they currently take medication. Similarly, there was a high number of CHR-negative (63%) and CHR-positive (95%) who met the criteria for at least one other DSM/ICD psychiatric disorder as measured by the MINI.

Table 3: Baseline Demographic and Clinical Characteristics of HC, CHR-negative and CHR-positive Participants

Characteristic	HC (N = 57)	CHR-negative (N = 43)	CHR-positive (N = 122)	df	Statistic	p	Significant post-hoc comparisons
Age (years), M ± SD	22.44 ± 3.42	23.16 ± 4.96	21.59 ± 4.25	2, 98	2.13**	0.12	
Gender, N female (%)	39 (68)	29 (67)	90 (74)		0.90*	0.64	
Years of education, M ± SD	16.54 ± 2.97	16.56 ± 3.57	15.17 ± 3.19	2, 219	5.04	0.01	HC vs CHR-positive, CHR-negative vs CHR-positive
GAF, median, range	88 (67 – 97)	70 (43 – 94)	58 (21 – 95)	2	H = 112.87	<0.01	HV vs CHR-negative, CHR-positive, CHR-negative vs CHR-positive
CAARMS Severity, median, range	0 (0 – 12)	6 (0 – 24)	28 (0 – 72)	2	H = 140.10	<0.01	
GF: Social, median, range	9 (8 – 10)	8 (6 – 9)	8 (5 – 10)	2	H = 73.24	<0.01	HC vs CHR-negative, CHR-positive, CHR-negative vs CHR-positive
GF: Role, median, range	9 (5 – 9)	8 (5 – 9)	8 (4 – 9)	2	H = 54.25	<0.01	HC vs CHR-negative, CHR-positive, CHR-negative vs CHR-positive
NART: Full IQ	114.19 ± 6.05	114.02 ± 6.22	114.19 ± 5.79	2, 209	F = 0.11	0.89	
NART: Verbal IQ	114.10 ± 6.63	113.84 ± 6.83	114.02 ± 6.41	2, 209	F = 0.03	0.97	
NART: Performance IQ	113.06 ± 4.77	112.81 ± 4.87	112.95 ± 4.50	2, 209	F = 0.02	0.98	
Medication, N (%)	1 (2)	20 (46.5)	62 (51)		52.61*	<0.01	
Anti-psychotic	0 (0)	1 (3)	1 (10)				
Mood stabiliser	0 (0)	0 (0)	1 (1)				
Anti-depressant	0 (0)	11 (26)	26 (21)				
Other	1 (2)	6 (14)	15 (12)				

Table continued	HC	CHR-negative	CHR-positive	df	Statistic	p	Significant post-hoc comparisons
Multiple	0 (0)	2 (6)	19 (15)				
Diagnosis, N (%)	5 (9)	27 (63)	116 (95)	3	142.14*	<0.01	
Anxiety disorders	2 (3.5)	20 (46.5)	106 (87)				
Mood disorders	0 (0)	10 (23)	61 (50)				
Eating disorders	0 (0)	1 (2)	13 (11)				
Suicide Risk	1 (2)	11 (26)	62 (51)				
Alcohol Dependence/Abuse	2 (3.5)	10 (23)	35 (29)				
Substance Dependence/Abuse	0 (0)	2 (5)	16 (13)				

*Fishers Test, ** Welch's F

A Kruskal Wallis test found statistically significant difference between all pairs in social and role functioning, with CHR-positive participants having the lowest functioning. As the social and role functioning scores are nominal variables the frequency of each of the reported categories were also considered. Participants were classified as having good functioning if they scored above 6 (mild impairments to superior functioning) or poor functioning if they scored 6 or less (moderate impairments to extreme dysfunction). In the HC group, 2% had poor role functioning compared to 2% of CHR-negative and 17% of CHR-positive. Similarly, 0% of HC had poor social functioning compared to 5% of CHR-negative and 15% of CHR-positive.

7.3 Cognitive Functioning

7.3.1 BACS

For each participant the individual score from each test was standardised by age and gender from a sample of 100 participants (Keefe et al., 2008) to produce z-scores and a composite score which are reported in Table 4.

Table 4: Neurocognitive Performance of HC, CHR-negative and CHR-positive Participants

	HC		CHR-negative		CHR-positive					
	N	**M ± SD**	**N**	**M ± SD**	**N**	**M ± SD**	**df**	**Statistic**	**P**	**Significant post-hoc comparisons**
					BACS					
Verbal Memory	57	0.08 ± 1.20	43	0.21 ± 1.30	122	-0.30 ± 1.52	2, 219	F = 2.80	0.06	
Working Memory	57	-0.22 ± 0.77	43	-0.08 ± 0.86	122	-0.27 ±1.00	2, 219	F = 0.78	0.46	
Motor Speed	57	0.28 ± 1.19	43	-0.25 ± 1.10	122	-0.64 ±1.41	2, 219	F = 9.78	<0.01	HC vs CHR-positive
Verbal Fluency	56	0.47 ± 1.27	43	0.19 ± 1.02	122	0.24 ± 1.25	2, 218	0.88	0.41	
Processing Speed	56	0.68 ± 1.13	43	0.69 ± 1.28	122	0.03 ± 1.20	2, 219	8.15	<0.01	HC vs CHR-positive, CHR-negative vs CHR-positive
Executive Functioning	57	0.27 ± 0.75	43	0.27 ± 0.89	120	0.19 ± 1.01	2, 217	0.19	0.83	
Composite Score	57	0.41 ± 0.80	43	0.26 ±1.02	122	-0.21 ±1.29	2, 219	6.93	0.01	HC vs CHR-positive
					Penn CNB					
Emotion Recognition	57	0 ± 1	43	-0.19 ±0.91	121	-0.15 ± 1.09	2, 218	0.55	0.58	
Emotion Recognition (RT)	57	0 ± 1	43	-0.18 ± 1.36	121	-0.55 ±1.61	2, 218	3.22	0.04	HC vs CHR-positive
Working Memory	57	0 ± 1	43	-0.24 ± 1.28	118	-0.34 ±1.44	2, 106	*1.94	0.15	

Table continued		HC		CHR-negative		CHR-positive				
	N	M ± SD	N	M ± SD	N	M ± SD	df	F	P	Significant post hoc comparisons
Working Memory (RT)	57	0 ± 1	43	0.11 ±1.02	120	0.08 ± 0.76	2, 217	0.24	0.78	
Attention	57	0 ± 1	43	-0.23 ± 2.73	119	-0.77 ± 2.74	2, 98	*3.76	0.03	HC vs CHR-positive
Attention (RT)	57	0 ±1	43	0.25 ±0.98	121	0.13 ± 0.84	2, 218	0.96	0.38	

*Welch's F

In the BACS composite score, the CHR-positive group had a significantly lower score, following a Hochberg's GT2 test post hoc, by comparison to HC with a medium effect size (g = 0.53).

Analysis at the test level using the Hochberg's GT2 post-hoc test revealed that motor speed was impaired in the CHR-positive group by comparison to HC with a medium effect size (g = 0.68). Similarly, processing speed was impaired in CHR-positive were impaired by comparison to HC (g = 0.55) and CHR-negative (g = 0.53) both with medium effect sizes.

To investigate the association between processing speed and motor speed a Spearman's correlation analysis was carried out. Performance on these two tasks were statistically significantly correlated for CHR-positive participants, $r_s = .33$ and HC, $r_s = .30$ but not CHR-negative, $r_s = .28$.

Statistically significant differences were additionally found between the CHR-positive and the BACS standardised controls. The CHR-positive group had impairments in the domains of verbal memory (g = 0.23), working memory (g = 0.27), motor speed (g = 0.51) and performed better in domains of verbal fluency (g = 0.21) and executive functioning (g = 0.19) with small to medium effect sizes.

