Neurocognitive and functional deficits in individuals at Clinical High Risk for Psychosis

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ABSTRACT

Background: Deficits in cognition and social and role functioning are characteristics of schizophrenia and have been found to impair every day functioning. A robust body of evidence has shown that such cognitive and functional deficits have been observed in individuals who are deemed to be at Clinical High-Risk (CHR) for developing psychosis. More severe cognitive dysfunction is associated with poorer functional outcomes in both schizophrenia and in CHR. Identifying the pattern and severity of cognitive and functional deficits for those who are CHR could identify important treatment targets for early intervention.

Aims: To identify differences in cognitive, social cognitive and psychosocial functioning in those who are at CHR of developing psychosis relative to controls. Additionally, we intent to identify to what extent does neuro- and social cognition explain poor functioning in the CHR population.

Methods: Baseline neuro- and social cognition was assessed along with GAF, social and role functioning measures in a sample of 110 CHR-participants and 46 healthy controls. Demographic and clinical characteristic data were also collected and analysed.

Results: CHR-participants showed deficits in the areas of motor speed, processing speed, working memory, global cognitive score and were significantly slower at recognising facial affect relative to controls. CHR-participants had significantly poorer social and role functioning and lower GAF scores. Regression analysis found response time for facial affect to be related to GAF and social functioning as baseline whilst global cognitive score was associated with role functioning. Exploratory analysis found response times for the recognition of sad faces to be associated with GAF whilst response times for the recognition of fearful face were associated with both social and role functioning at baseline.

Conclusions: Neuro- and social cognitive impairment, particularly in motor speed, processing speed, working memory and response times for emotion recognition has been observed in CHR-individuals. Response times for recognising emotion and global cognition have been associated with poor functioning at baseline. These findings highlight putative treatment targets for early intervention.

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Definitions/abbreviations

ANOVA:	Analysis if variance
APS:	Attenuated psychosis syndrome
ARMS:	At risk mental state
BACS:	Brief Assessment of Cognition in Schizophrenia
BLIP:	Brief limited intermittent psychosis
BS:	Basic symptoms
CAARMS:	Comprehensive Assessment of At-Risk Mental States
CBT:	Cognitive behavioural therapy
CHR:	Clinical high-risk
CNS:	Central nervous system
CNV:	Copy number variant
COMT:	Catechol-*O*-methyl transferase
CPT:	Continuous performance task
CT:	Computer tomography
DISC1:	Disrupted-in-schizophrenia 1
DSM:	Diagnostic and Statistical Manual of Mental Disorders
DTNBP1:	Dysbindin
FEP:	First episode of psychosis
GABA:	γ-Amino Butyric Acid
GAF:	Global assessment of functioning
GF Role:	Global functioning role scale
GF Social:	Global functioning social scale
GRD:	Genetic risk and deterioration syndrome
GRM3:	Metabotropic glutamate receptor 3

Gln:	Glutamine
Glu:	Glutamate
GWAS:	Genome-wide association studies
HR:	High risk
LNB:	Letter-number-back task
MRI:	Magnetic resonance imaging
NAA:	*N* -Acetylaspartic acid
NAPLS:	North American prodrome longitudinal study
NCP:	Non-clinical psychosis
NMDA:	*N* -methyl- d -aspartate
NRG1:	Neuregulin 1
RGS4:	Regulator of G-protein signaling 4
PAS:	Premorbid adjustment scale
PCA:	Perceptual-cognitive anomalies
PennCNB:	University of Pennsylvania computerized neuropsychological testing battery
PQ:	Prodromal questionnaire
RT:	Reaction time
SIPS:	Structured interview for prodromal symptoms
SOPS:	Scale of prodromal symptoms
SPI-A:	Schizophrenia proneness instrument-adult version
SPI-CY:	Schizophrenia proneness instrument-child and youth version
UHR:	Ultra-high-risk
UPS:	Unspecified prodromal symptoms

1. INTRODUCTION

Psychiatric disorders are major public health concerns with schizophrenia and schizoaffective disorder combined being the 5th leading cause of disability worldwide (WHO). Schizophrenia can result in a severe and chronic psychiatric disorder and is characterised by abnormalities in the domains of positive symptoms (delusions, hallucinations), negative symptoms (flattened affect, social withdrawal), disorganised thinking and cognition. Schizophrenia has a prevalence rate of 1.1% worldwide (National Institute of Mental Health, 2011). Due to the debilitating positive and negative symptoms of schizophrenia, in chronic cases an individual's functional capacity can be significantly impaired, resulting in long term unemployment coupled with long term medical and social care needs at enormous cost to the economy (Knapp, Mangalore & Simon, 2004).

Cognitive deficits are not included in the diagnostic criteria. However, they have consistently been found to be a core feature of the disorder (Rajji, Miranda & Mulsant, 2014) and are highly associated with functional disability (Rajji, Miranda & Mulsant, 2014). Over the last few decades, research into the prevalence, course and profile of cognitive dysfunctions has extended into groups of individuals who are considered to be at-risk of developing schizophrenia and related psychotic disorders.

This thesis will firstly review existing literature on the history and aetiology of schizophrenia before presenting a novel research study investigating the relationship between attenuated psychotic experiences, cognitive deficits and current psychosocial functioning.

1.1 History of the concept of Schizophrenia

What is now conceptualised as schizophrenia has existed historically under various names. Emile Kraepelin (Hoeing, 1983) combined the previously separate constructs of dementia paranoids, hebephrenia and catatonia into a single definition of 'dementia praecox' (Bruijnzeel, & Tandon, 2011). An important aspect of Kraepelin's work was the belief that there existed two distinct patterns of illness course around which many of the different conditions could be grouped: 1) dementia praecox and 2) manic depressive insanity (today known as bipolar disorder).

Kraepelin identified dementia praecox on the basis of its onset in adolescence, its deteriorating course and its outcome of demence or "mental dullness" (Hoeing, 1983). In

contrast, Kraepelin argued that manic depressive insanity was distinct from dementia praecox based on its fluctuating presentation and better outcome (Bruijnzeel, & Tandon, 2011). A key contribution to Kraepelin's understanding of dementia praecox came from his meticulous follow up of individual cases. Having been unsuccessful at specifying disorders based on purely anatomical, aetiological or psychopathological criteria, he therefore promoted his belief in the interdependence of disciplines, later adding course and treatment response (Hoeing, 1983).

Eugen Bleuler (1857-1939) coined the phrase schizophrenia. Bleuler and his apprentice Jung, who had both been influenced by Freud's work regarding the neuroses, aimed to introduce the 'psyche' to the concept of dementia praecox. Bleulers' publication '*Dementia praecox or the Group of Schizophrenias*' (1911) forwarded the name schizophrenia to highlight the 'split of several psychic functions' as one of the most important characteristics. He added the concept of *'loosening of associations'* and described four 'basic symptoms' of schizophrenia (the 4 As):

- Associational disturbances (tangential or loose-thought processes)
- Affective incongruenty (flat or inappropriate affect)
- Autism (withdrawal from reality to fantasy)
- Ambivalence (mental and / or physical vacillation or indecisiveness)

Experiences of hallucinations and delusions (which occur in other disorders as well as schizophrenia) were regarded as "accessory symptoms" which he believed were a result of adaptive and defensive reactions. (Häfner, 2014). Although Bleulers use of the terms '*loosening of associations'* and *'splitting'* have been interpreted over the years as a separation of thought and affect, many argue that this in fact refers to dissociation. Importantly Bleuler assumed continuity between normality and psychosis forming a basis for the dimensional model of schizophrenia, as opposed to Kraepelins categorical model, an argument with is still heavily debated today.

Schneider aimed to further define schizophrenia by differentiating between symptoms of first and second rank in his book '*Clinical Psychopathology'* (1959). Schneider regarded the presence of one or more of the first rank symptoms he had identified as sufficient for a diagnosis of schizophrenia (Warner & Girolamo, 1995). Similar to Kraepelin, Schneider considered symptoms to be early signs of an undetected somatic process. He adopted the use of the term "endogeneity" as a term used to mark the category of disorders of unknown biological origin as represented by schizophrenia (Häfner, 2014).

Although the terminology of the first rank symptoms are still widely used today, their diagnostic power has been heavily criticised. First rank symptoms are present in a range of psychiatric disorders and can be experienced in a similar way to those with a diagnosis of schizophrenia in terms of phenomenology, emotional impact and persistence over time (Renard, Huntjens, Lysaker, Moskowitz, Aleman, & Pijnenborg, 2017; Schroeder, Fisher & Schäfer, 2013). In the second half of the 20th century the emergence of neuroleptic drugs brought forward what was to be the most enduring biological hypotheses of schizophrenia – the dopamine hypothesis. This brought about a focus on brain chemistry and models of schizophrenia lost any focus on psychological and environmental influences. Schizophrenia was now known as a dopamine disorder after the psychosis inducing effects of dopamine releasing drugs such as amphetamines coupled with the efficacy of antipsychotic drugs known to block the dopamine D2 receptor (Carlson, 1988). This neurochemical understanding of schizophrenia transformed treatment of schizophrenia though anti-psychotic medications which allowed people to be treated in the community and out of hospital and even, in some cases, showing remission of some of the major symptoms of schizophrenia (Insel, 2010). However, these medications had unpleasant side effects, known as extrapyramidal symptoms, which include tremors and rigidity. A new wave of atypical anti-psychotics, which were hailed to be of increased efficaciousness, were found to reduce these extrapyramidal side effects but unfortunately are not significantly more efficacious than the original dopamine D2 receptor antagonists (Lieberman, Stroup, McEvoy, Swartz, Rosenheck & Perkins, 2005). Although these drugs have reduced the experiences of positive symptoms to some extent, they have been ineffective at improving the functional outcome of individuals with a diagnosis of schizophrenia. One explanation for this is that poor functional outcome in schizophrenia is largely due to the cognitive deficits, for example attention and working memory, which these drugs do not treat (Insel, 2010). Therefore, understanding and treating cognitive deficits, as well as positive symptoms, may be a more efficacious treatment target for schizophrenia.

Another well-accepted model of schizophrenia, and indeed general psychopathology, is the stress-vulnerability hypothesis (Nuechterlein & Dawson, 1984; Zubin & Spring, 1977; Katschnig, 1990). According to this model, symptoms of psychosis appear once a combination of stressors reach the individual's vulnerability threshold. However, as this concept is interactional it is inherently difficult to investigate (Myin-Germeys, van Os, Schwartz, Stone, & Delespaul, 2001). Support has come from reports of individuals with a diagnosis of schizophrenia as being more sensitive to the stress of daily life events relative

to their non-psychiatric counterparts (Bebbington, Wilkins, Jones, Foerster, Murray, Toone, & Lewis, 1993; Lukoff, Ventura & Nuechterlein, 1984).

1.2 Prevalence, Development and Course

The incidence of Schizophrenia is approximately 15.2/100,000 persons with the central 80% of estimates varying over a fivefold range (7.7–43.0/100,000). Variation of frequency has been found based on urbanicity, economic status, and latitude (McGrath, Saha, Chant & Welham, 2008). Although incidence has been found not to significantly differ between males and females (McGrath, Saha, Chant & Welham, 2008), gender differences have been found in relation to symptomology. Negative symptoms appear to be more pronounced in males and are associated with poorer outcomes. Additionally, diagnosis in males is associated with worse premorbid adjustment, more prominent cognitive dysfunction, and lower educational attainment (DSM IV). Cases which include more affective symptoms and brief presentations, which are often associated with better outcomes, are of equal prevalence in both genders. Typically, symptoms of schizophrenia emerge between late teens and mid-30s. Onset pre-adolescence can occur but is rare. Most commonly, the peek onset age for males is mid-20s and late-20s for females (DSM IV).

1.3 Symptoms and Features of Schizophrenia

The key features of schizophrenia spectrum disorders include delusions, hallucinations, disorganised thinking, grossly disorganised motor behaviour (including catatonia) and negative symptoms. Although not typically seen as criteria for a diagnosis, schizophrenia is associated with impairments in cognition, social and role functioning (Carrión, Goldberg, McLaughlin, Auther, Correll & Cornblatt, 2011). This has been a key focus of research and a large body of evidence has provided an overall profile of domains of dysfunction (e.g. cognitive, emotional and behavioural). It is important to note that schizophrenia is a heterogeneous clinical syndrome thus individuals will vary substantially on the presentation of clinical features of the disorder. For example, grandiosity is a common feature of schizophrenia but not everyone will experience this. Similarly, many individuals experience hallucinations but not all. Additionally, no single symptom of the disorder is pathognomonic of schizophrenia. Schizophrenia is diagnostically recognised by a cluster of the symptoms

associated with the disorder. This is often accompanied with deficits in social and role functioning (DSM 5).

1.4 Risk Factors

For over 40 years, researchers have aimed to identify genetic and environmental determinants of schizophrenia. A consensus of this research is that schizophrenia is a complex disorder that comprises interacting genetic and environmental risk factors. A wide range of risk factors for developing schizophrenia have been identified.

1.4.1 Genetic risk

Schizophrenia is seen as a highly heritable disorder (Gottesman & Shields, 1972) with a heritability rate of 64-81% (Giusti-Rodríguez & Sullivan, 2013). There have been many approaches to the study of genetics in schizophrenia. Converging data have suggested a role for both rare and common variants in elevating the risk of schizophrenia. Importantly, there is no evidence of Mendelian forms of schizophrenia (rare mutations with deterministic effects) (Giusti-Rodríguez & Sullivan, 2013). Studies of candidate genes have highlighted various disease predisposing DNA sequence variants in disrupted-in-schizophrenia 1 (*DISC1*), neuregulin 1 (*NRG1*), catechol-*O*-methyl transferase (*COMT*), regulator of G-protein signaling 4 (*RGS4*), metabotropic glutamate receptor 3 (*GRM3*), dysbindin (*DTNBP1*), *G72*, and other sequences (Harrison and Weinberger, 2005), however these findings have been difficult to replicate (Schmidt & Mirnics, 2015). There is evidence for rare copy number variants (CNVs) which may have large effect sizes which play a role in the predisposition of schizophrenia. These result from deletions or duplications of relatively large genomic regions. The CNVs implicated in schizophrenia span multiple genes and can increase the risk of developing schizophrenia or protect against it (Grozeva, Kirov, Ivanov, Jones, Jones, Green, et al., 2010). This is evidenced by findings of 22q11 hemideletion being associated with schizophrenia (Karayiorgou, Simon & Gogos, 2010), whilst 22q11 duplication has been suggested to protect against it (Rees, Kirov, Sanders, Walters, Chambert, Shi, et al., 2014). This suggests that expression levels, or 'dose' of specific genes are essential to typical and pathological brain development (Schmidt & Mirnics, 2015).

More recently, given the expanding patient cohorts and increasingly sophisticated methodological approaches, genome-wide association studies (GWAS) can analyse DNA

from tens of thousands of patients with a diagnosis of schizophrenia. This method has so far identified between 'one and several thousands of common alleles of very small effect' which are associated with schizophrenia (Schmidt & Mirnics, 2015; McAllister, 2014; Ripke, O'Dushlaine, Chambert, Moran, Kähler, Akterin, et al., 2013). Calcium signaling has appeared as a potentially important factor in the etiology of schizophrenia (Giusti-Rodríguez & Sullivan, 2013) as these are essential for learning, memory and synaptic plasticity (Moosmang, Haider, Klugbauer, Adelsberger, Langwieser, Müller, et al., 2005). The MicroRNA 137 has also appeared as a potentially relevant risk factor for the development of schizophrenia. (Ripke, O'Dushlaine, Chambert, Moran, Kähler, Akterin, et al., 2013). In previous research miR-137 has been found to be important for neurodevelopment, adult neural stem cell proliferation and differentiation and dendritic arborization (Giusti-Rodríguez & Sullivan, 2013).