7.3.2 Penn CNB

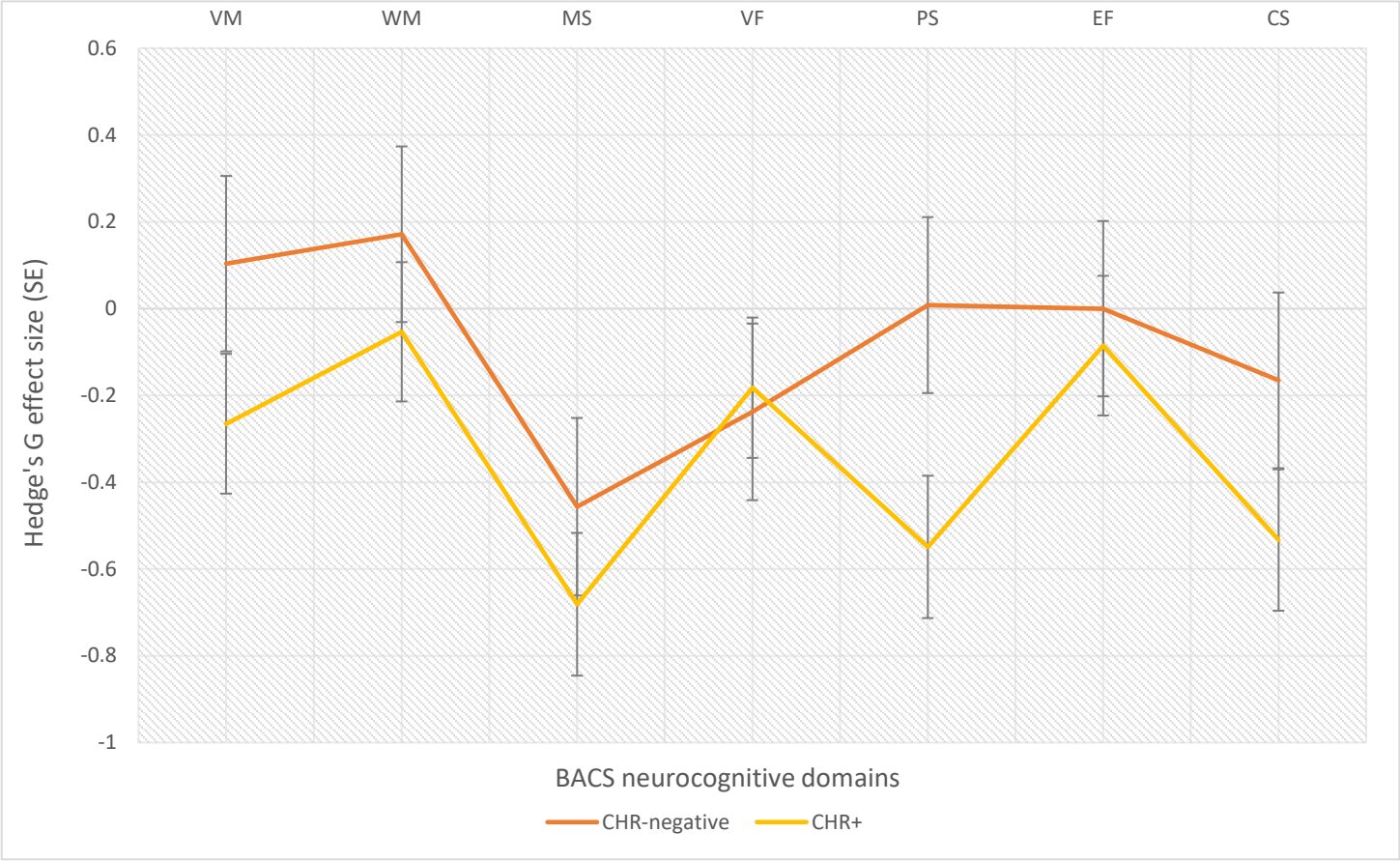
Scores in the Penn CNB were standardised to the YouR HC group to produce z-scores which are illustrated in Table 4. For each test an accuracy score (A) and reaction time (RT) were reported, the z-score for the latter was multiplied by -1 so a negative score for all scores signify a poorer score and a positive score, a better performance.

Following a Hochberg GT2 post-hoc analysis it was found that CHR-positive participants performed statistically significantly worse compared to HC in the CPT-A (Attention, g = 0.37) and ERT-RT (g = 0.41) specifically for 'happy' faces (g = 0.57) with small to medium effect sizes. See Appendix C for a full report of emotion specific responses between groups.

Figures 1 and 2 illustrate the Hedge's g effect sizes found between the HC and the experimental groups in the BACS and the Penn CNB, respectively. Error bars illustrate standard error (SE)

Figure 1: BACS: Effect sizes between HC and CHR-negative, CHR-positive

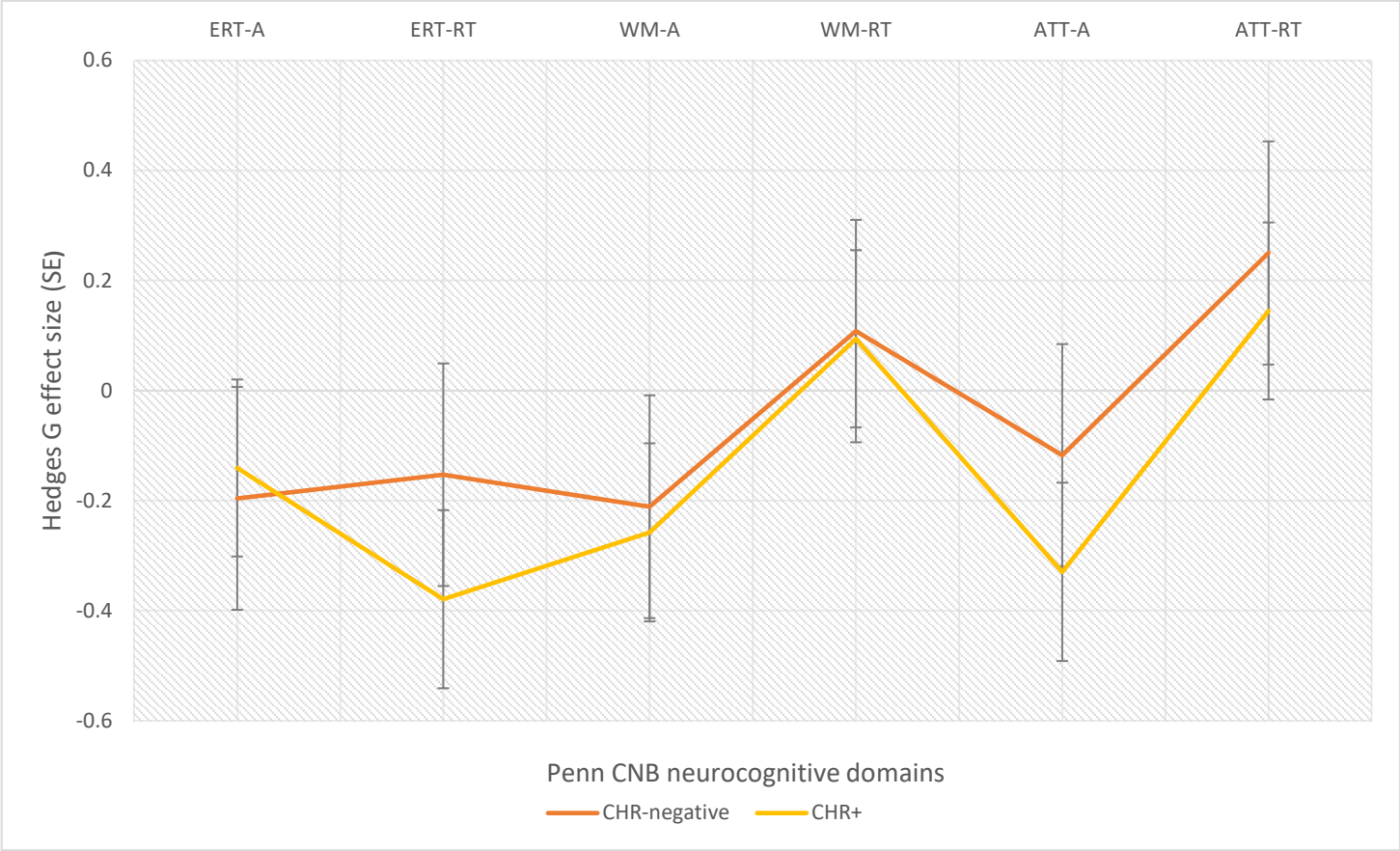
Error bars indicate standard errors of the mean. Effect sizes classified as small (0.2), medium (0.5) and large (0.8)



Abbreviations: VM = verbal memory, WM = working memory, MS = motor speed, VF = verbal fluency, PS = processing speed, EF = executive functioning, CS = composite score

Figure 2: Penn CNB: Effect sizes between HC and CHR-negative, CHR-positive

Error bars indicate standard errors of the mean. Effect sizes classified as small (0.2), medium (0.5) and large (0.8



Abbreviations: ERT–A = emotion recognition test accuracy score, ERT-RT = emotion recognition test reaction time, WM-A = working memory accuracy score, WM-RT = working memory reaction time, ATT-A = attention/vigilance accuracy score, ATT-RT = attention/vigilance reaction time

7.4 CHR Subgroups

Within the CHR-positive group there were 31 (26%) participants who met only the BS criteria, 38 (32%) who met only the UHR criteria and 48 (41%) who met both the UHR + BS criteria. See Appendix B for a summary of the clinical, functioning and neurocognitive characteristics of these groups. There were no statistically significant differences between the BS, UHR and BS+UHR groups in measures of functioning.