As schizophrenia risk is known to result from both genetic and environmental factors, researchers are now attempting to investigate both these factors together by looking at how specific environmental and genetic risk factors act to predispose or protect individuals from developing schizophrenia, whether the effects are additive, or there are gene x environment interactions (Giusti-Rodríguez & Sullivan, 2013).

1.4.2 Environmental factors

1.4.2.1 Pre- and perinatal risk

Infection: Studies are continuing to associate prenatal infection with the development of schizophrenia (Brown & Derkits, 2009). Exposure to rubella, toxoplasma and herpes simplex virus type 2 causes a range of developmental disorders, including learning disabilities, mental retardation and sensorineural dysfunction (Remington, Klein, Wilson & Baker, 2005). Toxoplasma gondii infection has most consistently been associated with schizophrenia. Studies have found that mothers with higher immunoglobulin G level had a relative risk of 1.73 (Pedersen, Stevens, Pedersen, Norgaard-Pedersen & Mortensen, 2011) and new-borns found to have T. gondii immunoglobulin antibodies were also associated with elevated levels of schizophrenia (Mortensen, Nørgaard-Pedersen, Waltoft, Sørensen, Hougaard, Torrey, & Yolken, 2007). However, the underlying mechanisms relating to risk factors of prenatal infection remain unclear.

Nutrition: A few studies have found elevated risk of schizophrenia in relation to famine. It was found that individuals who were in utero during a time of famine showed an increased risk of schizophrenia, depression and brain abnormalities. The association with increased risk of schizophrenia has been replicated in two Chinese studies which showed a two-fold increase in risk in relation to sustained famine (St Clair, Xu, Wang, Yu, Fang, Zhang, et al., 2005; Xu, Sun, Liu, Feng, Yu, Yang et al., 2009). Again, however, there is a lack of specificity in the association of famine pre- and perinatal famine and schizophrenia as it is also associated with mood disorders and antisocial behaviour, as well as a number of physiological abnormalities (Lumey, Stein, & Susser, 2011).

Low birth weight: Epidemiological studies have consistently found preterm and low birth weight (<37 weeks, <2055 g) to be a general risk factor for psychiatric disorders, including schizophrenia (Rapport et al., 2012). Such studies have identified a broad increase in disorders including attention deficit hyperactivity disorder, autism spectrum disorder and intellectual disability and are often found to be comorbid with cognitive impairment (Rapport et al., 2012).

1.4.2.2 Premorbid risk

Urban environment: It is increasingly being argued that schizophrenia and psychotic disorders can be understood as disorders of adaption to social context. A consistent association between urban living and schizophrenia has been found (van Os, Kenis, & Rutten, 2010). This has been shown to exist in a dose response relationship (March, Hatch, Morgan, Kirkbride, Bresnahan, Fearon, & Susser, 2008). There are a large number of possible confounds that can occur, for example, higher rates of schizophrenia seen in urban environments could be secondary to higher rates of drug use or ethnic minority status. For this reason, large studies have controlled for a number of possible confounders, including indexing for genetic risk to exclude environmental and genetic confounders (Krabbendam, & Van Os, 2005; Kelly, O'Callaghan, Waddington, Feeney, Browne, Scully, et al., 2010). Additionally, longitudinal studies have shown that changing environmental exposure and moving from urban to rural environments in childhood is associated with a corresponding decrease in the risk for psychotic outcomes (Pedersen & Mortensen, 2001).

Minority group status: Meta-analyses have consistently found an association between schizophrenia and minority group status across a wide range of settings and is thought to be relevant to both first and second-degree migrants (Cantor-Graae & Selten, 2005; Bourque,

van der Ven & Malla, 2011) and also for minority groups without recent migration (Bresnahan, Begg, Brown, Schaefer, Sohler, Insel et al., 2007). This indicates that the association with schizophrenia risk is not with migrations itself or pre-migration factors (van Os, Kenis, & Rutten, 2010). Moreover, studies have shown that the effect of minority status is dependent on other factors, such as the density of the population, for example, the higher the population of the individuals own ethnic group in that area, the lower the risk of schizophrenia (Veling, Susser, Van Os, Mackenbach, Selten, & Hoek, 2008). This suggests that migration and minority status constitute a risk factor in the context of social marginalisation and exclusion (Selten, & Cantor-Graae, 2005) and may be mediated by factors such as social diversity and discrimination (Morgan, Charalambides, Hutchinson & Murray, 2010).

Childhood trauma: Over the past decade, the relationship between childhood trauma and psychotic disorders has been an active area of research. These studies consistently find high rates of childhood trauma in individuals with psychotic disorders, particularly childhood sexual abuse and physical abuse. A review of such studies recently found that 42% of female patients reported childhood sexual abuse and 35% reported childhood physical abuse (Morgan & Fisher, 2007). In males, these numbers were 28% and 38% respectively and at least one form of abuse was found in 50% of patients irrespective of gender (Morgan & Fisher, 2007). Childhood abuse is increasingly seen as a causal factor for schizophrenia. More specifically, childhood sexual abuse is associated with symptoms such as hallucinations, particularly auditory hallucinations in the context of comments and command hallucinations (Read, Os, Morrison, & Ross, 2005).

Cannabis use: There is now robust evidence highlighting the association between cannabis and schizophrenia (Hall & Degenhardt, 2009; Moore, Zammit, Lingford-Hughes, Barnes, Jones, Burke & Lewis, 2007). There is an over representation of heavy cannabis use in new cases of schizophrenia (Barbee, Clark, Crapanzano, Heintz & Kehoe, 1989; Wheatley, 1998). This sparked debate as to whether cannabis use is a contributory factor in developing psychosis or whether this over representation reflects a trend for self-medication for early symptoms of schizophrenia (Hall & Degenhardt, 2008; Ferdinand, Sondeijker, Van Der Ende, Selten, Huizink & Verhulst, 2005). Cannabis has been found to cause transient psychotic symptoms and impaired cognition in healthy controls (Morrison, Zois, McKeown, Lee, Holt, Powell et al, 2009) and that this response is exaggerated in individual who are at genetic risk for psychosis (D'Souza, Abi-Saab, Madonick, Forselius-Bielen, Doersch, Braley et al, 2005).

1.5 Cognition in Schizophrenia

Cognitive deficits are a prominent feature of schizophrenia and can be found in almost all patients with a diagnosis of schizophrenia (Keefe & Harvey, 2012). Individuals have been found to be moderately to severely impaired over several cognitive domains with the average cognitive impairment reaching 2 standard deviations below that of non-psychiatric controls (Harvey & Keefe, 1997; Heinrichs & Zakzanis, 1998; Keefe, Fox, Harvey, Cucchiaro, Siu & Loebel, 2011).

Studies have found that 27% of people with a diagnosis of schizophrenia do not show cognitive deficits (Palmer, Heaton, Paulsen, Kuck, Braff, Harris, et al., 1997). This sub-group of patients tend to have the highest levels of premorbid functioning (Kremen, Seidman, Faraone, Toomey, & Tsuang, 2000), however, they show cognitive functioning that is significantly lower than what would be expected based on their premorbid functioning and parental education levels (Keefe & Harvey, 2012). In addition, up 98% of individuals with a diagnosis of schizophrenia perform more poorly than what would be expected based on parental education levels (Keefe, Eesley & Poe, 2005). Studies of monozygotic twins discordant for schizophrenia have found that almost all affected twins perform more poorly than their non-affected twin (Goldberg, Ragland, Torrey, Gold, Bigelow & Weinberger, 1990).

Neurocognitive assessments often assess more than one domain of cognitive functioning and many of these tests do not fit neatly into one single domain which has resulted in differences in the literature regarding the profile of neurocognitive impairment in schizophrenia (Keefe & Harvey, 2012). However, it is generally considered that the most important neurocognitive deficits in schizophrenia are in the domains of working memory, verbal learning and memory, motor ability, attention/vigilance, reasoning and problem solving, processing speed and social cognition (Dickinson, Ramsey & Gold 2007; Green, Nuechterlein, Gold, Barch, Cohen, Essock, et al., 2004).

Working memory: Working memory has been described as a core component of neurocognitive impairment in schizophrenia (Brekke, Long, Nesbitt, & Sobel, 1997; Goldman-Rakic, 1994; Keefe, 2000). Deficits in working memory have been found to be associated with functional outcomes such as employment status (Lysaker & Bell, 1995) and job tenure (Gold, Goldberg, McNary, Dixon & Lehman, 2002). Deficits in working memory has also been found to be strongly associated with other domains which are impaired in

schizophrenia such as attention, planning, memory (Silver, Feldman, Bilker & Gur, 2003) and intelligence (Keefe, 2000). Additionally, neuroanatomical research has found that neural circuitry, including prefrontal cortical regions, mediates particular aspects of working memory functioning (Baddeley, 1992; Callicott, Mattay, Bertolino, Finn, Coppola, Frank, et al., 1999) and that this circuitry may be impaired in individuals with schizophrenia (Baddeley, 1992; Goldman-Rakic, 1987).

Verbal learning and memory: This includes abilities in learning new information, retaining that information over time and recognising previously seen stimuli. Generally, individuals with a diagnosis of schizophrenia demonstrate larger deficits in learning than in retention (Keefe & Harvey, 2012). The tasks used to assess learning often involve the participant learning lists of word or written passages. There is substantial literature which highlights severe verbal memory impairments in schizophrenia (Aleman, Hijman, de Haan & Kahn, 1999). There is a strong connection between verbal learning and social functioning in individuals with a diagnosis of schizophrenia both in real work functioning (Green, 1996) and in performances on social competency tasks (McClure, Bowie, Patterson, Heaton, Weaver, Anderson & Harvey, 2007).

Motor ability: Schizophrenia is associated with deficits in pure motor speed (Hoff, Harris, Faustman, Beal, DeVilliers, Mone, et al., 1996). Motor procedural learning has been found to be intact (Schmand, Brand & Kuipers, 1992), however, bilateral and unilateral motor performance is impaired (Heinrichs & Zakzanis, 1998). Moreover, youths who later develop a schizophrenia spectrum disorder have been reported to show poorer motor function in childhood (Dickson, Laurens, Cullen & Hodgins, 2012).

Attention (and vigilance): Vigilance refers to the ability to maintain attention over time. This is important for following social conversations, following instructions, and even simple activities such as reading and watching TV (Keefe & Harvey, 2012). Deficits in vigilance are associated with various outcomes including skills acquisition, social deficits and community functioning (Green, 1996; Green, Kern, Braff & Mintz, 2000).

Reasoning and problem solving: Again, there are many differing measures for reasoning and problem solving. Previous studies have found that individuals with a diagnosis of schizophrenia had very poor performance on reasoning and problem-solving tasks and there was found to be reduced activity in the dorsolateral prefrontal cortex (Weinberger, 1987; Goldberg et al, 1987). This led to a drive in research towards a hypothesis of frontal hypo-activation in schizophrenia. However, many of these studies used the Wisconsin Card Sorting Test (WCST) as a measure of reason and problem solving which actually reflect a

number of cognitive functions and cannot be considered to be a pure measure of executive functions (Keefe, 1995).

Processing speed: Neurocognitive tasks can require participants to rapidly process information and performance can be compromised by deficits in processing speed. A common task for this is a coding task which has been found to demonstrate the most severe impairments in schizophrenia (Dickenson, Ramsey & Gold, 2007). Impairments in processing speed have been linked to a variety of clinically important features of schizophrenia such as daily life activities (Evans, Heaton, Paulsen, Palmer, Patterson & Jeste, 2003), job tenure (Gold, Goldberg, McNary, Dixon & Lehman, 2002) and independent living status (Brekke, Long, Nesbitt & Sobel, 1997).

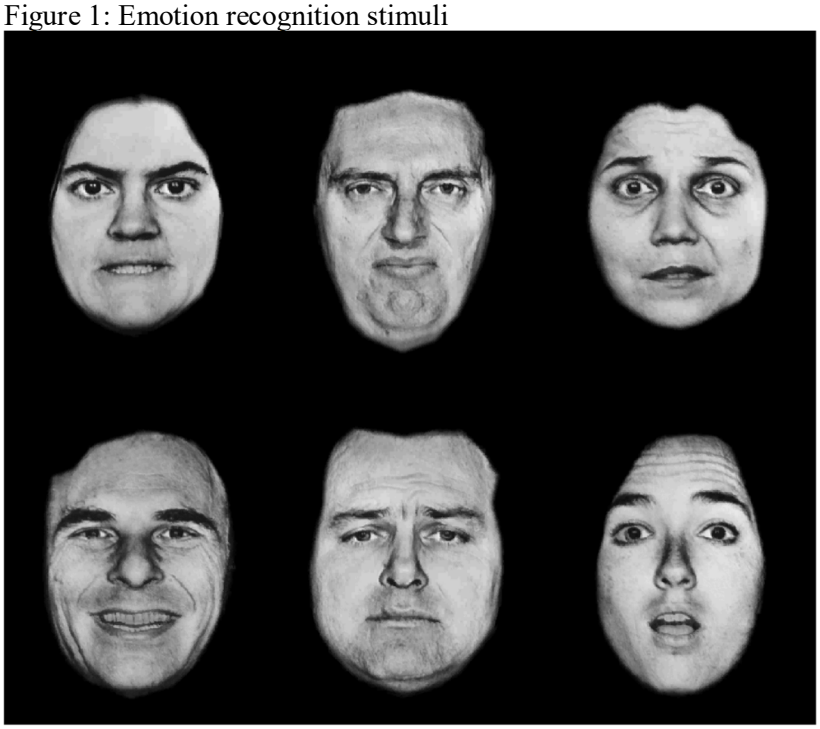
Social cognition: Theory of mind, emotion perception and recognition has been a key focus in social cognition research in schizophrenia (Keefe & Harvey, 2012). Theory of mind refers to the ability to infer another's intentions and/or to represent the mental states of others. Individuals with a diagnosis of schizophrenia have consistently been found to perform poorly on measures of theory of mind (Tan, Choo, Fones, & Chee, 2005; Corcoran, Mercer, & Frith, 1995). Facial emotion recognition is a well document deficit in schizophrenia and first episode psychosis (FEP) (Edwards, Jackson & Pattison, 2002; Hoekert, Kahn, Pijnenborg & Aleman, 2007; Kohler, Walker, Martin, Healey & Moberg, 2010). This is an important part of social cognition and is essential for guiding social interactions and therefore social functioning. Impairments in facial emotion recognition may therefore be implicit in deficits in social functioning which is a key feature of schizophrenia (Couture, Penn & Roberts, 2006; Pinkham, Penn, Perkins & Lieberman, 2003) and is also present in CHR samples (Addington, Penn, Woods, Addington & Perkins, 2008; Phillips & Seidman, 2008).

Edwards et al. (2002) reported deficits in fear and sadness in faces for the combined schizophrenia and other psychotic disorders groups relative to affective psychoses groups and non-psychiatric controls. These findings fit with evidence that the amygdala is important for the recognition of fear (Adolphs, Tranel, Damasio & Damasio, 1995; Fusar-Poli, Placentino, Carletti, Landi, Allen, Surguladze, et al., 2009) and sadness (Adolphs & Tranel, 2004; Aleman & Kahn, 2005) and imaging studies have shown the amygdala to be associated with the pathogenesis of schizophrenia (Aleman & Kahn, 2005) giving a theoretical rationale for specific deficits in fear and sadness in schizophrenia. However, other studies have found differing findings with some showing deficits for happiness, surprise and neutral (Edwards, Jackson & Pattison, 2002; Pomarol-Clotet, Hynes, Ashwin, Bullmore, McKenna & Laws,

2010). These inconsistencies may be partly explained by the range of emotion recognition tasks applied in the literature including a variety in the number of emotions examined, response times, response format and stimulus complexity (Edwards, Jackson & Pattison, 2002).