A statistically significant difference between UHR and BS + UHR was found following a Hochberg GT2 post hoc comparison with the UHR group performing worse with a medium effect size (*g* = -0.59). Comparisons to the HC group found that all groups performed statistically significantly worse than HC in motor speed with medium to large effect sizes (HC vs BS: g = -0.61, HC vs UHR: g = -1.11, HC vs BS+UHR: g = -0.70). Only the UHR group performed statistically worse in attention (g = -0.64), processing speed (g = -0.68) and had a lower composite score (g = -0.82) with medium to large effect sizes.

7.5 Comparison of Clinically and Community Recruited CHR Groups

Within the CHR group 90% (N = 110) were recruited from the general population (CHR-community) and 10% (N = 12) were recruited through clinical pathways (CHR-clinical). There were no statistically significant differences in CAARMS severity, GAF scores or social functioning between these two groups at baseline following a Mann-Whitney U test. The CHR-clinical group was statistically significantly impaired in role functioning was a small effect size (r = -0.19) by comparison to the CHR-community group. See Appendix A for a summary of clinical characteristics of these groups.

Neurocognitive performance between CHR-clinical, CHR-community and HC was compared using a one-way ANOVA analysis. There were no statistically significant differences between performance in the CHR-clinical and CHR-community recruited participants. Post-hoc comparisons using the Hochberg GT2 revealed statistically significant impairments in both groups in motor speed and processing speed and Games-Howell, a lower composite score. However, the CHR-clinical group had larger impairments (motor speed: g = -1.14, processing speed: g = -1.32, composite scores: g =

-1.32) than the CHR-community group (motor speed: g = -0.64, processing speed: g = -0.48, composite score: g = -0.49). The CHR-community group had additional impairments with small effect sizes in the emotion recognition (RT; g = -0.35) and attention (g = -0.32) compared to HC that were not observed in the CHR-clinical group.

7.6 Predicting Baseline Positive Symptom Severity and Functioning

A stepwise multiple linear regression analysis was conducted with the community recruited CHR-positive participants to determine if performance in the neurocognitive tests at baseline could predict CAARMS severity, global, role and social functioning. Only neurocognitive tests where there was a statistically significant difference between YouR HC or BACS standardised controls and CHR-positive participants were included (verbal memory, working memory, motor speed, processing speed, composite score, attention and emotion recognition response time). Table 5 outlines the findings from the regression analysis.

Table 5: Linear Regression for the Effects of Neurocognitive Performance on Clinical Characteristics at Baseline in Community Recruited CHR-positive Participants

	B (95% CI)	Standard Error B	β	R^2	F	p
CAARMS severity						
Model 1				0.04	3.98	0.05
Constant	27.52 (24.27, 30.76)	1.64				
ERT (RT)	1.97 (0.01, 3.82)	0.96	.19*			
GAF score						
Model 1				0.07	8.17	0.05
Constant	60.03 (57.65, 62.41)	1.20				
Verbal memory	2.25 (0.69, 3.81)	0.79	.27**			
Role Functioning						
Model 1				0.04	4.49	0.04
Constant	7.59 (7.40, 7.78)	0.10				
CS	0.16 (0.01, 0.32)	0.08	.20*			
Social Functioning						
Model 1				0.08	9.61	<0.01
Constant	7.61 (7.42., 7.80)	0.10				
CS	0.24 (0.09, 0.40)	0.08	.29**			
Model 2				0.12	7.12	<0.01
Constant	7.67 (7.47, 7.87)	0.10				
CS	0.20 (0.05, 0.36)	0.08	.24**			
EI (RT)	-0.13 (-0.25, -0.02)	0.06	-.19*			

*p<0.05, ** p<0.01, RT = response time

The RT from the ERT explained 4% of the variability in CAARMS severity scores. Higher CAARMS severity scores predicted slower response times. Verbal memory score accounted for 7% of the variance in GAF score, with high GAF score predicting higher verbal memory scores. The BACS composite score (CS) explained 4% and 8% of the variability of role and social functioning, respectively. Both CS and ERT (RT) together accounted for 12% of the variance in social functioning.

Following the statistically significant findings from the ERT an additional stepwise multiple linear regression analysis was conducted with the emotion specific response times (happy, fear, angry, sad and no emotion). Happy (RT) was found to account for 7% of the variance in CAARMS severity with slower response times predicting a higher severity. Angry (RT) accounted for 11% of the variance social functioning with slower response times predicting lower functioning. See Table 6 for a full summary of the emotion specific (RT) regression analysis.

Table 6: Effects of Emotion Specific (RT) on Clinical Characteristics at Baseline for Community Recruited CHR-positive Participants

	B (95% CI)	Standard Error B	β	R^2	F	p
CAARMS Severity						
Model 1				0.07	7.61	<0.01
Constant	26.77 (23.43, 30.11)	1.68				
Happy (RT)	3.06 (0.86, 5.27)	1.11	.26*			
Social Functioning						
Model 1				0.10	11.16	<0.01
Constant	7.62 (7.43, 7.81)	0.10				
Anger (RT)	-0.20 (-0.32, -0.08)	0.60	-.31*			

*P<0.01, RT = response time

7.7 Follow-up Analysis

Participants were assessed at 3 or 6 month intervals for up to 36 months. The following analysis examined follow-up data of CHR-positive participants, primarily from the 12-month assessments (N = 41, 84%). If data was not available at 12 months, it was taken from the 9-month assessment (N = 8, 16%). There were 33 (47%) CHR-positive participants who met the ARMS group at baseline but not follow-up (remission group), 16 (23%) who met the ARMS criteria at baseline and follow-up (non-remission group), 16 (23%) participants only met basic symptoms criteria at baseline and no CAARMS criteria at FU (no change group), 4 (6%) participants only met BS criteria at baseline but met ARMS criteria at FU and 1 (1%) participant who met psychosis threshold by FU. There were 55 participants who were included at baseline analysis that could not be included in the follow-up analysis because they were still awaiting their 9 or 12-month assessment (N = 46) or withdrew/disengaged (N = 9) from the study.

7.8 Missing Data

Participants included in the following analysis with only a 9-month assessment did not have a social and role functioning score because this was only administered at the 12-month assessment. In total, there were 6 remitters and 3 non-remitters without a social and role functioning score at follow-up.

7.9 Demographic, Symptomatic and Functioning Characteristics

Between group comparisons (see Table 6) of remitters (CHR-R) and non-remitters (CHR-NR) found no statistically significant differences in GAF or social and role functioning scores at baseline or follow-up. At baseline in the remitter group 6 (18%) met the criteria for poor role functioning and 5 (15%), poor social functioning. By comparison in the non-remitter group 3 (19%) met the criteria for poor role functioning and 4 (25%), poor social functioning. At follow-up, 3 (11%) and 8 (30%) of the remitters met the criteria for poor role and social functioning, respectively by comparison to 2 (15%) and 3 (23%) of the non-remitters. CHR-NR had a lower

CAARMS severity score at baseline than CHR-R but this did not reach statistical significance ($p = 0.07$).

The Wilcoxon Signed Ranks test, nonparametric alternative to the paired samples t-test was used to compare baseline and follow-up clinical characteristics within the CHR-R and CHR-NR groups. There were no significant differences between baseline and follow-up GAF scores in remitters ($z = -0.411$, $p = 0.68$) and non-remitters, ($z = -0.48$, $p = 0.65$). Similarly, there were no statistically significant differences within either group for role functioning (remitters, $z = -1.31$, $p = 0.23$ and non-remitters, $z = -0.69$, $p = 0.61$) or social functioning (remitter, $z = -0.64$, $p = 0.56$ and non-remitter, $z = -0.55$, $p = 0.82$). Both remitters ($z = -5.00$, $p < 0.01$) and non-remitters ($z = -3.24$, $p < 0.01$) had improvements in their CAARMS severity scores from their baseline to follow-up assessments.

7.10 Neurocognitive Characteristics

Baseline scores from the BACS and Penn CNB were calculated for CHR-R and CHR-NR and reported in Table 5. Following an independent t-test, CHR-NR performed poorer than CHR-R with medium effect sizes in the motor speed task ($g = 0.71$) and performed better in the attention (RT) task ($g = -0.60$) with medium effect sizes. A Mann-Whitney U analysis found that the CHR-NR group had more pronounced impairments in emotion recognition (RT) with a small effect size ($r = 0.32$), specifically for 'happy' faces with a large effect size ($g = -0.90$). A statistically significant difference in emotion recognition (RT) remained for CHR-NP by comparison to HC with a large effect size ($g = -0.60$). See Appendix D for a full report of the emotion specific comparisons between HC, CHR-R and CHR-NR.

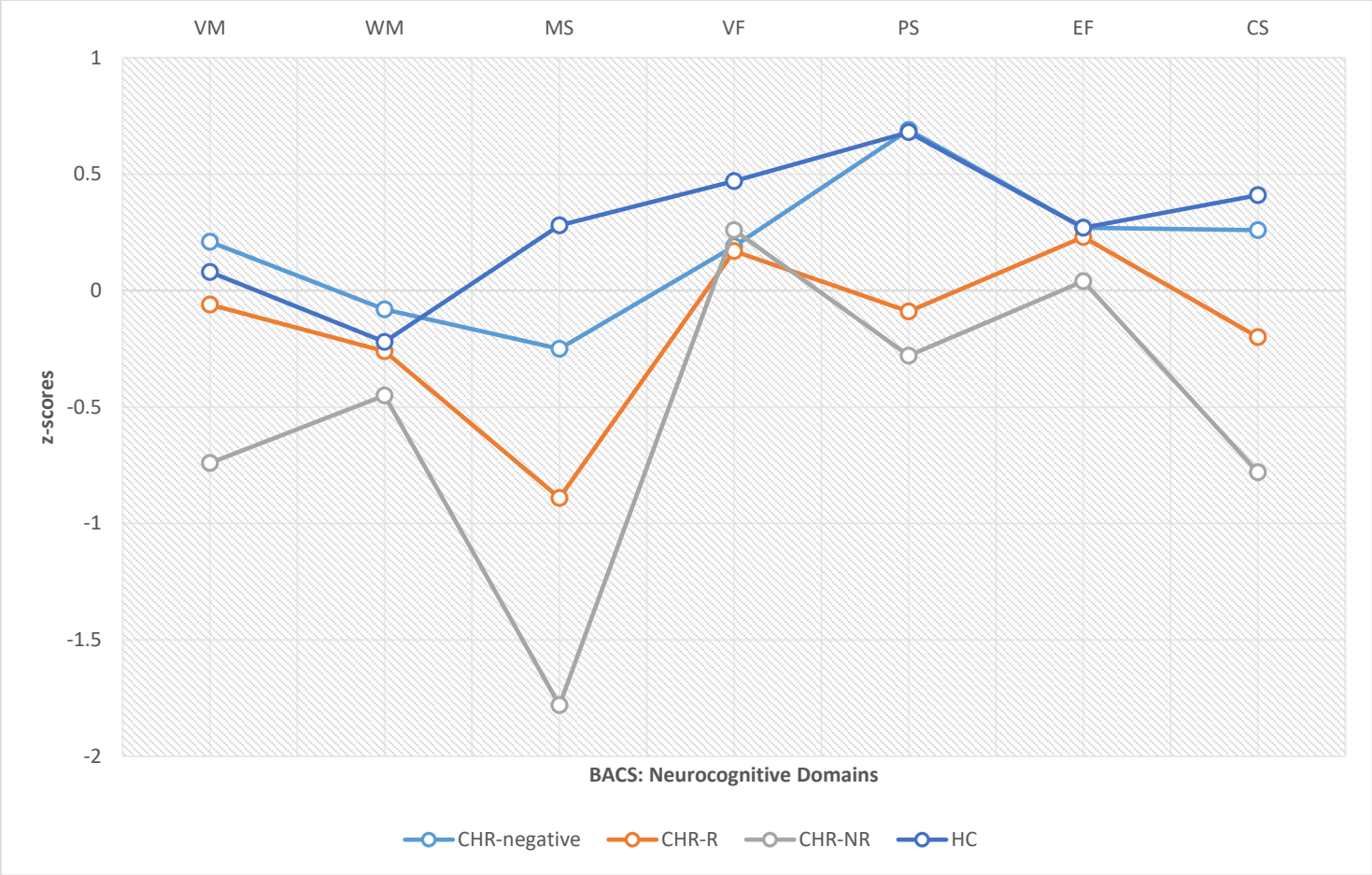
Additionally, as illustrated in Figures 3 and 4, the CHR-R group performed more similarly to the CHR-negative group and HC in the verbal memory and executive functioning tasks in the BACS together with the emotion recognition (RT) and working memory (A) in the Penn CNB.

Table 7: Baseline and Follow-up Clinical and Neurocognitive Characteristics of CHR-R and CHR-NR

	N	CHR-R	N	CHR-NR	Statistic	p
Demographics						
Age (mean ± SD)	33	21.64 ± 4.14	16	21.94 ± 4.36	U = 249.5	0.76
Female (N, %)	33	27 (82)	16	12 (75)	X^2 = 0.31	0.71
Current Psychological Intervention (N, %)	33	7 (21)	16	3 (19)	X^2 = 0.69	0.68
Medication (N, %)	33	16 (48)	16	8 (50)	X^2 = 0.01	1.00
Anti-psychotic		1 (3)		0 (0)		
Mood stabiliser		1 (3)		0 (0)		
Anti-depressant		6 (18)		2 (12.5)		
Other		2 (6)		3 (19)		
Multiple		6 (18)		3 (19)		
NART: Full IQ	33	113.56 ± 12.52	16	110.81 ± 9.01	U = 236.50	0.67
NART: Verbal IQ	33	110.03 ± 6.48	16	109.00 ± 8.29	t(46) = 0.47	0.64
NART: Performance IQ	33	111.09 ± 6.13	16	110.19 ± 7.91	t(46) = 0.44	0.66
Clinical Characteristics						
BL: CAARMS severity (median, range)	33	29 (4 – 66)	16	44 (12 – 52)	U = 179.50	0.07
FU: CAARMS severity (median, range)	33	8 (0 – 42)	15	27 (9 – 50)	U = 62.00	<0.01
BL: GAF (median, range)	33	60 (40 – 87)	16	58 (43 – 80)	U = 228.00	0.45
FU: GAF (median, range)	31	58 (21 – 88)	16	55.50 (38 – 78)	U = 193.50	0.22
BL: Role Functioning (median, range)	33	8 (5 – 9)	16	7.50 (6 – 9)	U = 221.50	0.34
FU: Role Functioning (median, range)	27	8 (5 – 9)	13	8 (4 – 8)	U = 127.50	0.13

Table continued	N	CHR-R	N	CHR-NR	Statistic	p
BL: Social Functioning (median, range)	33	8 (5 – 10)	16	8 (6 – 9)	U = 223.00	0.36
FU: Social Functioning (median, range)	27	8 (5 – 10)	13	8 (6 – 8)	U = 152.00	0.47
BACS						
Verbal Memory (mean ± SD)	33	-0.06 (1.40)	16	-0.74 (1.49)	U = 186.50	0.10
Working Memory (mean ± SD)	33	-0.26 (0.92)	16	-0.45 (1.11)	t (47) = 0.63	0.53
Motor Speed (mean ± SD)	33	-0.89 (1.22)	16	-1.78 (1.24)	t (47) = 2.37	0.02
Verbal Fluency (mean ± SD)	33	0.17 (1.02)	16	0.26 (1.27)	t (47) = -0.28	0.78
Processing Speed (mean ± SD)	33	-0.09 (0.95)	16	-0.28 (1.38)	t (47) = 0.55	0.59
Executive Functioning (mean ± SD)	33	0.23 (0.91)	16	0.04 (1.00)	U = 227.50	0.43
Composite Score (mean ± SD)	33	-0.20 (1.14)	16	-0.78 (1.43)	U = 204.00	0.20
Penn CNB						
ERT (mean ± SD)	33	-0.06 (0.84)	16	-0.34 (1.38)	U = 246.50	0.71
ERT (RT) (mean ± SD)	33	-0.38 (1.34)	16	-1.80 (2.35)	U = 159.00	0.02
Working Memory (mean ± SD)	32	-0.26 (1.05)	16	-1.19 (2.69)	U = 239.50	0.71
Working Memory (RT) (mean ± SD)	32	0.07 (0.74)	16	-0.09 (0.83)	t (46) = -0.67	0.50
Attention (mean ± SD)	32	-0.79 (2.72)	16	-1.46 (4.62)	U = 244.50	0.50
Attention (RT) (mean ± SD)	33	-0.09 (0.95)	16	0.44 (0.67)	t (47) = 0.21	0.05

Figure 3: Z-scores of BACS neurocognitive performance with CHR-R and CHR-NR



Abbreviations: VM = verbal memory, WM = working memory, MS = motor speed, VF = verbal fluency, PS = processing speed, EF = executive functioning, CS = composite score

Figure 4: Z-scores of Penn CNB neurocognitive performance with CHR-R and CHR-NR

Abbreviations: ERT = emotion recognition task, ERT-RT = emotion recognition task (RT), WM = working memory, WM = working memory (RT), ATT = attention, ATT–RT = attention (RT)

Chapter 8

Discussion

8.1 Summary of Main Findings

The following will summarise the main findings from the statistical analyses addressing the hypotheses discussed in Chapter 5 before discussing the results of the study as a whole whilst considering thoughts and findings from previous research.