Moreover, although many studies have found a range of deficits in facial recognition tasks (see Figure 1 for an example) (Mandal et al. 1998; Edwards, Jackson & Pattison, 2002.; Pinkham, Penn, Perkins & Lieberman, 2003), and often with a large effect sizes (Kohler, Walker, Martin, Healey & Moberg, 2009), some argue that this in itself does not support the hypothesis that facial emotion processing is an important deficit of schizophrenia (Pomarol-Clotet, Hynes, Ashwin, Bullmore, McKenna & Laws, 2010). This is due to individuals with a diagnosis of schizophrenia performing poorly on most cognitive tasks (Chapman & Chapman, 1973) which suggests that the disorder is associated with varying degrees of generalised cognitive deficit (McKenna, 2007; Reichenberg & Harvey, 2007).

Figure 1: Emotion recognition stimuli



Examples of emotion recognition stimuli of faces showing (above - left to right) anger, disgust, fear, (below – left to right) happiness, sadness, surprise.
Pomarol-Clotet, Hynes, Ashwin, Bullmore, McKenna & Laws, 2010.

There is an ongoing debate regarding relationship between facial emotion recognition and cognitive impairments. This debate concerns itself with whether facial emotion recognition is secondary to general neurocognitive impairment (Kohler, Bilker, Hagendoorn, Gur & Gur, 2000; Addington, Saeedi & Addington, 2006), or whether this deficit goes beyond neurocognition (Edwards, Jackson & Pattison, 2002; Kohler, Turner, Bilker, Brensinger, Siegel & Kanes, et al., 2003; Kohler, Walker, Martin, Healey & Moberg, 2009). Some argue

that there is growing evidence that social cognition is distinct, although closely related, to neurocognition (Eack, Mermon, Montrose, Miewald, Gur & Gur, et al., 2009; Sergi, Rassovsky, Widmark, Reist, Erhart & Braff, et al., 2007). Given this, it is reasonable to hypothesise that facial emotion recognition may be an independent vulnerability marker for psychosis.

On the other hand, supporting a relationship between generalized cognitive deficits and emotion processing, Pomarol-Clotet et al. (2010) recruited patients with a diagnosis of schizophrenia who did not show significant impairments in IQ. Additionally, they matched schizophrenia patients and controls on age, sex and estimated IQ (pre-morbid IQ in the patients). Faces showing emotions of anger, sadness, fear, disgust, surprise and happiness were presented (Figure 1). No deficits in emotion recognition accuracy were found, however the schizophrenia patients showed slower reaction times when responding to these emotions relative to controls. The authors argue that even the slower reaction times cannot be taken as evidence of deficits in emotion recognition as slowing of reaction times has been found to be a general feature of schizophrenia (Schatz, 1998). However, this claim was not investigated in their design and remains unsubstantiated. One possible way of addressing this would be to present a range of neurocognitive stimuli and record reaction times for all stimuli to assess whether slowing of reaction times are generalised or domain specific.

1.6 Cognition and Functioning in Schizophrenia

Impairments in social and occupational functioning are hallmarks of schizophrenia (Couture et al., 2006; McGurk & Meltzer, 2000). Deficits in functioning are largely responsible for the burden of psychotic disorders to patients, families, carers and wider society (Jungbauer, Wittmund, Dietrich & Angermeyer, 2004; Knapp, Mangalore & Simon, 2004; Ohaeri, 2003; Perlick, Rosenheck, Kaczynski, Swartz, Cañive & Lieberman, 2006; Magaña, Ramírez García, Hernández & Cortez, 2007). Impairments in functioning reduce independence, quality life, educational attainment and productivity (Fleischhaker, Schulz, Tepper, Martin, Hennighausen & Remschmidt, 2005). Impairments in social and role functioning appear to be the most significant in that individuals have difficulty in forming and/or maintaining traditional societal roles such as a worker, friend, parent, spouse or student (Nanko & Moridaira, 1993; Hutchinson, Bhugra, Mallett, Burnett, Corridan & Leff, 1999; Horan, Subotnik, Snyder & Nuechterlein, 2006; Harvey, 2013). Therefore, it is important to

understand the mechanisms and factors which lead to and maintain functional disability in individuals with psychosis.

There is substantial evidence in schizophrenia literature that neuro-cognitive and social cognitive impairments are highly associated with poor occupational and social outcomes (Green, Kern, Braff & Mintz, 2000; Hooker & Park, 2002; Fett, Viechtbauer, Dominguez, Penn, van Os & Krabbendam, 2011) making them a potential target for combining illness-specific symptomatology with at-risk criteria to improve sensitivity for transition to psychosis. For this reason, there have been various attempts at finding specific domains which appear to be the most important for functional impairment with the aim to target such domains for treatment. For example, one study analysed if neurocognition and clinical status could predict real life functioning for individuals with a diagnosis of schizophrenia (Tabarés-Seisdedos, Balanzá-Martínez, Sánchez-Moreno, Martinez-Aran, Salazar-Fraile & Selva-Vera, 2008). A longitudinal study assessed individuals at baseline and at one year follow up. They found that global functioning one year later was predicted by a composite cognition score and the specific domains of verbal memory, motor speed and vocabulary. Moreover, individuals who were at first episode of schizophrenia showed large generalised cognitive deficits and relative deficits in memory and executive functioning which were related to functional impairment (Bilder, Goldman, Robinson, Reiter, Bell, Bates & Geisler, 2000; Riley, McGovern, Mockler, Doku, ÓCeallaigh, Fannon et al., 2000). A recent systematic review and meta-analysis of social and neuro-cognitive factors in relation to functional outcomes in patients with a diagnosis of non-affective psychosis found that social cognition has a stronger relation to community functioning than neuro-cognitive factors (Fett, Viechtbauer, Dominguez, Penn, van Os & Krabbendam, 2011).

1.7 Neurobiology of Schizophrenia

Researchers have strived to identify the underlying biological mechanisms which would lead to such an abnormal developmental trajectory described by neurodevelopmental models which would result in the symptomology of schizophrenia. However, the causal mechanisms leading to schizophrenia are still unclear.

1.7.1 Anatomical/Neuroimaging Studies

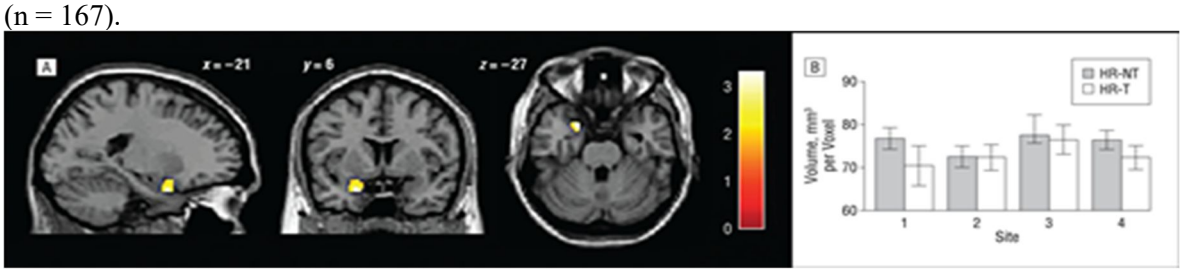
The past decades of research have resulted in mounting support for the neurodevelopmental model of schizophrenia. Much of this support comes from research into at-risk groups of schizophrenia. Physiological differences in neuropathological and neuroimaging studies of patients with chronic schizophrenia have also been observed in those who are experiencing their first episode and those who are deemed to be at-risk of developing schizophrenia. This suggests that neurobiological signatures cannot be an effect of chronicity but instead highlight that there are related to the development of the disorder itself (Harrison, 2008). Some of the main findings from the last 40 years of research are summarised here.

Neuroimaging: The first finding came from computer tomography (CT) studies in a landmark paper from Johnestone et al. (Johnstone, Frith, Crow, Husband & Kreel, 1976) which discussed the enlargement of the lateral ventricles in patients which chronic schizophrenia. This confirmed earlier pneumoencephalographic findings (Huber 1955; 1961) which renewed interest in the neurobiology and neuropathology of schizophrenia. This led to an explosion of studies using CT and magnetic resonance imaging (MRI) to investigate brain structure and function in the search for neural correlates of schizophrenia. Findings highlighted a range of quantitive structural differences in the brains of individuals diagnosed with schizophrenia including abnormalities in brain regions such as the hippocampus and parahippocampal gyrus, insula, thalamus, cingulate gyrus, and prefrontal and temporal cortices (Vita, Peri, Silenzi & Dieci, 2006). A mega-analysis which summarised 32 meta-analyses of MRI studies reported reduced grey matter in individuals with chronic schizophrenia and FEP in the frontal lobe gyri, thalamus, cingulate cortex, insula, postcentral gyrus and medial temporal regions and additionally increased volume of ventricles and cavum septum pellucidum (Shepherd, Laurens, Matheson, Carr & Green, 2012). Additionally, there is a marked reduction in whole brain volume.

More recently these findings have been extended to first episode and at-risk groups (Pantelis, Velakoulis, McGorry, Wood, Suckling, Phillips, et al., 2003). A meta-analysis of individuals who are at-risk of developing schizophrenia found that at-risk subjects showed reduced grey matter volumes in the prefrontal cortex bilaterally (right middle frontal gyrus, left medial frontal gyrus), temporal (right superior temporal), limbic (bilateral anterior cingulate regions, bilateral parahippocampal/hippocampal) and parietal (left precuneus) regions (Fusar-Poli, Borgwardt, Crescini, Deste, Kempton, Lawrie, et al., 2011). These regions have also been found to be structurally altered in schizophrenia spectrum disorders (Tan, Callicott & Weinberger, 2009; Boyer, Phillips, Rousseau & Ilivitsky, 2007). Moreover, grey matter

reductions in the right inferior frontal gyrus and superior temporal gyrus have been found in UHR subjects who later transition to frank psychosis but not in those who don't (Fusar-Poli, Borgwardt, Crescini, Deste, Kempton, Lawrie, et al., 2011) suggesting a possible neurobiological predictor of schizophrenia. Figure 2 shows baseline differences between high risk individuals who did and did not transition to psychosis during a 2-year follow-up (Koutsouleris, et al., 2009).

Figure 2: Structural brain alterations observed in HR individuals (n = 182) and matched controls (n = 167).



Baseline differences between HR individuals who did (HR-T, n = 48) and did not (HR-NT, n = 134) transition to psychosis during 2-year follow-up. The HR-T group show less gray matter volume than the HR-NT group in the left parahippocampal gyrus, bordering the uncus. The plot shows mean gray matter volumes for the 2 HR subgroups at each site (1 indicates London, United Kingdom; 2, Basel, Switzerland; 3, Munich, Germany; and 4, Melbourne, Australia). Error bars represent SD (Koutsouleris, et al., 2009).

The causes of these differences in grey matter have been at the centre of ongoing debate regarding whether such differences are caused by: 1) early developmental insults and are stable over time or 2) by a progressive loss due to effects of the disorder. To address this issue, research is investigating those who are at genetic risk of schizophrenia, at-risk groups and individuals with chronic schizophrenia.

1.7.2 Neurotransmitters: Glutamate/GABA

Investigations into mechanisms which underlie the loss of brain volume in schizophrenia have suggested that the glutamatergic system is involved (Harrison and Weinberger, 2005). Increased hippocampal glutamatergic levels in unmedicated patients with schizophrenia have been correlated with hippocampal volume reductions (Kraguljac, White, Reid & Lahti, 2013). Glutamate (Glu) is the most abundant excitatory neurotransmitter in the central nervous system (Fonnum, 1984) and has been found to be reduced in individuals with chronic schizophrenia and increased in medication naïve patients (Poels, Kegeles, Kantrowitz, Javitt, Lieberman, Abi-Dargham & Girgis, 2014). Therefore, it is conceivable that although glutamate levels are increased in the early stages of the disorder, they decrease after antipsychotic medication treatment (Marsman, Mandl, Klomp, Bohlken, Boer, Andreychenko et al, 2017).

A recent meta-analysis which included a total of 647 schizophrenia patients and 608 controls across 28 studies also reported reduced Glu. Interestingly, group-by-age associations found that Glu decreased faster with age in schizophrenia patients compared to controls. It appears that FEP-groups show an increase in Glu whilst individuals with chronic schizophrenia show a decrease in Glu (Port & Agarwal, 2011). Researchers have hypothesised that initially Glu levels are increased which then leads to excitotoxicity which then in turn brings about neuronal death which can be seen as decreases in *N* -Acetylaspartic acid (NAA). NAA can be seen as a marker of viable neurons, axons and dendrites (Merugumala, Ramadan, Keenan, Liao, Wang & Lin, 2014).

A recent meta-review also reported increases in glutamine (Gln) in schizophrenia (Marsman, van den Heuvel, Klomp, Kahn, Luijten & Hulshoff Pol, 2011) which could be due to deficits in glutaminase (the enzyme that converts Gln into Glu) which would explain the decreased glutamate and the increased Gln shown in studies of patients with chronic schizophrenia. However, it is argued that the results of these studies are questionable as the majority of studies have not had their methods validated (Merugumala, Ramadan, Keenan, Liao, Wang & Lin, 2014).

Additionally, it has been found that aberrant glutamatergic neurotransmission in schizophrenia is related to a dysfunction in *N* -methyl- d -aspartate (NMDA) receptors. This is supported by findings that NMDA-receptor agonists, such as ketamine and phencyclidine, induce psychotic symptoms in healthy volunteers (Javitt and Zukin 1991).

Differences in γ-Amino Butyric Acid (GABA) neurotransmission, the major inhibitory neurotransmitter in the central nervous system (CNS) (Merugumala, Ramadan, Keenan, Liao, Wang & Lin, 2014), have been found to be an important feature in the pathophysiology of schizophrenia which are evidenced by reduced GABA synthesis. This is supported through decreased activity of GAD67 expression (Gonzalez-Burgos, Hashimoto & Lewis, 2010).

Moreover, research has found that GABA receptors may be upregulated which suggests a compensatory response to the decrease in GABA levels (Jarskog, Gilmore, Glantz, Gable, German, Tong & Lieberman, 2007). Reductions in GABA-level have been linked to cognitive performance as a recent study reported a reduction of GABA in chronic schizophrenia patients in the anterior cingulate which was correlated with lower attention performance (Rowland, Kontson, West, Edden, Zhu, Wijtenburg & Barker, 2012).

Studies investigating glutamate and GABA levels are becoming increasingly sophisticated with the advancements of ever more powerful imaging methods. A recent 7 T ^{1}H-MRS study found that patients with schizophrenia showed significantly lower prefrontal GABA levels, However, no differences were found in glutamate. Interestingly, GABA was negatively correlated with total IQ in patients with schizophrenia. The authors argue that this suggests processes involving GABA in the prefrontal cortex are distinguished from glutamate and that GABA may have a compensatory role in the prefrontal cortex in high functioning individuals with a diagnosis of schizophrenia (Marsman, Mandl, Klomp, Bohlken, Boer, Andreychenko et al, 2017).

Differences in GABA/Glutamate-levels may, however, be potentially confounded by the effects of antipsychotic medication. A recent study found that the concentration of GABA measured in the anterior cingulate was negatively correlated with the dose of medication. Any significant differences in GABA did not hold once the patients on such medications had been excluded from analysis (Tayoshi, Nakataki, Sumitani, Taniguchi & Shibuya-Tayoshi, et al., 2010).