The primary aim of the current research project was firstly to investigate if neurocognitive impairments typically observed in clinically recruited CHR individuals could be extended to those recruited from the general population and secondly to explore their relationship with positive symptom severity and functioning. In line with Hypothesis 1, community recruited CHR-participants displayed cognitive impairments by comparison to healthy controls but not to the same extent as the clinically recruited CHR-participants. Consistent with previous studies using clinically recruited participants, the community recruited group were impaired specifically in the domains of motor speed, processing speed, emotion recognition (RT), attention and in the neurocomposite score by comparison to healthy controls. Furthermore, positive psychotic symptom severity was significantly associated with emotion recognition (RT), specifically for 'happy' faces, contrary to Hypothesis 2 that predicted that positive symptom severity would be independent from cognition. As expected by Hypothesis 3 neurocognitive test performance was significantly associated with functioning, specifically performance in verbal memory predicted the GAF score while the neurocomposite score explained variances in social and role functioning. In a second model, variances in social functioning were further explained with the addition of the emotion recognition (RT), specifically for 'angry' faces.

Neurocognitive impairments were also explored in CHR-negative participants who scored below the threshold CHR criteria but were characterised by psychiatric comorbidities to investigate the contribution of non-psychotic symptomatology to cognitive impairments. Contrary to Hypothesis 4, there were no statistically significant differences in neurocognitive

functioning between the CHR-negative group and healthy controls. Additionally, CHR-positive participants were statistically significantly impaired by comparison to CHR-negative participants in processing speed.

The third aim investigated the association between baseline neurocognitive functioning on clinical outcome at 12 months. Harmonious with Hypothesis 5 those who did not remit from their baseline APS had more pronounced deficits at baseline in motor speed and emotion recognition (RT) than those who remitted. Furthermore, the CHR-R group performed more similarly to the healthy controls and CHR-negative group in the verbal memory and executive functioning tasks in the BACS together with the emotion recognition (RT) and working memory (accuracy score) in the Penn CNB.

8.2 Description of Sample

8.2.1. Symptomatology and Functioning

The CHR-positive group had significant impairments in social and role functioning by comparison to HC. The median score for both scales reflects ‘good functioning’ however this can be misleading as the functioning scores ranged from ‘major impairment’ to ‘superior functioning’ (Cornblatt et al., 2007). Similarly, the median GAF score was 58 representing ‘moderate symptoms’ but again scores ranged from ‘inability to function in almost all areas’ to ‘no symptoms’ (Yung et al., 2006) highlighting the heterogeneity with CHR samples.

Following the distinction in recruitment pathways, it was found that the clinical sample had significantly lower role functioning but not social functioning than those from the community. There were no significant differences between these two groups in the severity of positive symptoms or GAF scores. However, these statistical comparisons were underpowered due to the small number of clinically recruited CHR-participants so results have to be interpreted with caution. A non-statistical comparison of these results supports previous findings that those recruited clinically had a higher positive symptom severity and lower levels of functioning

(Mills et al., 2017). More demographically matched CHR participants from clinical pathways would have to be recruited to determine if these observations were statistically significant.

Similar to findings in clinically recruited populations (Fusar-Poli et al., 2012), the community recruited CHR-positive participants in the current study were characterised by a high prevalence of non-psychotic disorders, primarily depression and anxiety. Furthermore, three quarters of the community recruited CHR-positive participants reported seeking psychological intervention which supports the notion that community recruited CHR-participants should not be viewed as a non-help seeking population (Mills et al., 2017).

The CHR-negative group had statistically significantly higher social, role and global functioning compared to the CHR-positive group. Although one of the reasons the inclusion of this group was to address the influence of comorbid psychiatric disorders the CHR-negative group had a lower prevalence of these disorders so the results have to be interpreted with caution. At present, it cannot be concluded that positive psychotic symptomatology uniquely contributes to poor functioning in the CHR group in the current study. However, previous studies have consistently associated the presence of non-psychotic disorders with poor functional outcomes in CHR populations (Lin et al., 2015; Rutigliano et al., 2016)

8.2.2 Neurocognitive Characteristics

CHR-positive participants compared to HC had specific impairments in motor speed, processing speed, emotion recognition (RT) and attention in addition to a lower composite score derived from the BACS. Motor speed was the most pronounced deficit in CHR-positive participants which is consistent with evidence that illustrates early motor abnormalities in children who develop ScZ in adulthood (Dickinson, Laurens, Cullen & Hodgins, 2012). However, although motor impairments are viewed as a core feature of ScZ (Morrens et al., 2006) less research is available for at-risk samples. Studies that have independently assessed this domain report mixed findings, with some reporting deficits (Carrión et al., 2011; Niendam

et al., 2006) and others intact abilities (Keefe et al., 2006; Woodberry et al., 2010). Fewer studies have utilised the token motor test used in the current analysis but two recent studies have reported impairments by comparison to healthy controls in UHR participants using this task (Allot et al., 2018; Ohmuro et al., 2018) suggesting its possible utility in detecting impairments in at-risk groups.

Moderate impairments in the CHR-positive group by comparison to HC were observed for processing speed assessed using the DSST supporting consistent findings from previous research (e.g. Hauser et al., 2017; Pukrop et al., 2010; Seidman et al., 2010). Moreover, impairments in processing speed were also observed in the CHR-positive group by comparison the CHR-negative group however as the CHR-negative group had a lower prevalence of non-psychotic disorders it cannot be concluded that deficits in processing speed are unique to positive psychotic symptomatology. Further studies would have to include more CHR-negative participants with comorbid psychiatric disorders are needed to investigate this further.

Performance in the DSST and token motor task were found to be positively correlated in both HC and CHR-positive participants but not CHR-negative participants. The finding between HC and CHR-positive participants supports previous reports from individuals with ScZ and healthy controls (Keefe et al., 2004). Although there has been an argument to delineate motor speed from processing speed (Morrens et al., 2006) performance between these specific tasks appears to be mediated by a shared underlying factor.

A significant impairment in the neurocomposite score from the BACS supports the notion put forward by Gold and colleagues (2009) that impairments in composite scores reflect the contribution of deficits in individual tasks rather than an impaired general cognitive ability factor as a number of tasks in the neurocognitive testing battery were preserved in CHR-positive participants. Deficits in verbal memory, verbal fluency, working memory and executive functioning were not found although they are widely reported in previous research (e.g. Fusar-Poli et al., 2012; Hauser et al., 2017). Impairments in these domains have been associated with transitions to frank psychosis (Carrión et al., 2018; Fusar-Poli et al., 2012). As the current CHR-positive sample had only one transition to frank psychosis within the 12-

month follow-up this may be reflected in the lack of positive findings in these domains. High levels of educational attainment in the CHR- positive group may have also contributed to negative findings as previously this has been suggested to act as a protective factor, especially for verbal fluency (Keefe et al., 2008).

From the Penn CNB, CHR-positive participants had a significantly slower response time in the emotion recognition task but an intact accuracy score. This suggests that this group has an impairment in processing facial information but participants are able to compensate by slowing down their responses to achieve high accuracy scores. These findings in the CHR-positive group are not consistent with previous studies that have reported accuracy impairments (Addington et al., 2008; Amminger et al., 2011; Comparelli et al., 2013; Kohler et al., 2014) but no differences in reaction time (Glenthøj et al., 2018) in CHR groups by comparison to healthy controls. However, abnormal neural activation has been recorded in a small number of UHR participants who exhibited intact behavioural responses during an emotion discrimination task (Seiferth et al., 2008) suggesting difficulties may be present in at-risk samples but these cannot always be captured by accuracy scores.

Further analysis to identify impairments in specific facial expressions of emotion found significantly slower response times for 'happy' faces within the CHR-positive group by comparison to healthy controls. Previous studies have highlighted impairments only in negative emotions including 'sad', 'fear' and 'disgust' faces (Amminger et al., 2011; Comparelli et al., 2013) but the results from the current analysis suggest processing impairments may also be present for positive emotions. Additionally, the CHR-positive group did not present with significant impairments in accuracy or reaction time for facial expressions that conveyed 'no emotion'. This does not support previous studies that have reported a tendency for UHR participants and unaffected relatives of individuals with ScZ to attribute negative emotions to neutral faces (Allot et al., 2014; Eack et al., 2010; van Rijn et al., 2011).

Attention was also significantly impaired in CHR-positive participants by comparison to HC. Attention has been argued to be a stable vulnerability marker in at-risk populations (Francey, Jackson, Phillips, Wood, Yung & McGorry, 2005); Lencz, Smith, McLaughlin, Auther,

Nakayama, Hovey & Cornblatt, 2006) as deficits are more pronounced in individuals who later transition to psychosis compared to those who do not (Seidman et al., 2016). The results from the current study support previous findings that highlight its centrality to the CHR state (Bora et al., 2014; Fusar-Poli et al., 2012; Hauser et al., 2017).