1.7.3 Neurodevelopmental vs Neurodegenerative

These findings along with the identification of genetic and environmental risk factors have not only helped shape an understanding of the aetiology of schizophrenia but have provided evidence for an ongoing fundamental debate around the trajectory of dysfunction in schizophrenia spectrum and other psychotic disorders. Traditionally, schizophrenia was considered a neurodegenerative disorder. Kraepein's description of dementia praecox encapsulates the neurodegenerative theory which posits that progressive neurodegeneration is the driving force behind the mental decline of the disorder (Kochunov & Hong, 2014). However, to this day there is little evidence for this hypothesis. Nonetheless, it is often proposed degeneration could be explained by as excessive synaptic pruning or inflammation (Howes, Fusar-Poli, Bloomfield, Selvaraj, McGuire, 2012).

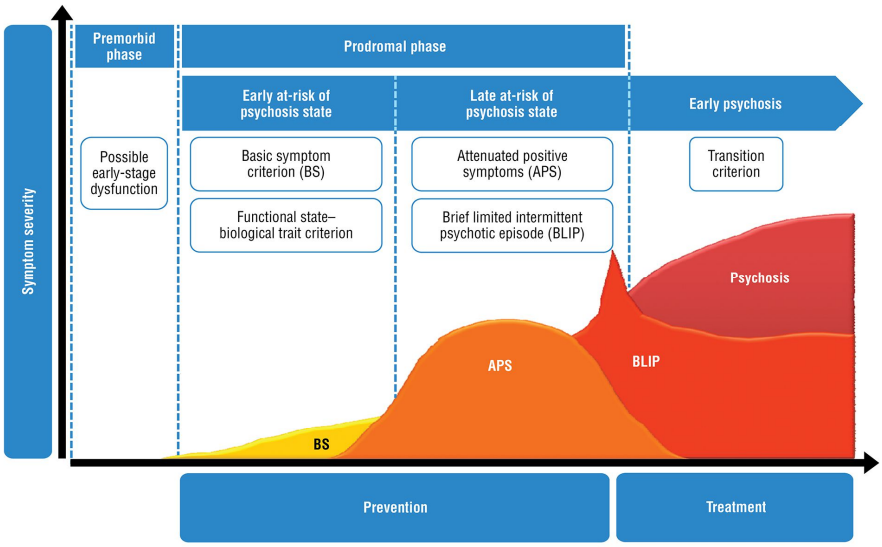
Neurodevelopmental models argue that genetic and environmental factors are at play during prenatal, perinatal and early adolescent stages that impact upon the typical course of neurodevelopment (Lewis & Levitt, 2002; Rapoport, Giedd, & Gogtay, 2012). Neurodevelopmental models view schizophrenia as being the final stage of such abnormal neurodevelopmental processes which begin many years before the onset of the disorder. Cognitive and longitudinal studies have been crucial in developing the understanding of

neurodevelopmental processes and risk factors associated with these. A main finding of these studies has been that individuals who go on to develop schizophrenia have impaired cognitive and motor performance even in childhood (Dickson, Laurens, Cullen & Hodgins, 2012). However, impairment of cognition, language and motor function are common in childhood and are generally seen to be risk factors to a wide range of psychopathological outcomes in adulthood and thus not specific to schizophrenia (Johnstone, Ebmeier, Miller, Owens & Lawrie, 2005; Lawrie, Olabi, Hall, & Mcintosh, 2011). The neurodevelopmental hypothesis of schizophrenia strongly supports the idea that cognitive dysfunction is a core feature of the illness (Gold, 2004; Green, Nuechterlein, Gold, Barch, Cohen, Essock, et al., 2004).

1.8 Prodromal Phase, Basic Symptoms and UHR

Many of the symptoms of schizophrenia can be observed long before the full manifestation of the disorder (Beiser, Erickson, Fleming & Iacono 1993; Yung & McGorry, 1996). This period, known as the prodromal phase, involves changes in mood, such as anxiety and/or depression, social withdrawal, attenuated subthreshold psychotic symptoms (APS), disorganisation and cognitive deficits. 'At-risk or 'at-risk mental state' (ARMS) (Yung & McGorry, 1996a; Yung & McGorry, 1996b) criteria have been developed, i.e. clinical high-risk (CHR), also known as high-risk (HR), and ultra-high-risk (UHR) (Fusar-Poli., Deste, Smieskova, Barlati, Yung & Howes, et al., 2012). A model of the onset of psychosis from the clinical high-risk state is shown in Figure 3. This shows the course of the prodromal phase from its initial stages into first episode psychosis. It is important to note that meeting criteria for ARMS is considered a risk factor for developing psychosis but does not, however, mean that transition to psychosis is inevitable (Yung & McGorry, 1996a; Yung & McGorry, 1996b). Importantly, one of the outcomes of research in ARMS groups has highlighted the potential development of both psychotic and non-psychotic disorders, again highlighting this phase as an important target for early intervention.

Figure 3: Model of psychosis onset from the clinical high-risk state.



Model of psychosis onset from the clinical high-risk state. The higher the line on the y-axis, the higher the symptom severity. Fusar-Poli et al. (2013).

Schizophrenia and related disorders typically manifest during late adolescence/early adulthood which is an important transitional time in terms of biological development as well as social, psychological and occupational development. Moreover, emerging evidence suggests that the debilitating negative and cognitive symptoms are evident even before a full manifestation of schizophrenia. Cortical changes during this time have been associated with motivational, social and cognitive dysfunctions which once manifested are difficult to improve, even after successful treatment of positive symptoms (McGorry, Yung & Phillips, 2001). Given this, early intervention, and a focus on negative symptoms, is important not only for early detection to avoid a delay in treatment but also to identify phase-specific interventions for individuals in the early stages of the disorder (Chang, 2011). Such interventions could not only delay onset and limit functional decline, but also potentially avoid the development of frank psychosis altogether (Fusar-Poli et al, 2012).

Two main approaches have emerged from research involving ARMS groups, the basic symptom approach (BS) and the attenuated psychotic symptoms (APS) approach. Basic symptom approach encapsulates the early stages of the prodrome which consists of subtle sub-clinical changes in mood, cognition, motivation and motor action. The UHR classification conceptualises the APS approach. Criteria for UHR status are aimed at capturing experiences in the later stages of the prodromal phase which includes experiences of attenuated psychotic symptoms. The focus of such research is on the transition to full

manifestation of psychosis with an aim to identifying biomarkers, outcomes and targets for early intervention.

The term *prodromal* was first used in 1932 by Mayer-Gross whose work was an influential force for the seminal work of Huber and Gross (1989) in first promoting the concept of basic symptoms (Schultze-Lutter, Addington, Ruhrmann & Klosterkötter, 2007). More recently, work involving basic symptoms has been the focus of the German Early Detection Team which has highlighted the importance of basic symptoms as predictors of psychosis (Häfner, Maurer, Ruhrmann, Bechdolf, Klosterkötter, Wagner et al., 2004; Schultze-Lutter, Ruhrmann & Klosterkötter, 2006). Basic symptoms are experienced as subtle, sub-clinical, subjective disturbances over the domains of perception, thought processes, attention, language, affect and motor action. They have been found to be present before the first episode of psychosis, between psychotic episodes, and after. Basic symptoms have also been found to be present during psychotic episodes themselves and are understood to be the first psychopathological expression of the underlying symptoms associated with the development of psychosis. These are phenomenologically distinct from attenuated psychotic symptoms measured in UHR (Schultze-Lutter, Addington, Ruhrmann, Klosterkotter & 2007). Unlike UHR criteria, basic symptoms are not associated with any unusual thought content and individuals are not at the stage of reality testing. In addition, individuals may be away of the experiences psychopathological nature (Schultze-Lutter, 2009).

Basic symptoms are measured using the Schizophrenia Proneness Instrument-Adult version (SPI-A) (Schultze-Lutter, Addington, Ruhrmann & Klosterkotter, 2007) and the Schizophrenia Proneness Instrument-Child and Youth version (SPI-CY) (Schultze-Lutter, Marshall & Koch, 2012). These measure self-perceived, subjective disturbances around the domains of drive, stress-tolerance, affect, motor disturbance and body perception. Items are clustered around two sub-categories of COPER (10 cognitive-perceptive basic symptoms) and COGDIS (9 cognitive criteria) with the latter being the most predictive of later transition to psychosis (Schultze-Lutter, Klosterkötter, Picker, Steinmeyer & Ruhrmann, 2007). It has been demonstrated in a help seeking population that a subset of basic symptoms demonstrated a good predictive value for developing frank schizophrenia in the next 9-10 years. The highest predictive accuracy was associated with perceptive and cognitive basic symptoms (KlosterKotter, Hellmich, Steinmeyer & Schultze-Lutter, 2001).

A UHR classification generally defines the later stages of the prodrome and requires one of the following to meet criteria: attenuated psychotic symptoms (APS); brief limited intermittent psychotic episode (BLIPS); a genetic risk factor plus marked functional decline

(genetic risk and deterioration syndrome (GRD) and unspecified prodromal symptoms (UPS) (Fusar-Poli et al, 2012). A number of measures have been developed to assess for these subgroups within UHR status. The most widely used being the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung, Phillips, Simmons, Ward, Thompson, French, & McGorry, 2006) and the Structured Interview for Prodromal Symptoms (SIPS) and its companion Scale of Prodromal Symptoms (SOPS) (Miller, McGlashan, Rosen, Cadenhead, Cannon, Ventura, McFarlane et al., 2003).

UHR criteria have been the most extensively researched approach and recruitment has focused primarily on help-seeking/clinical populations recruited through prodromal and early intervention clinics. More recently, researchers have increasingly used combined BS and UHR criteria that has produced improved prediction rates for psychosis (Ruhrmann, Schultze-Lutter, Salokangas, Heinimaa, Linszen & Dingemans, et al., 2010). In terms of neuro-cognitive studies, cognitive deficits appear to be less pronounced in studies using the basic symptom approach, intermediate in studies using the UHR approach and most pronounced in studies using a combined approach (Fusar-Poli et al, 2012).

1.9 Cognition in CHR

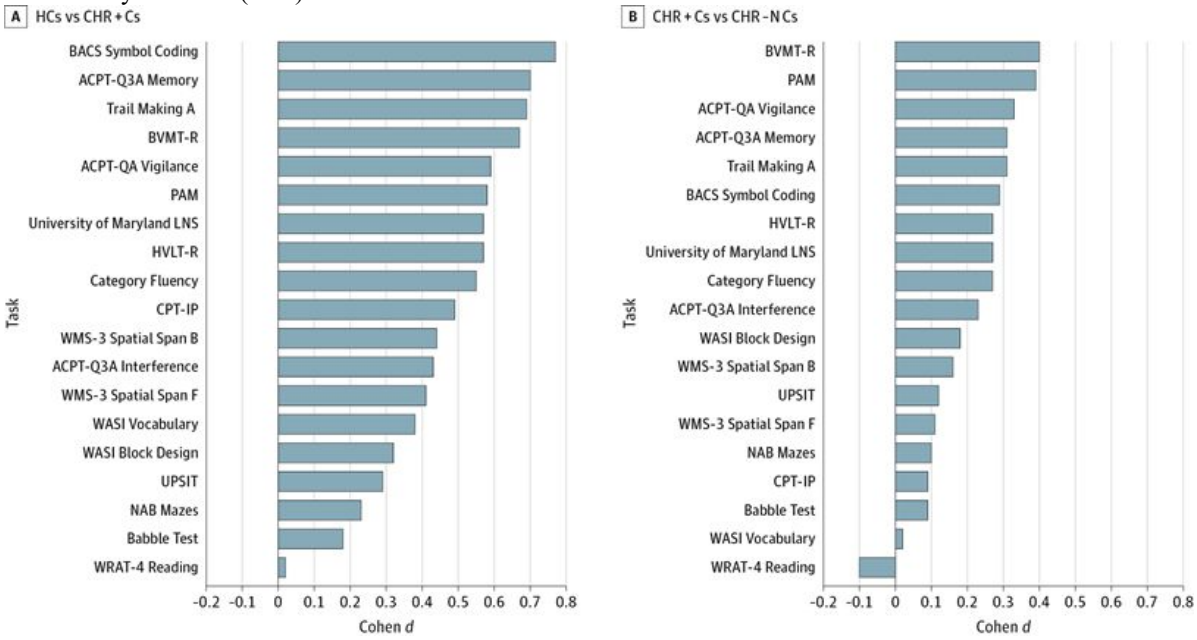
Cognitive deficits are considered as vulnerability markers of psychosis (Bora, Lin, Wood, Yung, McGorry & Pantelis, 2014) and can be useful treatment targets. As cognitive dysfunctions are already present at first episode, this suggests that such dysfunctions may be a marker of psychosis before the manifestation of the disorder. There is substantial evidence of cognitive deficits in UHR groups (Fusar-Poli et al, 2012) and evidence that such deficits exist before the prodromal phase (Bora & Murray, 2014). Cognitive functioning in patients who were diagnosed with schizophrenia later in life, as well as their siblings, were found to be stable from age 4 to 7 suggesting that cognitive deficits are stable vulnerability markers throughout the premorbid phase (Cannon, Bearden, Hollister, Rosso, Sanchez & Hadley, 2000).

Generally, the profile of cognitive deficits in UHR samples reflects those of frank schizophrenia. Significant impairments have been found in various domains of neurocognitive functioning including working memory, attention, speed of processing, verbal memory executive functions have been found in UHR populations (Seidman, Giuliano, Smith, Stone, Glatt, Meyer, et al., 2010; Bora et al, 2014; Kelleher, Clarke, Rawdon, Murphy & Cannon, 2013). Early studies of cognitive functioning in UHR

populations have found that CHR-UHR-individuals showed impairments in cognition relative to controls and these deficits were less substantial than in FEP (Hawkins, Addington, Keefe, Christensen, Perkins, Zipurksy, et al. 2004).

In the largest CHR study to date, Seidman et al. (2016) found CHR-individuals to be significantly impaired in all neurocognitive domains compared to controls. In a sample of 689 CHR-participants and 264 controls, they found the largest deficits to be in attention and working memory abilities, and declarative memory abilities which showed large effect sizes (see Figure 4). CHR-individuals who transitioned to psychosis were significantly impaired in attention and working memory abilities, and in declarative memory abilities relative to CHR-individuals who did not transition to psychosis (Seidman, Shapiro, Stone, Woodberry, Ronzio, Cornblatt, et al., 2016).

Figure 4: Effect Sizes (Cohen d) for Individual Tests Adjusted for Age, Site, and Maternal Education for Clinical High-Risk Converters to Psychosis (CHR + Cs), Clinical High-Risk Nonconverters (CHR − NCs), and Healthy Controls (HCs)



Effect sizes are rank ordered from largest to smallest. ACPT indicates Auditory Continuous Performance Test (QA are simply the letters; Q3A, the number of letters between an "A" and a "Q"); BACS, Brief Assessment of Cognition in Schizophrenia symbol coding; BVMT-R, Brief Visuospatial Memory Test–Revised; CPT-IP, Continuous Performance Test–Identical Pairs; HVLT-R, Hopkins Verbal Learning Test–Revised; LNS, Letter Number Span; NAB, Neuropsychological Assessment Battery mazes; PAM, Paired Associate Memory; UPSIT, University of Pennsylvania Smell Identification Test; WASI, Wechsler Abbreviated Scale of Intelligence; WMS-3, Wechsler Memory Scale–Third Edition spatial span; and WRAT-4, Wide Range Achievement Test 4. Taken from Seidman, Shapiro, Stone, Woodberry, Ronzio, Cornblatt, et al., 2016.