8.3 Neurocognition in Community and Clinically Recruited CHR Groups

Following the distinction of recruitment pathways within CHR-positive participants no statistically significant differences in neurocognitive performance were revealed between those recruited clinically and those from the general population. When statistical comparisons were made between clinical and community CHR groups with healthy controls clinically recruited CHR-participants had large impairments motor speed, processing speed and the composite score. However, due the small number of clinically-recruited CHR-participants these analyses are underpowered and thus need to be interpreted with caution.

In support of Hypothesis 1 the CHR-community group presented with moderate effect sizes in motor speed, processing speed and in the neurocomposite score in addition to small effect sizes in emotion recognition (RT) and attention compared to healthy controls. Previous meta-analyses using clinically recruited CHR-participants have reported similar moderate effect sizes to those observed in the current community recruited group in processing speed assessed using the DSST (Fusar-Poli et al., 2012; Hauser et al., 2017) although larger impairments have also been reported (Bora et al., 2014). Similar sized deficits in attention, assessed using the CPT, have also been reported in clinical populations (Bora et al., 2014; Fusar-Poli et al., 2012; Hauser et al., 2017). These findings suggest that neurocognitive impairments in processing speed and attention observed in clinical groups from the previous studies may be extended to CHR individuals in the general population supporting growing evidence that deficits may be an endophenotype of psychosis. As discussed, the emotion recognition (RT) has not been widely studied but the impairment revealed in the current analysis highlights its potential association with attenuated psychotic symptoms in individuals in the general population.

8.4 Association between Neurocognition and Positive Psychotic Symptom Severity

Within the CHR-community group the association between positive symptom severity and neurocognitive impairment was examined. Hypothesis 2 expected that positive psychotic symptom severity would be independent from cognitive functioning. Although a regression analysis indicated that neurocognitive assessments overall were not a strong predictor of the positive symptom severity there was one statistically significant contributor. The response time taken in the emotion recognition task, with slower responses predicting higher severity scores accounted for 4% of the variance. Specifically, reaction times for 'happy' facial expressions of emotion explained 7% of the variance with slower reaction times predicting higher severity scores. This is partially supported by previous findings that have reported an association between emotion recognition and the degree of attenuated positive psychotic symptoms (Glenthøj et al., 2018) and transitions to frank psychosis (Allot et al., 2014) in UHR populations. However, other studies have failed to find a significant association between emotion recognition and positive psychotic symptomatology but posit that deficits contribute to the creation and exacerbation of delusions (Amminger et al., 2012).

Overall, the variance accounted for by emotion recognition (RT) was relatively low suggesting that other factors contribute more to the severity of positive symptoms in community recruited CHR groups. Additionally, non-significant findings for other neurocognitive tests are supported by previous research, suggesting their relative independence in the severity of positive symptoms in both clinical and community recruited groups (Niendam et al., 2006; Ventura, Helleman, Thames, Koellner & Nuechterlein, 2009).

8.5 Association between Neurocognition and Functioning

In support of Hypothesis 3 significant associations were found between neurocognitive tasks and measures of functioning. Verbal memory significantly predicted 7% of the variance in GAF score, with a better performance predicting a higher score supporting previous studies that investigated social and occupational functioning and quality of life outcomes (Lin et al., 2011) and social functioning (Niendam et al., 2006) in clinically recruited CHR individuals. This

finding additionally complements a previous study that observed that verbal memory alongside processing speed, reasoning and problem solving had the strongest correlation with real world functioning (Keefe, Poe, Walker & Harvey, 2006).

The composite score from the BACS explained 4% and 8% in the variances in role and social functioning respectively, with higher scores predicting better functioning. This finding is similar to that of Carrión and colleagues (2011) who reported that the neurocomposite score they used explained 8% and 5% of the variance in social and role functioning, respectively. The composite score combined with ERT (RT) in a second predictive model explained 12% of the variance in social functioning. Following a regression analysis investigating specific emotional expressions, the response time for identifying 'anger' faces explained 10% of the variance in social functioning, with slower responses predicting lower functioning. This supports the notion that emotion recognition is integral to social cognition and functioning (Amminger et al., 2012) and that difficulties interpreting emotional expressions can cause stress and make it challenging to engage in social interactions and communication (Bediou et al., 2007) in turn negatively impacting social and role functioning.

Additionally, results from the regression analysis highlight a possibility to why significant differences were not identified between CHR-positive participants and HC in verbal memory and the response time for 'angry' faces, as deficits in these tasks appear to be associated with poorer social and role functioning which was not experienced by the majority of the CHR-positive group.

8.6 Neurocognition in CHR subgroups

Comparisons within the CHR-positive group of individuals who met either the BS, UHR or BS+UHR criteria revealed subtle, non-significant differences in neurocognitive performance between the BS and UHR groups with the UHR performing worse. This finding is supported by previous studies that have reported small, non-significant neurocognitive impairments in studies that used the BS criteria compared to those who used the UHR (Fusar-Poli et al., 2012). Another study reported that those in the late prodromal stage had deficits in all neurocognitive domains assessed compared to the specific impairments in executive control/processing speed

observed in those in the early prodromal stage suggesting that certain deficits can be observed very early and progressive impairments occur towards the end of the prodrome (Fromman et al., 2011). In the current study, UHR participants were impaired by comparison to HC in motor speed, processing speed and attention/vigilance while BC participants were only significantly impaired in motor speed suggesting that this could be a marker for early psychosis risk.

8.7 Follow-up Analysis

8.7.1 Description of Sample

By the 12 month follow-up assessment, 66% of the CHR-positive participants who met the ARMS at baseline were in remission, 32% maintained these symptoms and 2% transitioned to psychosis. Compared to previous longitudinal studies using exclusively clinically recruited participants the number of transitions is dramatically lower (Fusar-Poli et al., 2012; Yung & McGorry, 2004) suggesting that CHR-participants in the current study, who were recruited mainly from the general population, were not enriched for psychosis risk. Although there is a considerable number of participants still experiencing ongoing attenuated psychotic symptoms the majority were in remission suggesting that the sample was diluted by a high number of false positives. The CHR criteria focuses on positive symptomatology which alone has a low to moderate predictive power of psychosis onset (Klosterkotter et al., 2001; Yung et al., 2005). As previous studies have highlighted that transitional psychotic experiences are commonly experienced by healthy individuals (van Os et al., 2001; Morey et al., 2005; Rössler et al., 2007) using only positive psychotic symptomology risks incorrectly labelling healthy individuals as CHR. The high number of non-transitions and remissions in the current study compared to previous studies suggests that recruiting from the general population over prodromal services increases this risk further.

As a high number of individuals who experience a first episode of psychosis are not seen by prodromal services (Ajnakina et al., 2017) it remains important to look out with prodromal services for individuals at risk. To increase the predictive power additional criteria may have to be met to minimise the dilution of samples. In their review Fusar-Poli and colleagues (2012)

reported that the following clinical variables were observed in the NAPLS (Seidman et al., 2010) and PACE (Thompson, Nelson & Yung, 2011) clinics to be associated with transitions to psychosis: high unusual thought content scores, low functioning and genetic risk with functional decline. Additionally, cognitive functioning may also improve predictive power alongside clinical variables (Lencz et al., 2006; Riecher-Rössler et al., 2009).

8.7.2 Symptomatology and Functioning

At 12 months, as would be expected non-remitters reported a statistically significantly higher positive symptom severity score than non-remitters. However, there was an overlap in the range of scores suggesting that some individuals in both groups were straddling the boundary between threshold and subthreshold attenuated psychotic symptoms. Comparisons at baseline found no statistically significant differences in positive symptom severity between remitters and non-remitters. Although, subtle non-significant differences were observed with non-remitters having a higher positive symptom severity score suggesting that those who present with a higher severity at intake are more likely to remain symptomatic by 12 months. This supports previous research that has highlighted psychotic symptom severity to be a reliable characteristic differentiating converters from non-converters (Fusar-Poli et al., 2013) specifically at the baseline assessment (Hengartner et al., 2017). From baseline to follow-up both groups displayed an improvement in positive psychotic symptom severity. Previous research observing symptom severity over a longer period with close follow-up assessment intervals have reported a non-linear progression from attenuated to frank psychotic symptoms reporting that participants may appear to be in remission but soon develop threshold symptoms (Hengartner et al., 2017). It may be likely that the group allocations in the current study do not reflect the long term transitional outcome of the group.

The current study explored the heterogeneity of outcome in CHR-participants by distinguishing between ‘remitter’ and ‘non-remitter’ groups, however this may have been too simplistic. A recent study argued that more nuanced groups need to be constructed to accurately reflect the different clinical trajectories taken by at-risk groups (Polari et al., 2018). Polari and colleagues (2018) defined recovery as being in remission from APS for over 6 months. From their study

they reported that 20% of their participants had a reoccurrence of their UHR status after remission but before recovery and 4% had a relapse after recovery at 4 assessments over 12-months. This highlights the fluctuating state of psychotic symptoms within CHR groups and implies remitters and non-remitters in the current study may have experienced remission and relapse within this time frame and their symptoms at 12 months may not be an accurate representation of their clinical status. As more follow-up assessments are completed within the CHR-positive group it would be interesting to study closer the clinical trajectory of community recruited participants over a longer period of time to determine if they complement those observed in clinical populations (Polari et al., 2018). Identifying the long term pathways of CHR individuals is important for research and clinical practice as it could help to identify the underlying biopsychosocial predictors for each trajectory to better direct treatment.

At 12 months remitters and non-remitters had similar psychosocial functioning scores that did not change significantly from their baseline to follow-up assessment. Both groups reported a median GAF score that reflected 'moderate symptoms' and a social and role functioning score that represented 'good functioning', although there was a considerable range of functioning between participants in both groups. Furthermore, both groups had similar frequencies of participants who met the criteria for poor functioning suggesting that CHR individuals may still have unfavourable outcomes regardless of their positive symptom status at 12 months, supporting previous findings that have highlighted that non-psychotic outcomes are not synonymous with good functioning (Lin et al., 2015; Polari et al., 2018).

There is accumulating evidence that neurocognitive impairments contribute to poor functional outcomes regardless of transitional status in clinically recruited CHR-participants (Lin et al., 2011). In the current study there were not enough CHR individuals who met the criteria for 'poor functioning' by 12 months to compare baseline neurocognitive impairments. As more follow-up data is gathered from the YouR study it would be interesting to identify if 'poor functioning' was as common an outcome for community recruited participants as it was for clinically recruited participants and furthermore explore the influence of neurocognitive impairments at baseline on functioning outcome.

8.7.3 Neurocognitive Characteristics

At baseline non-remitters were statistically significantly more impaired in motor speed and emotion recognition (RT) by comparison to remitters. Furthermore, remitters but not non-remitters presented with a similar performance to healthy controls and CHR-negative participants in verbal memory, working memory, executive functioning and emotion recognition. These findings support previous results that observed heterogeneity in neurocognitive performance at baseline between remitters and non-remitters (Lee et al., 2014) and suggests that preserved neurocognitive functioning at baseline could be a marker for remission. A previous study highlighted a statistically significant association between immediate verbal memory and remission from psychosis (Simon et al., 2012). Due to small sample sizes the utility of neurocognitive functioning in the prediction of remission from psychosis could not be investigated. Overall, one interpretation of the above findings is that preserved neurocognitive functioning acts as a protective buffer against ongoing psychotic symptoms alternatively however it could be argued that remitters were experiencing transitionary psychotic experiences and were never at real risk of psychosis onset.

Remitters did not display a similar baseline performance to healthy controls in all neuropsychological tests. As neurocognitive performance was not re-tested at the follow-up assessment the neurocognitive trajectory between remitters and non-remitters is unknown. An earlier study reported that remitters displayed an improved performance in semantic fluency between baseline and follow-up whereas non-remitters performance worsened suggesting that semantic verbal fluency is a trait marker of psychosis (Lee et al., 2014). In the current study, verbal fluency at baseline was preserved in both groups so it would be insightful to investigate if performance deteriorated in those with increasing positive symptom severity.

8.8. Implications of the Study

The current study observed neurocognitive impairments specifically in attention, emotion recognition, motor speed and processing speed in at-risk of psychosis individuals recruited from the general population by comparison to healthy controls suggesting they are an

endophenotype of psychotic symptomatology. Furthermore, their association with psychosocial functioning highlights these domains as possible targets for intervention to improve long term clinical and functional outcome. Specific neurocognitive impairments were identified in at-risk participants by comparison to healthy controls in motor speed and emotion recognition following the token motor test and emotion recognition test that have not been widely used in previous research. Motor speed deficits have not consistently been reported in studies using the Finger Tapping Test (Fusar-Poli et al., 2012; Hauser et al., 2017) however, findings from the current analysis support growing research (Allot et al., 2018; Ohmuro et al., 2018) that suggest the Token Motor Test's utility in detecting motor impairments in at-risk groups. Similarly, although accuracy scores from emotion recognition tests have been widely used, response times have not. In the current study, it was revealed that at-risk participants had significantly slower reaction times but not accuracy scores compared to healthy controls. Thus, it is proposed that slower reaction times may reflect compensatory mechanisms used in at-risk participants that cannot be utilised during threshold psychosis. Furthermore, reaction times in the emotion recognition test were found to predict positive psychotic symptom severity and social functioning suggesting their possible utility in predicting transitional and poor functional outcomes.

The 12 month clinical outcome of CHR individuals recruited from the general population was also explored. Overall, the sample experienced high non-transition and remission rates supporting the argument that additional criteria need to be met in order to distinguish false-positive from those at true risk. Statistically significant differences in baseline neurocognitive functioning specifically in motor speed and emotion recognition suggest their potential utility in predicting symptom remission among community recruited CHR individuals.

8.9. Limitations of the Study

The results of this analysis have to be considered with the limitations of the study in mind. Firstly, specific subgroups of participants had small sample sizes (clinically recruited CHR-positive participants, remitters and non-remitters) which may limit the generalisability of these findings. Additionally, females were also overrepresented in all subgroups for reasons that are

unclear. It is important to develop different strategies to recruit more males from the community especially as males have been reported to experience more severe negative symptoms and poorer functioning (Thorup et al., 2007; Walder et al., 2013; Walker et al., 2002).

It is also possible that neurocognitive impairments that significantly accounted for the variance in functioning may have been mediated by negative symptoms (Meyer et al., 2014). As the current study did not assess for negative symptoms their relationship with neurocognition and functioning could not be investigated here.

The SPI-A assessment was not conducted at the 12 month follow-up assessment so CHR-positive individuals who met the BS criteria as baseline were excluded from the follow-up analysis. At 12 months, 16 (80%) of these individuals did not meet the ARMS criteria at follow-up and 4 (20%) did. It is possible that individuals who met only the BS criteria at baseline and not the ARMS at follow-up may have still met the criteria for BS. Furthermore, participants who met both the BS+UHR criteria at baseline who were seen as being in remission at follow-up may have continued to have met the BS criteria. This is supported by a previous study that reported that 12% of participants who met either the UHR or BS+UHR criteria at baseline met only BS symptoms at follow-up (Polari et al., 2018).

8.10 Statistical Limitations

There were some statistical limitations concerning the regression analyses. Firstly, to increase the power of the analyses only the neurocognitive variables that differed significantly between the CHR-positive and healthy controls were included. It is possible that some of the excluded variables may have explained some additional variance in positive psychotic symptom severity and measures of functioning. This was demonstrated following the statistically significant contribution made by ‘angry’ faces (RT) to social functioning, despite no statistically significant differences existing at baseline.

Secondly, conducting a stepwise multiple regression analysis may have omitted some neurocognitive predictors because it increases the risk of Type II errors via suppressor effects.

Chapter 9

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Appendices

Appendix A: Within CHR Group Comparisons of Clinically and Community Recruited Participants

	N	HC	N	Community	N	Clinical	df	Statistic	p	Significant post-hoc tests
BL: CAARMS severity (median, range)	-	-	110	28.50 (0 – 72)	12	23 (14 – 54)	-	U = 620.50	0.74	-
BL GAF score (median, range)	-	-	110	59 (21 – 95)	12	56.50 (43 – 75)	-	U = 566.50	0.43	-
BL: Role functioning (median, range)	-	-	110	8 (4 – 9)	12	6 (6 – 9)	-	U = 433.00	0.04	-
BL: Social functioning (median, range)	-	-	110	8 (5 – 10)	12	7.50 (6 – 9)	-	U = 563.50	0.39	--
Psychological Intervention	-	-	110		12					-
Current (N, %)				15 (14)		3 (25)				
Past (N , %)				54 (49)		6 (50)	2	1.56*	0.49	
≥ 1 Non-psychotic diagnosis (N, %)	-	-	110	104 (94.5)	12	12 (100)	1	$X^2 = 0.69$	0.64	-
						BACS				
Verbal Memory (mean ± SD)	57	0.08 ± 1.20	110	-0.27 ± 1.50	12	-0.60 ± 1.77	2, 176	1.675	0.19	