Hawkins et al. (2004) found a group of 36 high risk (HR) individuals to be no different in intellectual performance relative to controls on 3 out of 4 subtest, however, the HR group did perform more poorly on the 4th subtest, the Digit Symbol test which measures processing speed. This may be due to the small sample size and the possibility that the study was underpowered leading to an increased chance of Type II errors. They found the HR group to

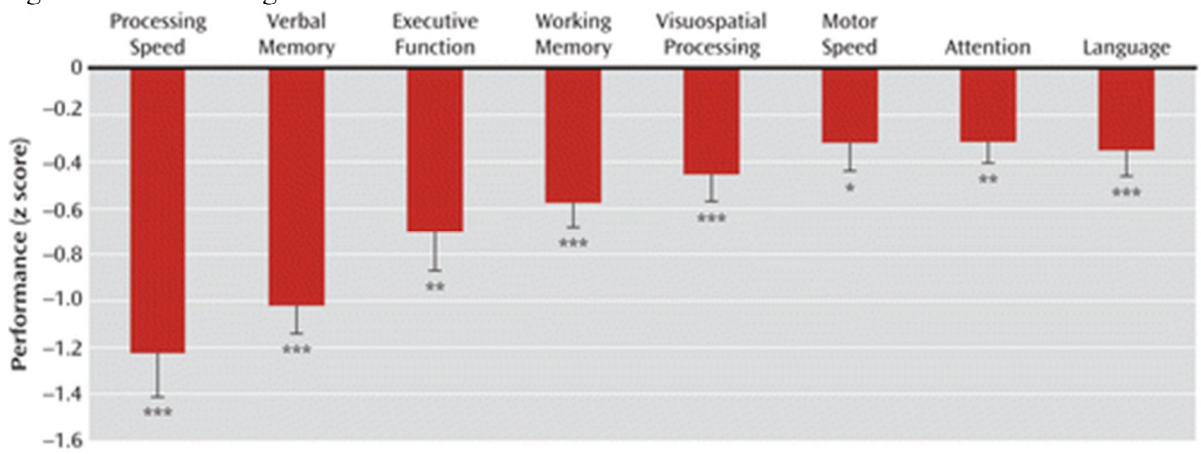
be significantly impaired in all other tests with the most pronounced deficits being in measures of visual attention, set shifting and verbal fluency. Notably, the HR group were not found to have the same level of impairment as individuals who were at first episode of psychosis. This suggests a process of cognitive deterioration which may go along with the progression to frank psychosis. However, there is not robust evidence for this so far. Another study found a UHR group to be significantly impaired in tasks of spatial working memory, spatial span and delayed matching-to-sample (Wood, Pantelis, Proffitt, Phillips, Stuart & Buchanan, et al., 2003). Similarly, Smith, Park & Cornblatt (2006) found spatial working memory to be significantly impaired in age and IQ matched adolescents at clinical high risk of psychosis relative to controls.

However, findings have been somewhat inconsistent with differences in profiles being reported and the more prominent domains differing across studies. In these studies, spatial working memory has been found to be impaired in UHR groups and associated with negative symptoms (Wood, Pantelis, Proffitt, Phillips, Stuart & Buchanan, et al., 2003). Many studies have found at-risk groups to be impaired in each domain relative to controls (e.g. Bora et al, 2014; Hou, Xiang, Wang, Everall, Tang & Yang, et al., 2016) although inconsistent in which impairment is most prominent. Follow up studies have suggested that certain domains may indicate stable vulnerability markers (e.g. sustained attention) (Francey, Jackson, Phillips, Wood, Yung & McGorry, 2005) whereas others may be predictive of transition to psychosis (e.g. verbal IQ, processing speed, verbal memory, working memory) (Brewer, Francey, Wood, Jackson, Pantelis, Phillips, et al., 2005; Lencz, Smith, McLaughlin, Auther, Nakayama, Hovey, et al., 2006; Seidman, Giuliano, Smith, Stone, Glatt & Meyer, et al., 2010). There has been support for both processing speed and verbal memory as the main predictors for transition to psychosis (Lencz, Smith, McLaughlin, Auther, Nakayama, Hovey, et al., 2006; Lin, Wood, Nelson, Brewer, Spiliotacopoulos, Bruxner, et al., 2011; Fusar-Poli, Deste, Smieskova, Barlati, Yung, Howes et al., 2012). However, these findings remain inconsistent (Keefe, Perkins, Gu, Zipursky, Christensen & Lieberman, 2006). Moreover, processing speed and verbal memory have been found to endure throughout the course of the illness and have been associated with the major disability which is associated with schizophrenia (Green & Harvey, 2014).

It has been argued that processing speed is the core cognitive deficit in psychosis and possibly the driving cognitive deficits in other domains (Dickinson, 2008). However, it has also been found that the effect size of processing speed can be moderated by a number of variable, most importantly by anti-psychotic medication (Knowles, David & Reichenberg, 2010). This has led to some debate as to as to the role of processing speed as a core deficit

of schizophrenia. Support for the speed of processing hypothesis in UHR has been consistently demonstrated. One study conducted a population based assessment of prodromal symptoms in adolescents. Those who met UHR criteria were found to show deficits in many areas with processing speed being the most pronounced (see Figure 5) (Kelleher, Murtagh, Clarke, Murphy, Rawdon & Cannon, 2013).

Figure 5: Profile of cognitive function of CHR-individuals relative to controls



The non-psychiatric control group was set to 0 and standard deviation to 1. Error bars show standard errors of the mean. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Taken from Carrión, Goldberg, McLaughlin, Auther, Correll & Cornblatt, 2011.

The progressiveness of neuro-cognitive deficits over the prodromal and frank psychosis trajectory is still being debated with some reporting no change over time, others suggesting that deficits get progressively worse (Brewer, Wood, Phillips, Francey, Pantelis & Yung, et al., 2006). One study compared cognitive functioning of two at risk groups (one group met criteria for predictive basic symptoms and the other for UHR criteria based on SIPS/SOPS) with those at first episode and help seeking controls (Simon, Cattapan-Ludewig, Zmilacher, Arbach, Gruber, Dvorsky et al., 2007). They found that all 4 groups performed below normative levels with the at-risk groups being intermediate between normative values and first episode. The basic symptom group was found to be comparable in cognitive functioning to the help seeking controls but more impaired that the UHR group. Other studies have suggested that neurocognitive deficits are stable throughout the prodrome, treatment phase and first episode (Hawkins, Keefe, Christensen, Addington, Woods, Callahan, et al., 2008) whilst a recent meta-analysis showed some improvement after first episode (Bora & Murray, 2014). These inconsistencies may be reflective of confounds such as medication, psychological treatments, poor physical health and institutionalisation (Fusar-Poli, Deste, Smieskova, Barlati, Yung & Howes, et al., 2012). This highlights a benefit of conducting research with medication naïve UHR samples as many of these confounds can be avoided.

Reasons for these inconsistencies may include varying measures across studies, different classifications of 'at-risk' or differing UHR subcategories. This is an important issue as it has been suggested that impairments differ across UHR sub-groups with individuals who are further along the prodromal trajectory being the most significantly impaired (Fusar-Poli et al., 2012). False positives and comorbidity are other important factors to consider when studying at-risk groups. The majority of participants who meet UHR criteria will not go on to develop psychosis (Fusar-Poli et al., 2012; Cannon, Cadenhead, Cornblatt, Woods, Addington & Walker, et al., 2008) with transition rates between 10-30 % (Fusar Poli et al, 2012). Moreover, this suggests that impaired neurocognitive functioning may be more indicative of being at risk to a wider scope of psychopathology rather than being exclusive to psychosis (Velthorst, Nieman, Linszen, Becker, de Haan & Dingemans, et al., 2009; Lin, Yung, Nelson, Brewer, Riley & Simmons, et al., 2013). Therefore, it is important to identify subclinical illness specific symptomatology in which to improve sensitivity and specificity in at risk groups (Ballon, Kaur, Marks & Cadenhead, 2007).

A recent meta-analysis (Bora & Murray, 2014) found UHR to be impaired in every domain of cognition relative to controls. The most robust deficits were observed for symbol coding task (a measure of processing speed), visuospatial working memory and a smell identification task all with medium effect sizes. Cognitive deficits were found to be significantly more severe in those who later developed psychosis.

An earlier meta-analysis (Fusar-Poli et al, 2012) observed significant impairments in general intelligence relative to controls and an overall impairment in neuro-cognitive functioning. In relation to transition to psychosis the most prominent deficits were observed in visual and verbal memory. Overall there were no impairments found in the domain of processing speed. However, there was a significant difference found in the digit symbol substitution task (symbol coding task) when compared to controls. UHR individuals were best distinguished from controls on the performance of the digit symbol substitution task, letter number sequencing task and continuous performance task. This suggests that although speed of processing was found to be non-significant overall, this may be due to the differing methods of measuring processing speed, or that the digit symbol substitution task is measuring something more specific. There was also a significant difference in the overall domain of social cognition relative to controls.

1.10 Social Cognition in CHR

CHR studies have found deficits emotion recognition, theory of mind and social perception (Thompson, Bartholomeusz & Yung, 2011). However, compared to existing literature on neurocognition, the number of studies examining social cognition in CHR-populations is small. Studying emotion recognition in CHR-populations is important given the abundant of deficits in schizophrenia (Mandal, Pandey & Prasad, 1998; Aleman & Kahn, 2005; Trémeau, 2006) that are associated with impairments in social skills (Hooker & Park, 2002; Pinkham & Penn, 2006; Ikebuchi, 2007). In CHR, a similar profile of impaired facial emotion recognition has been reported (Thompson, Papas, Bartholomeusz, Allott, Amminger, Nelson, et al., 2012; Amminger, Schäfer, Klier, Schlögelhofer, Mossaheb, Thompson, et al., 2012a; Amminger, Schafer, Papageorgiou, Klier, Schlogelhofer, Mossaheb, et al., 2012b; van Rijn, Aleman, de Sonneville, Sprong, Ziermans, Schothorst, et al., 2011; Green, Bearden, Cannon, Fiske, Hellemann, Horan, Kee, et al., 2012) and deficits remained significant after controlling for important covariates/confounders. This suggests that emotion recognition deficits may emerge during or even before the prodrome. A recent meta-analysis found that UHR participants demonstrate significant moderate deficits in emotion recognition in faces (van Donkersgoed, Wunderink, Nieboer, Aleman & Pijnenborg, 2015). They reported that the majority of studies did not find a correlation between social cognitive impairments and transition to psychosis suggesting that general social cognition may not be a useful marker of transition to psychosis. However, some studies suggest there may possible predictive value in specific forms of social cognition, in particular the recognition of specific emotions.

Allott, et al. (2014) found lower accuracy of faces showing neutral emotion and higher accuracy of faces showing fear to be predictive of transition to psychosis within 12 months after controlling for baseline positive, negative and global symptoms and functioning. This supports previous findings from schizophrenia and UHR-literature which suggests that emotion recognition may be a trait marker of psychosis as UHR-groups perform significantly poorer than controls on a facial recognition task and not significantly different from first episode and multiple episode individuals (Addington, Penn, Woods, Addington, Perkins, 2008a; Amminger, Schäfer, Klier, Schlögelhofer, Mossaheb & Thompson, et al, 2012). However, Green et al (2012) found CHR-individuals to be significantly impaired in emotion recognition relative to controls and less impaired relative to first episode and chronic schizophrenia groups.

Many studies have found a particular deficit in the identification of neutral emotion (Addington, Penn, Woods, Addington, Perkins, 2008a; Eack, Mermon, Montrose, Miewald, Gur & Gur, et al., 2010; van Rijn, Aleman, de Sonneville, Sprong, Ziermans & Schothorst, et al., 2011), although this is somewhat inconsistent (Pinkham et al. 2007). Amminger et al., (2011) compared groups of UHR-participants, individuals at first episode of psychosis and controls on an emotion recognition task. They found that UHR-individuals showed deficits in emotion recognition in both faces and voices, specifically fear and sadness, relative to controls, and that UHR group deficits were comparable to first episode. van Rijn et al (2011) observed deficits in emotion recognition in a sample of UHR individuals when compared to controls. Specifically, UHR individuals made more errors in recognising faces showing no emotion. Further analysis showed that UHR individuals would misattribute faces showing no emotion for anger.

However, findings for emotion recognition in at-risk for psychosis literature are conflicting. There have been a number of studies which did not observe any deficits in CHR-UHR populations. Pinkham et al. (2007) compared groups of individuals at CHR for psychosis, those at first episode of psychosis, those with chronic schizophrenia and controls. They found that emotion recognition deficits were observed only in the first episode and chronic schizophrenia groups. Findings from phase 2 of the North American Prodromal Longitudinal Study (NAPLS-2) did not find any significant differences between those at CHR (N=675) and controls after controlling for IQ and age (Barbato, Liu, Cadenhead, Cannon, Cornblatt & McGlashan et al., 2015). These findings were similar to Thompson et al. (2012) who observed no significant differences of emotion recognition between those at UHR for psychosis and controls when controlling for age, gender and IQ.

In a 5-year longitudinal study of UHR individuals Kim et al (2011) found that combining social-cognitive and neurocognitive variables significantly predicted transition to psychosis. This, combined with evidence from schizophrenia studies (e.g. Sergi et al., (2007) reported social cognition as contributing to predictions of functional outcome in chronic schizophrenia) suggests that such deficits are evident throughout the entire course of the illness, including the prodromal phase therefore can be considered as risk markers for psychosis. Given the potential of social cognition as a predictive factor, it is important to include measures of social cognition in UHR research.

1.11 Cognition and functioning

Recently research has investigated levels of functioning in those who are at-risk for psychosis and the relationship between neurocognitive functioning and functional outcomes. Addington et al (2008b) found a CHR group of individuals to be significantly impaired in social functioning relative to controls but comparable to first episode and multiple episode groups. In addition, the CHR group performed poorer than controls on role functioning but better than the multiple episodes group. In studies that have investigated functional outcomes in UHR groups, social functioning outcomes appear to be more stable than role functioning and has been shown to be associated with transition to psychosis (Cornblatt, Auther, Niendam, Smith, Zinberg & Bearden et al, 2007; Velthorst, Nieman, Linszen, Becker, de Haan & Dingemans et al., 2010). This suggests that along with neuro-cognitive and social cognitive factors, deficits in social functioning are evident before the onset of psychosis and may be a trait marker of the disorder.

Studies have looked at the association between neurocognition and functioning in at-risk groups with conflicting findings. In UHR samples, it has been found that impairments in processing speed and verbal learning and memory are predictive of current social functioning which is independent of negative and positive symptom severity. However, general functioning was associated with negative symptoms and not neurocognitive functioning (Niendam, Bearden, Johnson, McKinley, Loewy, & O'Brien et al., 2006). After an eight month follow up period, improvements in functioning were not associated with the severity of neurocognitive performance at baseline, but with improvements in processing speed and visual learning and memory (Niendam, Bearden, Zinberg, Johnson, O'brien & Cannon, 2007). On the other hand, another study found that improvement in neurocognitive performance was not associated with social functioning measured by Global Assessment of Functioning (GAF) scores in an at-risk sample with six months follow up (Jahshan, Heaton, Golshan & Cadenhead, 2010).

A recent study extended this research and examined the development of impairments in cognition and their relationship to functioning (Carrión, Goldberg, McLaughlin, Auther, Correll & Cornblatt, 2011). The CHR group had significant impairment in neurocognition particularly in the domains of processing speed, verbal memory, executive function and working memory. Moreover, impairments in both social and role functioning were present that were related to neurocognitive performance independent of positive symptoms. More specifically, speed of processing was the most significantly impaired and predictive of

poorer social and role functioning at baseline relative to controls. This suggests that the relationship between neurocognition and functioning exists before the onset of frank psychosis and is not an outcome of the illness. Lin, et al. (2011) observed in a sample of UHR individuals (N=203) that poor functional outcome was associated with impaired baseline performance in verbal learning and memory, processing speed, attention and verbal fluency but not global cognitive performance. Additionally, they found that reduced performance on a verbal story recall task combined with negative symptoms at baseline was the best predictor of poor outcome later on. Positive psychotic symptoms and GAF scores at baseline were not associated with poor outcome later on. Importantly, they found that poor functional outcomes were associated with specific neurocognitive domains, regardless of transition to psychosis.

1.12 Early interventions in high risk

The identification of UHR-populations has been combined with interventions that could potentially stop the transition to psychosis or delay onset of psychotic symptoms. A randomised control trial of cognitive behavioural therapy (CBT) for the prevention of psychosis in individuals at UHR (Morrison, French, Walford, Lewis, Kilcommons, Green et al. 2004) found that 6 months of CBT significantly reduced the likelihood of transitioning to psychosis within a 12-month period and improved the severity of positive symptoms. Some benefits were still evident at 3-year follow up, specifically a reduced likelihood of being prescribed anti-psychotic medication. However, CBT did not affect the likelihood of transition to psychosis over the 3-year follow up period (Morrison, French, Parker, Roberts, Stevens, Bentall & Lewis, 2006). A randomised controlled trial compared CBT to supportive therapy and assessed individuals at follow up on attenuated positive symptoms, negative symptoms, anxiety, depressions and social functioning. After 18 months, only individuals in the supportive therapy group transitioned to psychosis. However, the difference in transition rates did not reach significance (Addington, Epstein, Liu, French, Boydell & Zipursky, 2011). Both groups improved in the severity of attenuated positive symptoms (although positive symptoms improved more quickly in the CBT group), anxiety and depression but social functioning and negative symptoms did not improve. This suggests that social functioning is independent of positive symptoms however may be related to negative symptoms of psychosis.

Pharmaceutical studies have also found promising results. A randomised controlled trial of an active treatment of risperidone (1-3 mg/day) along with modified CBT compared to a needs-based intervention (McGorry, Yung, Phillips, Yuen, Francey, Cosgrave et al, 2002). They found that significantly transition rates were significantly lower in the active treatment group (9.7% vs 36%). Another study looked at the efficacy of the antipsychotic olanzapine in a randomised, double-blinded placebo controlled trail. They found that at one-year follow-up 16% of the olanzapine treatment group had transitioned to psychosis compared to 35% of the placebo group however this difference was not significant. Moreover, the olanzapine treatment group overall showed greater improvements in symptoms than did the placebo group (McGlashan, Zipursky, Perkins, Addington, Miller, Woods et al., 2006). However, a recent meta-analysis reported that there is no reliable evidence as to whether psychosocial (such as CBT), anti-psychotic medication, or potentially neuroprotective agents (such as Omega -3 fatty acids) are the most effective in preventing psychosis in at-risk groups. The safest treatments are then recommended which are psychosocial interventions and Omega -3 fatty acids.

A meta-analysis of interventions in those who are UHR for developing psychosis found that overall such interventions are effective (van der Gaag, Smit, Bechdolf, French, Linszen, Yung, et al., 2013). They found that the risk of onset was reduced by 54% to 52% within the first 12 months and by 37% to 35% between 2 to 4 years. These diminishing results, although show efficacy at delaying onset, suggest that such treatment may not be effective at preventing psychosis. Similarly, Fusar-Poli et al. (2013) reported that overall preventative treatments in psychosis are feasible and can be effective. There are many large scale clinical trials currently being carried out which will provide much needed evidence for best clinical practice in at-risk states (Morrison, Stewart, French, Bentall, Birchwood, Byrne, et al., 2011).

Early intervention studies have also investigated the course of neurocognitive functioning in the prodrome and at first episode of psychosis (Hawkins, Keefe, Christensen, Addington, Woods, Callahan, et al., 2008). An olanzapine double blind treatment study found that neither the anti-psychotic nor transition to psychosis altered the course of neurocognitive function. Overall, it has been demonstrated that although pharmacological treatments have had some success at treating positive symptoms, there has been little success in treating negative symptoms and cognitive impairments (Keefe, Bilder, Davis, Harvey, Palmer, Gold, et al., 2007).

1.13 Aims

CHR literature has reported robust deficits in neurocognitive functioning (Fusar Poli et al., 2012; Bora & Murray, 2014) and well reported but somewhat conflicting deficits in social cognition (van Donkersgoed, Wunderink, Nieboer, Aleman & Pijnenborg, 2015). Emotion recognition has emerged as a potentially important factor for CHR populations, although, findings are conflicting with more research needed (van Donkersgoed, Wunderink, Nieboer, Aleman & Pijnenborg, 2015). Fewer studies have assessed the relationship between neurocognitive functioning and functional outcomes and have found differing findings (Niendam, Bearden, Johnson, McKinley, Loewy, & O'Brien et al., 2006; Carrión, Goldberg, McLaughlin, Auther, Correll & Cornblatt, 2011). There is a gap in the literature regarding the relationship between emotion recognition and functional outcomes.

This study will explore the relationship between neurocognitive and social cognitive variables with current psychosocial functioning. The association of neurocognitive impairments and functional parameters are somewhat understudied in CHR-literature and with even less literature existing in relation to social cognitive factors in relation to functioning.

The main questions that will be addressed:

1) What are the differences in cognitive, social cognitive and psychosocial functioning in those who are at-risk of psychosis relative to controls?
2) To what extent does neuro- and social cognition explain poor functioning in the CHR population?

We expect to find that, relative to controls, CHR participants will show significant impairments in many domains of cognition with the most prominent impairments being found in processing speed. In addition, we expect that CHR participants will display impaired global, social and role functioning at baseline and that processing speed may be a predictor of poor functioning. In relation to emotion recognition, we expect to find that CHR participants will have poorer emotion recognition abilities relative to controls with a potential for recognition of faces showing neutral emotion being the most impaired. In addition, we will explore the relationship between emotion specific recognition and current psychosocial functioning in individuals who are CHR for psychosis. To the best of our knowledge this is the first study to investigate this association, therefore, this part of the analysis is exploratory.

2. METHODS

2.1 Design

The data presented in this thesis are part of a longitudinal the Youth Mental Health Risk and Resilience (YouR) study. This thesis will utilise a cross-sectional design to assess the neuro- and social cognitive functioning of individuals who are CHR for psychosis relative to controls. Clinical characteristics and demographic data will also be assessed. Finally, we will assess the relationship between neuro- and social cognitive factors and functional parameters at baseline.

The principal investigator obtained ethical approval and the study is being carried out according to the Research Governance Framework for Health and Community Care (Second edition, 2006).

2.2 Participants

We recruited 110 participants who met CHR criteria (mean age: 22, SD: 3.07) and 44 controls (mean age: 22, SD: 4.16). We recruited potential participants from the general population through a website (www.your-study.org.uk), flyers and public transport advertisement. An email containing information about the study and a link to the study website was also circulated through a number of Glasgow universities and colleges. We developed close relationships with NHS Greater Glasgow and Clyde and NHS Lothian services including General Practitioners, primary care and secondary mental health services which included ESTEEM First Episode Psychosis Service (Glasgow), the Early Psychosis Support Service (Lothian), Community Mental Health Teams, and non-statutory (third sector) mental health services. Potential participants were initially informed of the study by a member of their direct care team either face to face or by post. Potential participants could then either obtain information through leaflets or were directed to the study website to complete the online screening questionnaire. Inclusion/exclusion criteria were assessed prior to and during the screening visit. See Table 1 for inclusion / exclusion criteria.

Table 1: Inclusion and exclusion criteria for CHR-participants and controls

Inclusion criteria (CHR)	**Exclusion criteria (CHR)**
Written informed consent	An existing neurological disorder
Male or non-pregnant female ≥16 years of age	> 35 years of age
UHR-criteria according to CAARMS/SIPS or SPI-A	Metal implants in body parts
Normal to corrected vision	Pregnancy
	Suicidal ideation
Inclusion criteria (controls)	**Exclusion criteria (controls)**
Written informed consent	An existing neurological disorder
Male or non-pregnant female ≥16 years of age	> 35 years of age
Normal to corrected vision	Metal implants in body parts
	Pregnancy
	1st degree relative with a diagnosis of Schizophrenia
	Suicidal ideation

2.3 Measures

2.3.1 Pre-screening

Online screening questionnaire: This comprised the 16-item prodromal questionnaire (PQ-16) (Ising, Veling, Loewy, Rietveld, Rietdijk & Dragt, et al., 2012) and assessed attenuated psychotic symptoms. This is a self-report questionnaire designed to measure attenuated psychotic symptoms and identify individuals who are at risk of developing psychosis. The PQ-16 was developed from the full 92 item prodromal questionnaire (PQ) (Loewy, Bearden, Johnson, Raine & Cannon, 2005). Secondly, a 9 item-scale for the assessment of perceptual-cognitive anomalies (PCA) was included. Informed consent was taken at the point of the online screening. Criteria to qualify for a screening interview were 6 or more on the PQ-16 items and/or 3 items on the PCA-scale.

2.3.2 CHR Assessment

A combination of basic symptoms and UHR criteria were used to assess clinical high-risk status. This combined approach has been shown to produce improved prediction rates for psychosis (Ruhrmann, et al., 2010).

The Schizophrenia Proneness Instrument, Adult Version (SPI-A) (Schultze-Lutter, Addington, Ruhrmann & Klosterkötter, 2007) is a semi-structured interview which measures diagnostic criteria of basic symptoms. This consists of 3 subscales and totals 33 items of cognitive, perceptual, and motor disturbances assessed on a 7-point severity scale (score, 0-6). The maximum frequency of occurrence during the preceding 3 months is the guiding criterion. Based on these criteria, individuals are diagnosed as COPER and/or COGDIS. COPER and COGDIS refer to two partially overlapping basic symptom criteria which define the initial stage of the prodrome of psychosis. A COPER diagnosis is based on the 10 cognitive-perceptive basic symptoms and is based on the predictive accuracy of single basic symptoms. COGDIS represents cognitive disturbances, a cluster of 9 cognitive basic symptoms which were repeatedly selected as the most predictive of later transition to psychosis (Schultze-Lutter, Klosterkötter, Picker, Steinmeyer & Ruhrmann, 2007).

The CAARMS (Yung et al, 2006) is a semi-structured interview that assess attenuated psychotic criteria for an at risk mental state diagnosis. CAARMS ratings are made three subscales 1) Positive symptoms consisting of unusual thought content and non-bizarre ideas 2) Perceptual Abnormalities and 3) Disorganised speech (see Table 2 for diagnostic criteria).

Table 2: Diagnostic criteria for ARMS categories measured by the CAARMS

BLIPS*	**1) A Global Rating Scale score of 6 on Unusual Thought Content, Non-bizarre Ideas, or Disorganized Speech; or 5–6 on Perceptual Abnormalities**
	2) A Frequency Scale score of 4–6 on the relevant symptom scale 3) Symptoms are present for less than one week 4) Symptoms resolve without medication 5) Symptoms occurred during the past year
Attenuated symptoms	A. Subthreshold intensity 1) A Global Rating Scale score of 3–5 on Unusual Thought Content or Non-Bizarre Ideas; or 3–4 on Perceptual Abnormalities; or 4–5 on Disorganized Speech 2) A Frequency Scale score of 3–6 on the relevant symptom scale 3) Symptoms are present for more than one week 4) Symptoms occurred during the past year B. Subthreshold frequency: 1) A Global Rating Scale score of 6 on Unusual Thought Content, Non-Bizarre Ideas, or Disorganized Speech; or 5–6 on Perceptual Abnormalities 2) A Frequency Scale score of 3 on the relevant symptom scale 3) Symptoms occurred during the past year
State-plus-trait	1) History of psychosis in a first-degree relative or identification of Schizotypal Personality Disorder 2) 30% drop in GAF** score from pre-morbid level, sustained for at least one month, within the past year or a GAF score of 50 or less for at least the past year

UHR inclusion criteria and subcategories for CAARMS *BLIPS, Brief Limited Intermittent Psychotic Symptoms; **GAF, Global Assessment of Functioning

2.3.3 Functioning

Global Assessment of Functioning (GAF) is used to measure the severity of illness in psychiatry (Aas, 2011) (see appendix 1). This measure gives a single score based on the most severe symptoms and functioning during the past month. In addition, GF Social and GF Role scales were used to measure social and occupational functioning (Cornblatt, Auther, Niendam, Smith, Zinberg & Bearden et al, 2007). These scales were developed to be complementary to each other. Both scales are scored on a range of one to ten with one being the most severely impaired and ten indicating superior functioning (Cornblatt, Auther, Niendam, Smith, Zinberg & Bearden et al, 2007). Anchor points for GF social and GF Role can be found in appendices 2 & 3. A benefit of these scales is that they avoid confounding functioning with psychiatric symptoms. The GF social assesses relationships with peers and

family members along with peer conflict. The GF role assesses performance and amount of support needed in an individual's specific role with questions relating to school, work or housekeeping duties.

2.3.4 Premorbid Adjustment Scale

The Premorbid Adjustment Scale (PAS) (van Mastrigt & Addington, 2002) measures premorbid functioning from a developmental perspective. Good premorbid adjustment is conceptualised as the achievement of age-appropriate developmental and social milestones. This is examined over 4 areas of development: sociability and withdrawal, peer relationships, ability to function outside of the family and capacity to form intimate socio-sexual ties. These are measured over 4 developmental stages (childhood [up to age 11], early adolescence [12–15 years], late adolescence [16–18 years] and adulthood [19 years of age and older]).

2.3.5 Cognition

The Brief Assessment of Cognition in Schizophrenia (BACS) version 3.1 (Keefe, Gold, Goldberg & Harvey, 1999) was administered to assess cognition. The BACS has been developed for clinical trials where the domains of cognitive function assessed are those which are consistently found to be impaired in schizophrenia. The BACS measures verbal memory, working memory, motor speed, attention, executive functions and verbal fluency. The measure requires less than 35 minutes to complete (Keefe, Goldberg, Harvey, Gold, Poe & Coughenour, 2004). Table 3 describes the BACS domains and their related tasks and measures.

Table 3: BACS domains and related tasks.

Domain	Task and measure
Verbal memory and learning	*Task* – list learning. A list of 15 words is presented. Participants are asked to recall as many of these words as possible. This procedure is repeated 5 times. *Measure* – Verbal recall (number of words recalled). *Range* - 0-75
Working memory	*Task* – Digit sequencing. The researcher read out clusters of numbers of increasing length. Participants were asked to reorder the clusters to be in order from lowest to highest with the longest sequence recalled consisting of 8 digits. *Measure* – number of correct responses. *Range* – 0-28.
Motor speed:	*Task* – Token motor task. 100 plastic tokens are placed on a table. Participants are asked to use both hand to simultaneously pick up 2 tokens at the same time and place them into a container as quickly as possible. *Measure* – number of tokens correctly placed into the container within the 60 seconds timeframe. *Range* – 0-100.
Verbal Fluency:	*Task* – Semantic fluency. Participants are given 60 seconds to name as many words as possible within a given category. *Measure* – number of words named. *Task* – Letter fluency. In 2 separate trials, participants are given 60 seconds to name as many words as possible beginning with a specific letter. *Measure* – number of words named.
Executive function:	*Task* – Tower of London. Participants are shown two pictures simultaneously. Each picture displayed three balls of different colours arranged on three pegs. The balls in each picture were arranged differently. Participants were asked to give the number of moves it would take for the arrangement of balls in the first picture to look like the arrangement of balls in the second picture. *Measure* – number of correct responses. *Range* – 0-20.
Speed of processing:	*Task* – symbol coding. Participants were presented with a key describing how unique symbols correspond with numerals 1 – 9. They were asked to fill out the corresponding number beneath a series of symbols as quickly as possible. Participants had 90 seconds to code as many as possible. *Measure* – Number of correctly coded symbols.

Additional tasks from the University of Pennsylvania Computerized Neuropsychological Testing Battery (PennCNB) were administered.