Table continued	N	HC	N	Community	N	Clinical	df	Statistic	p	Significant post-hoc tests
Working Memory (mean ± SD)	57	-0.22 ± 0.77	110	-0.25 ± 1.00	12	-0.48 ± 1.06	2, 176	0.41	0.67	
Motor Speed (mean ± SD)	57	0.28 ± 1.19	110	-0.58 ± 1.42	12	-1.12 ± 1.33	2, 176	9.97	<0.01	HC vs CHR-community, CHR-clinical
Verbal Fluency (mean ± SD)	56	0.47 ± 1.27	110	0.25 ± 1.26	12	0.15 ± 1.22	2, 175	0.69	0.50	
Processing Speed (mean ± SD)	56	0.68 ± 1.13	110	0.11 ± 1.22	12	-0.68 ± 0.68	2, 176	8.55	<0.01	HC vs CHR-community, CHR-clinical
Executive Functioning (mean ± SD)	57	0.27 ± 0.75	109	0.20 ± 1.01	11	0.14 ± 1.13	2, 174	0.16	0.85	
Composite Score (mean ± SD)	57	0.41 ± 0.80	110	-0.14 ± 1.25	12	-0.86 ± 1.50	2, 29	8.53	<0.01	HC vs CHR-community, CHR-clinical
						Penn CNB				
Emotion Recognition (mean ± SD)	57	0 ± 1	110	-0.15 ± 1.07	11	-0.19 ± 1.32	2, 175	0.42	0.66	
Emotion Recognition (RT) (mean ± SD)	57	0 ± 1	110	-0.51 ± 1.62	11	-0.97 ± 1.39	2, 28	4.55	0.02	HC vs CHR-community
Working Memory (mean ± SD)	57	0 ± 1	107	-0.31 ± 1.46	11	-0.57 ± 1.28	2, 28	2.07	0.14	
Working Memory (RT) (mean ± SD)	57	0 ± 1	109	0.10 ± 0.75	11	-0.08 ± 0.84	2, 174	0.39	0.67	
Attention (mean ± SD)	57	0 ± 1	109	-0.77 ± 2.82	10	-0.78 ± 1.79	2, 28	3.86	0.03	HC vs CHR-community
Attention (RT) (mean ± SD)	57	0 ±1	110	0.16 ± 0.80	11	-0.08 ± 1.21	2, 175	0.81	0.45	

Appendix A: CHR-subgroup Comparisons

	HC (N = 57)	BS (N = 31)	UHR (N = 38)	BS + UHR (N = 48)	df	Statistic	p	Significant post-hoc comparisons
BL: CAARMS severity (mean ± SD)	0 (0 – 12)	13 (0 – 54)	23 (4 – 53)	40 (11 – 72)	3	H = 156.39	<0.01	HC vs BS, UHR, BS+UHR. BS vs UHR, BS+UHR. UHR vs BS+UHR
BL GAF score (mean ± SD)	88 (67 – 97)	63 (48 – 95)	59 (21 – 91)	53.50 (38 – 80)	3	H = 98.84	<0.01	HC vs BS, UHR, BS+UHR. BS vs UHR, BS+UHR.
BL: Role functioning (mean ± SD)	9 (5 – 9)	8 (6 – 9)	8 (6 – 9)	7.50 (4 – 9)	3	H = 49.96	<0.01	HC vs BS, UHR, BS+UHR
BL: Social functioning (mean ± SD)	9 (8 – 10)	8 (6 – 10)	8 (5 – 10)	8 (5 – 9)	3	H = 61.65	<0.01	HC vs BS, UHR, BS+UHR
				BACS				
Verbal Memory (mean ± SD)	0.08 ± 1.20	-0.27 ± 1.72	-0.47 ± 1.59	-0.18 ± 1.35	3. 81	F = 1.07	0.36	
Working Memory (mean ± SD)	-0.22 ± 0.77	-0.10 ± 0.87	-0.40 ± 1.09	-0.27 ± 1.01	3, 170	F = 0.40	0.75	
Motor Speed (mean ± SD)	0.28 ± 1.19	-0.53 ± 1.51	-0.75 ± 1.45	-0.61 ± 1.35	3, 170	F = 6.04	<0.01	HC vs BS, UHR, BS+UHR,
Verbal Fluency (mean ± SD)	0.47 ± 1.27	0.15 ± 0.96	0.01 ± 1.52	0.49 ± 1.16	3, 169	F = 1.75	0.16	
Processing Speed (mean ± SD)	0.68 ± 1.13	0.06 ±1.25	-0.13 ± 1.25	0.14 ± 1.14	3, 170	F = 3.99	<0.01	HC vs UHR

Table continued	HC (N = 57)	BS (N = 31)	UHR (N = 38)	BS + UHR (N = 48)	df	Statistic	p	Significant post-hoc comparisons
Executive Functioning (mean ± SD)	0.27 ± 0.75	0.12 ± 1.26	-0.07 ± 1.03	0.44 ± 0.77	3, 79	F = 1.83	0.15	
Composite Score (mean ± SD)	0.41 ± 0.80	-0.14 ± 1.12	-0.58 ± 1.62	0.04 ± 1.02	3, 79	F = 4.82	<0.01	HC vs UHR
				Penn CNB				
Emotion Recognition (mean ± SD)	0 ± 1	-0.05 ±1.01	-0.18 ± 1.24	-0.20 ± 1.03	3, 169	F = 0.33	0.80	
Emotion Recognition (RT) (mean ± SD)	0 ± 1	-0.44 ± 1.57	-0.45 ± 1.19	-0.69 ± 1.90	3, 80	F = 0.35	0.79	
Working Memory (mean ± SD)	0 ± 1	-0.18 ± 1.26	-0.55 ± 1.83	-0.27 ± 1.18	3, 81	F = 0.96	0.42	
Working Memory (RT) (mean ± SD)	0 ± 1	0.17 ± 0.62	-0.11 ± 0.59	0.17 ± 0.91	3. 90	F = 1.91	0.13	
Attention (mean ± SD)	0 ± 1	-0.65 ± 1.75	-1.77 ± 4.15	-0.05 (1.25)	3, 75	F = 2.78	0.05	HC vs UHR, UHR vs BS+UHR
Attention (RT) (mean ± SD)	0 ±1	0.85 ± 0.78	-0.14 ± 0.81	0.37 (0.84)	3, 169	F = 2.72	0.05	

Appendix C: Specific Emotion between Group Comparisons

	HC (N = 57)	CHR-negative (N = 43)	CHR-positive (N = 121)	df	Statistic	p-value	Significant post hoc comparisons
Happy	0 ± 1	0.06 ± 0.84	-0.09 ± 0.86	2, 218	F = 0.65	0.52	
Happy (RT)	0 ± 1	-0.49 ± 1.30	-0.68 ± 1.37	2, 104	7.06*	0.01	HC vs CHR-positive
Angry	0 ± 1	-0.01 ± 0.88	-0.02 ± 0.94	2, 218	F = 0.02	0.98	
Angry (RT)	0 ± 1	0.71 ± 0.94	-0.18 ± 1.63	2, 218	F = 0.67	0.51	
Fear	0 ± 1	-0.02 ± 0.70	0.05 ± 0.86	2, 218	F = 0.18	0.84	
Fear (RT)	0 ± 1	-0.12 ±1.30	-0.25 ± 2.43	2, 217	F = 1.57	0.21	
Sad	0 ± 1	-0.02 ± 0.77	0.03 ±0.99	2, 218	F = 0.06	0.94	
Sad (RT)	0 ± 1	-0.22 ± 1.31	-0.61 ± 1.88	2, 218	F = 1.52	0.22	
No Emotion	0 ± 1	0.88 ± 0.15	0.88 ± 0.15	2, 218	F = 0.14	0.87	
No Emotion (RT)	0 ± 1	0.06 ± 1.11	-0.27 ± 1.58	2, 218	F = 1.31	0.27	

*Welch's F

Appendix B: Specific Emotion Comparisons with HC, CHR-R and CHR-NR

	HC (N = 57)	CHR-R (N = 33)	CHR-NR (N = 16)	df	Statistic	p-value	Significant post hoc comparisons
Happy	0 ± 1	0.03 ± 0.62	-0.38 ± 1.00	2, 103	F = 1.43	0.24	
Happy (RT)	0 ± 1	-0.61 ± 1.02	-1.83 ± 1.82	2, 34	34.92*	<0.01	HC vs CHR-R, CHR-NR CHR-R vs CHR-NR
Angry	0 ± 1	-0.25 ± 0.88	0.13 ± 0.92	2, 103	F = 1.11	0.33	
Angry (RT)	0 ± 1	-0.15 ± 1.37	-0.60 ± 1.63	2, 103	F = 1.48	0.23	
Fear	0 ± 1	0.18 ± 0.70	0.07 ± 0.78	2. 103	F = 0.39	0.68	
Fear (RT)	0 ± 1	-0.22 ± 1.38	-1.73 ± 3.61	2, 32	1.98*	0.15	
Sad	0 ± 1	0.05 ± 0.82	0.00 ± 0.91	2, 103	F = 0.02	0.98	
Sad (RT)	0 ± 1	-0.38 ± 1.20	-1.52 ± 2.39	2, 32	2.11*	0.14	
No Emotion	0 ± 1	0.92 ± 0.09	0.81 ± 0.20	2, 37	2.36*	0.11	
No Emotion (RT)	0 ± 1	-0.07 ±1.00	-1.03 ± 2.01	1, 19	3.23*	0.09	

*Welch