Penn Continuous Performance Test (PCPT; Kurtz et al., 2001): The PCPT is a standard CPT paradigm where participants are asked to respond to a set of 7-segment displays which are

presented 1 per second. Following an example trial, participants are asked to respond by pressing the space bar when they see a fully formed digit (NUMBERS) or letter (LETTERS). The test lasts for 6 minutes with NUMBERS forming the initial 3 minutes and LETTERS forming the final 3 minutes. The CPT paradigm is widely used for measuring vigilance and has been used in detecting genetic susceptibility to psychosis (Chen & Faraone, 2000).

The Letter N-Back task (LBN; Ragland et al., 2002): Letter are presented for 500ms and then gives and additional 2000ms for the participant to respond by pressing the spacebar or not. There are 3 conditions to this task. The 0-Back – instructions are to press the spacebar when the letter "X" appears; 1-Back- press the spacebar when the letter presented is the same as the previous letter; and 2-Back – press the spacebar when the letter presented is the same as the one prior to the previous letter. Following an example trial, participants test begins and participants are given 3 blocks of each condition in a predetermined order. There is a total of 135 trials.

The 40-item facial affect identification test (ER40; Gur et al., 2002): was used as a measure of emotion identification. There are 5 conditions consisting of 4 emotions (happy, sad, fear, angry) and a no emotion condition (neutral). There are 8 facial displays for each condition and the participant is given a multiple-choice format to identify the emotion. The facial stimuli are balanced for age, ethnicity and gender.

2.4 Procedure

All visits were carried out by trained research assistants and postgraduate students (MSc and PhD). Participants first completed the 25-item online screening questionnaire. Informed consent was taken for online participation. Those who met online criteria were then invited to attend a screening interview at the University of Glasgow Psychology department. Informed consent was taken before the screening interview which included demographics, a brief clinical history and interviews for SPI-A and CAARMS. GF: Role GF: Social measures were completed during a follow-up visit with the neurocognitive assessments being completed on a third visit. Participants first completed the BACS followed by the three PennCNB tasks. Instructions for the BACS were read aloud verbatim by a researcher whilst the PennCNB tasks included on screen instructions and practice sessions.

3. RESULTS

All statistical analysis was performed using IBM SPSS version 24. Each individual subscale of cognitive tasks was assessed for normality and raw test scores were standardized by creating z scores using the means and standard deviations of non-psychiatric controls. Data for the Letter N Back test were found to be significantly non-normally distributed therefore the standardization process was not conducted for this subscale. A BACS global score was calculated by summing all the standardized BACS domain scores and again re-standardizing.

3.1 Demographics and Functioning

To examine differences in demographics between groups t tests were performed for continuous data and a chi square test was used to examine differences for nominal data.

Table 4: Baseline demographic and clinical characteristics of Clinical high-risk participants and controls

Characteristic	Control (N=44)	SD	CHR (N=110)	SD	*F*	df	*P*	Cohen's *d*
Age (years)	22.11	3.07	21.85	4.16	1.40	1,152	0.71	
Years of education	16.17	2.71	15.06	3.15	4.12	1,142	0.04*	0.41
GAF	88.69	6.72	60.36	13.84	149.67	1,141	<0.001***	2.6
GF: Social	8.87	0.41	7.65	1.01	53.57	1,137	<0.001***	1.58
GF: Role	8.59	0.79	7.47	1.12	32.6	1,138	<0.001***	1.16
PAS								
Childhood	0.05	0.06	0.17	0.14	24.41	1,137	<0.001***	-1.11
Early adolescence	0.08	0.05	0.2	0.14	28.46	1,135	<0.001***	-1.14
Late adolescence	0.1	0.09	0.21	0.14	16.38	1,130	<0.001***	-0.93
	N	**%**	**N**	**%**	X^2	**df**	***P***	
Gender					1.52	1	0.22	
Male	16	36%	29	26%				
Female	28	64%	81	74%				
Medication status					53.1	5	<0.001***	
None	44	100%	51	46%				
Anti-psychotic	_	_	1	1%				
Mood stabiliser	_	_	1	1%				
Anti-depressant	_	_	23	21%				
Other	_	_	15	14%				
Multiple	_	_	19	17%				
Occupational status					1.59	5	0.91	
Full time paid	3	7%	5	6%				
Part time paid	2	5%	4	4%				
Voluntary	1	2%	1	1%				
Student	36	81%	91	83%				
Unemployed	2	4%	9	7%				

Baseline demographics and clinical characteristics of the control and UHR groups. *p<0.05, **p<0.01, ***p<0.00. Effect sizes are classified as small (d = 0.2), medium (d = 0.5), and large (d ≥ 0.8).

Table 4 summarises the baseline demographic and clinical characteristics of CHR and control participants. CHR and controls did not differ significantly on age (at consent), gender ratio or occupational status. Participants did significantly differ on years of education, premorbid adjustment in childhood, early and late adolescence and medication status. Non-psychiatric controls had a higher mean of years of education and lower scores on the premorbid adjustment scale (higher scores reflect poorer premorbid adjustment).

The clinical high-risk group demonstrated significantly poorer social ($p < 0.001$, Cohen's d =1.58) and role functioning ($p < 0.001$, Cohen's d =1.16) as well as lower GAF scores ($p < 0.001$, Cohen's d =2.6). Social functioning for the CHR group ranged from (5 - Serious impairment in social/interpersonal functioning to 10- Superior social/interpersonal functioning), role functioning ranged from (4 - Major impairment in role functioning to 9 - Above average role functioning) and GAF ranged from (38 - Some serious symptoms or impairment in functioning to 95- No symptoms).

At the time of consent the 46% of CHR-participants were not taking any medication, 21% were taking anti-depressants, 14% were taking other types of medication than mentioned in table 2, 17% were taking multiple types of medication, 1% were taking anti-psychotics and 1% were taking mood stabilisers. At time of testing 83% of CHR-participants were students, 7% were unemployed, 6% were in full time work, 4% in part time work and 1% in voluntary work.

ANOVAs were performed to assess differences between CHR-participants meeting differing CHR-categories (SPI-A, CAARMS, and SPI-A+CAARMS) and to assess differences between CHR-participants who were recruited through clinical services and those who were not.

Table 5: Mean scores for BACS total, GAF, social and role functioning for CHR-individuals meeting differing CHR-criteria and recruitment paths.

	CAARMS	**SPI-A**	**CAARMS + SPI-A**	***F***	**df**	***P***
N (%)	32 (31%)	24 (22%)	42 (42%)			
BACS	-0.96	-0.41	-0.55	0.9	2,94	0.41
GAF	61.72	68.38	56.21	7.98	2,95	0.001***
Social Functioning	7.53	7.82	7.64	0.51	2,93	0.61
Role Functioning	7.53	7.82	7.23	2.06	2,94	0.13
	CHR CS	**CHR Other**		***F***	**df**	***P***
N (%)	13 (12%)	97 (88%)				
BACS	-1.77	-0.55		6.5	1,92	0.012*
GAF	56.38	61.59		1.96	1,101	0.17
Social Functioning	7.17	7.72		3.2	1,98	0.077
Role Functioning	6.83	7.55		4.42	1,99	0.038*

CHR CS (CHR-participants recruited through clinical services), CHR Other (CHR-participants not recruited through clinical services). * $p < 0.05$, *** $p < 0.001$.

Table 5 shows clinical characteristics between the CHR-subgroups and referrals vs non-referrals. In the clinical high-risk group 42% met criteria for CAARMS and SPI-A items, 31% for CAARMS only and 22% for SPI-A only. Differences in BACS global score, GAF, social and role functioning between CHR-subgroups were assessed using ANOVA. CHR-subgroups were found not to have a significant effect of BACS global score (F (2,94) = 0.9, p = 0.41). No differences were found for social (F (2,93) = 0.51, p = 0.61) or role (F (2,94) = 2.06, p = 0.13) functioning. There was a significant difference between CHR-subgroups for GAF (F (2,95) = 7.98, p = 0.001). Using Hochberg's GT2 test, post hoc analysis was conducted to assess the effect of CHR-subgroup on GAF scores. The SPI-A subgroup (mean GAF: 68.38) were significantly different to SPI-A+CAARMS subgroup (mean GAF: 56.21), $p < 0.001$.

Differences between CHR-participants recruited through clinical services and CHR-participants who were not recruited through clinical services were assessed using ANOVA (see Table 5). Those who were recruited though clinical services performed more poorly on BACS total score (F (1,92) = 6.5, p = 0.012), role functioning (F (1,99) = 4.42, p = 0.038) with a statistical trend observed for social functioning (F (1,98) = 3.2, p = 0.077) compared to those who did not. No significant differences were observed for GAF.

3.2 Neuro-Cognition

Individual ANOVAs were performed on individual neurocognitive domains to assess for differences between CHR participants and controls.

Table 6: Neurocognitive performance of Clinical High-risk participants.

Domain	UHR Mean	N (CHR/ Control)	SD	Df	*F*	*P*	Cohens *d*
BACS							
Verbal Memory	0.009	97 / 41	1.29	1,136	0.002	0.97	
Motor Speed	-0.96	97 / 41	1.14	1,136	21.72	<0.001***	0.89
Processing Speed	-0.51	97 / 41	1.17	1,136	5.81	0.017*	0.46
Verbal Fluency	-0.07	97 / 40	0.98	1,135	0.15	0.7	
Executive Function	-0.21	95 / 41	1.24	1,134	0.91	0.34	
Working Memory	-0.05	97 / 41	1.26	1,136	0.05	0.82	
BACS Global	-0.69	94 / 40	1.54	1,132	6.74	0.011*	0.53
Penn CNB							
Emotion Recognition	-0.13	87 / 26	0.96	1,111	0.35	0.56	
Emotion Recognition RT	0.71	87 / 26	1.73	1,111	3.93	0.05*	-0.96
Attention	-0.79	87 / 26	2.79	1,111	2.65	0.11	
Attention RT	-0.25	87 / 26	1.1	1,111	0.1	0.3	
Working Memory RT	-0.02	86 / 26	0.88	1,110	0.009	0.93	
	Mean Rank	**N (CHR/ Control)**	**Mean Rank**	**Df**	***U***	***P***	
Working Memory (LNB task)	53.53	86 / 26	68.6	113	829.5	0.031*	

Mean standardised scores of UHR-participants across domains of neuro-cognitive functioning including statistical *p* values, Cohen's *d* and effect sizes. RT (response times). *$p < 0.05$, ** $p < 0.01$ ***$p < 0.001$. Effect sizes are classified as small (d = 0.2), medium (d = 0.5), and large (d ≥ 0.8).

Table 6 summarises the individual univariate ANOVAs carried out for each cognitive domain. Individual ANOVAs revealed that CHR-participants (n = 94; control n = 41) were significantly impaired in the domains of motor speed (F (1,136) = 21.72, p <0.001), processing speed (F (1,136) = 5.81, p = 0.017), and BACS global score (F (1,132) = 6.74, p

= 0011). From the PennCNB tasks, CHR-participants (n = 86; control n = 26) were impaired in emotion recognition response times (F (1,111) = 3.93, p = 0.05). A non-parametric test was used for the PennCNB test of working memory (LNB task) as these data were negatively skewed. This suggests a possible ceiling effect. A Mann-Whitney U test found that working memory was significantly impaired in the CHR-group relative to controls (U (113) = 829.5, p = 0.031). Large effect sizes were found for motor speed (d = 0.89), BACS global (d = 0.53) and emotion recognition RT (d = -0.96) and a medium effect size was shown for processing speed (d = 0.46).

Between group differences were assessed for emotion specific recognition with individual ANOVAS.

Table 7: Emotion specific recognition of Ultra High-risk participants

Emotion	**UHR Mean**	**N (CHR/ Control)**	**SD**	**Df**	***F***	***P***	**Cohens *d***
Anger	-0.27	87 / 26	1.28	1,111	9.31	0.32	
Fear	-0.22	87 / 26	0.88	1,111	0.01	0.92	
No Emotion	-0.24	87 / 26	1.19	1,111	0.89	0.35	
Happy	-0.27	87 / 26	1.24	1,111	1.01	0.32	
Sad	0.17	87 / 26	0.91	1,111	0.62	0.42	
Emotion RT	**UHR Mean**		**SD**	**Df**	***F***	***P***	**Cohens *d***
Anger	0.16	87 / 26	1.32	1,124	0.30	0.59	
Fear	0.65	87 / 26	2.06	1,124	2.43	0.12	
No Emotion	0.68	87 / 26	2.54	1,124	1.78	0.19	
Happy	1.16	87 / 26	1.72	1,124	10.35	0.02*	-0.81
Sad	0.76	87 / 26	2.92	1,124	1.68	0.21	

Mean of standardised scores of the UHR-participants for emotion specific recognition including statistical p values, Cohen's d and effect sizes. RT (response times). *$p < 0.05$. Effect sizes are classified as small (d = 0.2), medium (d = 0.5), and large (d ≥ 0.8).

Table 7 summarises the individual univariate ANOVAs carried out for emotion specific recognition. CHR-individuals did not differ significantly in the recognition of specific emotions relative to controls. CHR-participants (n = 87; control n = 26) were significantly slower in their response times for in recognising happy faces (F (1,124) = 10.35, p = 0.02) which showed a large effect size (d = -0.81).

3.3 Cognition and Functioning

Stepwise multiple linear regressions were performed to assess the relationship between neurocognitive domains and functional outcomes. Predictor variables included were the domains of neurocognition which were found to be significantly impaired. These were motor function, processing speed, BACS composite and emotion recognition response times.

Table 8: Linear regression results for the effects of neurocognitive performance on GAF, social and role functioning at baseline in CHR-participants

			GAF		
Variable	B	SE	B	*P*	ΔR^2
Emotion Recognition RT	-2.3	0.88	-.28	0.01*	0.07
			Social Functioning		
Emotion Recognition RT	-0.2	0.06	-.32	0.003**	0.09
			Role functioning		
BACS Global	0.22	0.08	.31	0.004**	0.09

RT (response times). *$p < 0.05$, **$p < 0.01$.

Table 8 shows that emotion recognition response times was a significant predictor of GAF and social functioning at baseline. BACS global score was a significant predictor of role functioning. Emotion recognition RT accounts for 7% and 9% of the variance for GAF and social functioning respectively. BACS global score accounts for 9% of the variance for role functioning.

Additional exploratory analyses were carried out for the effect of emotion specific response times on functional outcomes in the CHR-group. Response times for each emotion were entered into a stepwise linear regression model.

Table 9: Linear regression results for the effects of emotion specific response times on GAF, social and role functioning at baseline in CHR-participants

			GAF		
Variable	B	SE	B	*p*	ΔR^2
Sad RT	-1.3	0.6	-0.4	0.04*	0.1
			Social Functioning		
Fear RT	-0.2	0.05	-0.3	0.002**	0.1
			Role Functioning		
Fear RT	-0.2	0.06	-.34	0.001**	0.1

RT (response times). *$p < 0.05$, **$p < 0.01$.

Table 9 shows response time for sad faces was found to be a significant predictor of GAF scores at baseline. Response time for fearful faces was found to be a significant predictor for both social and role functioning. Sad RT accounted for 10% of variance for GAF. Fear RT accounted for 10% of variance for both social and role functioning.

4. DISCUSSION

Neurocognitive deficits are a hallmark of schizophrenia (Keefe & Harvey, 2012) and evidence shows that such deficits are found in the prodromal phase of the disorder (Fusar-Poli et al, 2013; Bora & Murray, 2014). Specifically, deficits in the areas of working memory, attention, speed of processing, verbal memory, executive functions and emotion recognitions have been reported in CHR-populations (Seidman, Giuliano, Smith, Stone, Glatt, Meyer, et al., 2010; Bora et al, 2014; Kelleher, Clarke, Rawdon, Murphy & Cannon, 2013).

This thesis aimed to extend these findings by exploring neurocognitive and social cognitive variables in relationship to subthreshold psychotic symptoms as well as current psychosocial functioning.

The main questions in this thesis were:

1) What are the differences in cognitive, social cognitive and psychosocial functioning in those who are at-risk of psychosis relative to controls?
2) To what extent does neuro- and social cognition explain poor functioning in the CHR population?

4.1 Cognition

4.1.1 Neurocognition

There is a robust body of evidence for impairments in neurocognitive functioning in CHR-populations (Fusar-Poli et al., 2012; Bora & Murray, 2014). Data from phase 2 of the largest CHR-study to date, the North American Prodrome Longitudinal Study (NAPLS-2), has shown CHR individuals to be impaired in all areas of neurocognition relative to controls (Seidman, Shapiro, Stone, Woodberry, Ronzio, Cornblatt, et al., 2016) with small to medium effect sizes. However, CHR studies have reported conflicting findings regarding the profile of cognitive impairment in CHR with some reporting impairments in only some domains (Niendam, Bearden, Johnson, McKinley, Loewy, O'Brien et al., 2006; Kelleher, Murtagh, Clarke, Murphy, Rawdon & Cannon, 2013).

In the current study, we found CHR-individuals to be significantly impaired in the domains of emotion recognition response times (RT), motor speed, processing speed and working memory with medium to large effect sizes. BACS global score was also impaired. Emotion recognition RT was the most prominent of these followed by motor speed and finally processing speed. In contrast, CHR-participants were found to be intact on the digit sequencing task, verbal fluency, verbal memory, executive function, and Penn CNB measures of attention, attention response times, working memory response times and emotion recognition.

These findings are partially in line with existing literature. A number of studies have reported processing speed to be the most prominent impairment (Carrión, Goldberg, McLaughlin, Auther, Correll & Cornblatt, 2011; Kelleher, Murtagh, Clarke, Murphy, Rawdon & Cannon, 2013). Kelleher et al. (2013) found processing speed and non-verbal working memory to be the only domains impaired in those who met UHR criteria with processing speed being the most prominent of these. However, they did not report effect sizes and their sample of individuals meeting UHR criteria was small (n=19). Carrión et al. (2011), in a sample of 127 treatment seeking CHR-individuals found impairments across all domains of neurocognition with the most prominent deficit being processing speed. The authors of these papers argue that these findings show support for processing speed as being central to neurocognitive dysfunction in CHR-participants. Our findings offer some support for this hypothesis as impairments in processing speed were observed in our CHR-group with a medium effect size.

Schizophrenia literature emphasise the importance of attention (Cornblatt & Keilp, 1994) and working memory (Park & Gooding, 2014). Evidence is emerging of deficits in declarative memory in first episode psychosis (Saykin, Shtasel, Gur, Kester, Mozley, Stafiniak, et al., 1994) and in CHR populations (Seidman, Shapiro, Stone, Woodberry, Ronzio, Cornblatt, et al., 2016). The domain of attention has been argued to represent a stable vulnerability marker in CHR-populations (Francey, Jackson, Phillips, Wood, Yung & McGorry, 2005; Lencz, Smith, McLaughlin, Auther, Nakayama, Hovey & Cornblatt, 2006). More recent data from the NAPLS-2 cohort have demonstrated impairments in working memory and attention in CHR-participants who later transitioned to psychosis relative to CHR-participants who did not transition (Seidman, Shapiro, Stone, Woodberry, Ronzio, Cornblatt, et al., 2016). Given the conflicting findings between our working memory tasks and the lack of significance for attention, our findings have not supported the hypothesis of the centrality of attention and working memory in CHR populations (Seidman, Shapiro, Stone, Woodberry, Ronzio, Cornblatt, et al., 2016).

We found that the CHR and control groups differed significantly only in one of the working memory tasks in the current study which may be due to a difference in task demands. The BACS digit sequencing task requires participants to manipulate the order of numbers. The Penn CNB Letter-N-Back task involves the participant indicating when the currently presented stimuli match stimuli presented n (0, 1 or 2) steps earlier. CHR-individuals showed deficits in the latter of these two tasks. Our findings suggest that our CHR-participants may display a deficit which is task specific. Similar findings have been reported in other domains. In a meta-analysis Fusar-Poli et al. (2012) did not find UHR-participants to be impaired in processing speed, however, there was a significant difference between UHR-participants and controls specifically for the Digit Symbol Substitution Test (symbol-coding task).

Additionally, impairments in verbal fluency and memory have been reported as important factors in CHR-groups (Fusar-Poli, Deste, Smieskova, Barlati, Yung & Howes, et al., 2012). In a meta-analysis, Fusar-Poli et al. (2012) found verbal fluency and memory to be associated with subsequent transition to psychosis. Neuropsychological findings from phase 1 of the NAPLS project (NAPLS-1) reported that general neuropsychological functioning did not contribute uniquely to the prediction of transition to psychosis beyond clinical symptoms, however, poorer verbal memory was found to predict more rapid transition (Seidman, Giuliano, Meyer, Addington, Cadenhead, Cannon & Woods, 2010). In our sample, we did not find verbal fluency or verbal memory to be significantly different between groups.

BACS global cognition did not differ significantly between differing CHR-criteria (SPI-A, CAARMS, and SPI-A+CAARMS). However, a significant difference was observed for BACS global cognition between CHR-participants who were recruited through clinical services vs CHR-participants who were not. This fits with existing literature which shows that more severe neurocognitive impairments are associated with poorer outcomes for CHR-individuals (Seidman, Shapiro, Stone, Woodberry, Ronzio, Cornblatt, et al., 2016). Together, these findings highlight neurocognitive impairments as a putative treatment target for early intervention. However, sample sizes for these groups were small and statistical analysis may have been underpowered.

4.1.2 Social cognition

We expected to find that CHR-participants would be characterized by poorer emotion recognition relative to controls. This hypothesis was partially supported. In our sample, emotion recognition RT was found to be the most significantly impaired in CHR-participants when compared with controls. Emotion recognition is an important factor in CHR-populations as it has been argued that deficits in emotion recognition may be a trait marker for schizophrenia (Edwards, Jackson & Pattison, 2002) and is a predictor for transition to psychosis (Allott, Rice, Bartholomeusz, Klier, Schlögelhofer & Schäfer, et al., 2014). Specifically, Allott et al. (2014) found that lower accuracy of recognising neutral faces and higher accuracy for fearful faces are predictive of transition to psychosis within a 12-month period. Many studies have found a specific deficit in the identification of neutral emotion in CHR-populations (Addington, Penn, Woods, Addington, Perkins, 2008a; Eack, Mermon, Montrose, Miewald, Gur & Gur, et al., 2010; van Rijn, Aleman, de Sonneville, Sprong, Ziermans & Schothorst, et al., 2011) although this is not always the case. Pinkham et al. (2007) found that CHR-individuals did not differ from controls on emotion recognition tasks. Findings from non-clinical psychosis (NCP-brief psychotic like experiences which occur in 5-7% of the general population; van Os et al., 2009) have shown similar results. Pelletier et al. (2013) found a group of individuals who scored high for non-clinical psychosis to be significantly impaired in the recognition of fearful face relative to a group of individuals who scored low for non-clinical psychosis.

In the current study, accuracy of emotion recognition was intact while the speed with which emotions were processed was decreased. Overall, the CHR group were significantly slower than controls and this deficit was specifically driven by an impairment to respond to happy

faces. Although the majority of studies investigating emotion recognition in CHR-samples have found deficits (Addington, Penn, Woods, Addington, Perkins, 2008a; Eack, Mermon, Montrose, Miewald, Gur & Gur, et al., 2010; van Rijn, Aleman, de Sonneville, Sprong, Ziermans & Schothorst, et al., 2011; Allott, Rice, Bartholomeusz, Klier, Schlögelhofer & Schäfer, et al., 2014), some studies have also reported intact reactions to emotional stimuli (Gee, Karlsgodt, van Erp, Bearden, Lieberman & Belger, et al., 2012; Seiferth, Pauly, Habel, Kellermann, Shah & Ruhrmann, et al., 2008; Thompson, Papas, Bartholomeusz, Nelson, & Yung, 2013). The majority of studies do not report response times for emotion recognition stimuli. The reporting of reaction times can be a useful measure of processing speed (Salthouse, 1996). In a review paper, Salthouse (1996) proposes that a reduction in the speed in which many processing operations can be carried out then leads to impairments in cognitive tasks.

IQ and level of functioning have also been implicated as important factors in relation to emotion processing in CHR and schizophrenia literature. Findings from the NAPLS-2 cohort (n=675 CHRs) have reported deficits in general emotion recognition with a specific deficit for the recognition for sad faces with small effect sizes. These were no longer significant after controlling of age and IQ (Barbato, Liu, Cadenhead, Cannon, Cornblatt, McGlashan & Woods, 2015). The authors argue that based on their results, IQ appears to have an impact on facial emotion recognition, however, due to the limited number of studies assessing the relationship between IQ and emotion recognition, a clear hypothesis could not be given. To the best of our knowledge, there are only another 2 studies which have looked at the relationship between IQ and emotion recognition, both with differing results. Thompson et al (2012) found no differences between CHR individuals and controls whilst Amminger et al (2011) found CHR participants to be impaired in the recognition of fear and sadness. A similar relationship between IQ and emotion recognition has been found in schizophrenia literature. Pomarol-Clotet et al. (2010) did not find any group differences in emotion specific recognition in a group of individuals with established schizophrenia. However, the clinical group were significantly slower at responding than controls. Importantly, the participants were matched on IQ. The authors argue that when steps are taken to reduce the effects of general intellectual impairment, there is no deficits in emotion recognition in schizophrenia. Considering our high functioning sample, this may help to explain our lack of findings of emotion recognition deficits. However, this claim cannot be substantiated due to the lack of IQ measurement.

Similarly, in a sample of individuals with a diagnosis of schizophrenia emotion recognition was not impaired in a high functioning group whilst emotion recognition deficits were present in a low functioning group (Karpouzian, Alden, Reilly & Smith, 2016). The authors argue that these findings suggest that emotion recognition deficits may be an important component of poor functioning, rather than a trait marker for schizophrenia.

4.3 Cognition and Functioning

Impairments in social and role functioning are key features of schizophrenia (Couture et al., 2006; McGurk & Meltzer, 2000) and are related to the burden of psychotic disorders to patients, families, carers and the wider society (Jungbauer, Wittmund, Dietrich & Angermeyer, 2004; Knapp, Mangalore & Simon, 2004; Magaña, Ramírez García, Hernández & Cortez, 2007). There is now a robust body of evidence that these deficits are present in CHR-populations (Addington, Penn, Woods, Addington & Perkins, 2008b, Cornblatt, Auther, Niendam, Smith, Zinberg & Bearden et al, 2007; Velthorst, Nieman, Linszen, Becker, de Haan & Dingemans et al., 2010) and that neurocognitive functioning is related to functional deficits (Carrión, Goldberg, McLaughlin, Auther, Correll & Cornblatt, 2011) and baseline-deficits predict functioning at follow-up (Lin, Wood, Nelson, Brewer, Spiliotacopoulos & Bruxner, et al., 2011; Lin, Yung, Nelson, Brewer, Riley & Simmons, et al., 2013).

In the current study, we expected to find that the CHR-participants would display impaired global, social and role functioning at baseline. Moreover, based on previous findings (Carrión, Goldberg, McLaughlin, Auther, Correll & Cornblatt, 2011), we expected that processing speed is a predictor of poor functioning in CHR-participants. Our hypotheses were partially supported.

4.3.1 Functioning in CHR-Participants

The CHR and control groups did differ significantly on all three measures of functioning (GAF, GF Social and GF Role). The differences measured between groups on the three levels of premorbid adjustment (childhood, early and late adolescence) and the three measures of functioning all show large effect sizes. GAF measures current psychosocial

functioning along with symptom prevalence whilst GF social and GF Role measure functioning in each specific domain independent each other and of symptoms.

CHR-participants in the current study had a mean GAF score of 60.36 which is higher than what is typically observed in CHR-literature (Ruhrmann, Schultze-Lutter, Salokangas, Heinimaa, Linszen Dingemans & Morrison, 2010). Results from the prospective European prediction of psychosis study (Ruhrmann, Schultze-Lutter, Salokangas, Heinimaa, Linszen Dingemans & Morrison, 2010) covered clinical characteristics of CHR-populations reported the mean of 245 at-risk participants (UHR and COGDIS) to be 51.1. Moreover, reduced GAF-scores may also relate to transitioning to psychosis (Velthorst, Nieman, Becker, van de Fliert, Dingemans, Klaassen, et al., 2009). For those CHR-individuals who do not convert, there is evidence that functioning may improve over time (Addington, Cornblatt, Cadenhead, Cannon, McGlashan & Perkins, et al., 2011).

The CHR group in our sample demonstrated significant impairments in social and role functioning. Carrión et al. (2011) reported in a sample of clinically-referred CHR-participants lower group social (5.94) and role (5.46) functioning. However, it is important to note that their sample were also younger as age may be an important factor for functioning. Similar findings were also reported by, Karlsgodt, Niendam, Bearden & Cannon (2009). However, Pelletier et al. (2013) measured non-clinical psychosis (NCP) in a group of individuals and those where found to have high-NCP (those who scored highest in NCP) reported functioning scores which were higher than our CHR group; social (8) and role (7.9). Similar to our sample, the participants in the latter study were university students. Our sample was predominantly students (university and college) as well as recruited through clinical services.

Analysis of functioning between differing CHR-criteria revealed no significant differences for social and role functioning. Baseline GAF scores were significantly different between groups with the CAARMS+SPI-A group having poorer functioning relative to the CAARMS group and the SPI-A group. There were no significant differences between the CAARMS group and the SPI-A group. One explanation for the null findings for social and role functioning and the significant findings for GAF is that these are due to symptom severity rather than functional impairment. GAF measures a mixture of symptom severity, social and role functioning.

Basic symptoms reflect the early stages of the prodrome (Schultze-Lutter, Addington, Ruhrmann & Klosterkötter, 2007) whilst CAARMS captures experiences in the later stages (Yung et al, 2006). Thus, individuals meeting only basic symptom criteria will be less

symptomatic than individuals who meet CAARMS criteria. A combination of CAARMS and SPI-A has been found to be associated with poorer outcomes and are the most effective at predicting transition to psychosis (Ruhrmann, Schultze-Lutter, Salokangas, Heinimaa, Linszen & Dingemans, et al., 2010). This is reflected in our findings with the SPI-A subgroup having the highest GAF scores followed by the CAARMS subgroup and finally CAARMS+SPI-A. Moreover, findings from a recent meta-analysis found that lower baseline global functioning predicted later transition to psychosis (Fusar-Poli, Rocchetti, Sardella, Avila, Brandizzi & Caverzasi, et al., 2015). Taken together these findings suggest that functional impairments may be important treatment targets for early intervention.

Furthermore, CHR-individuals who were recruited from clinical services were more severely impaired in role functioning, and a statistical trend was observed for social functioning. GAF scores did not differ significantly between these groups. This suggests a potential difference between in CHR-individuals who are currently accessing clinical care. However, these results should be interpreted with caution. Individuals who were not recruited from clinical services may have had previous or current clinical care.

These findings are similar to Mills et al. (2017) who compared individuals who met UHR criteria from a community sample to UHR-individuals recruited from clinical services. The community UHR-participants had less severe positive and negative symptoms and less severe general psychopathology. They had higher levels of social and role functioning relative to the UHR-participants from clinical services but lower levels of social and role functioning relative to healthy controls (Mills, Fusar-Poli, Morgan, Azis & McGuire, 2017). The community UHR-participants were similar to UHR-participants from clinical services in age, ethnicity, gender, employment status, years of education, cannabis use and history of childhood trauma. The community UHR-participants were more likely to be first generation migrants.

Moreover, Mills et al. (2017) from a general population sample found that those who met UHR criteria were much more likely to have reported an unmet need for clinical care when compared to those who did not. Approximately half of the community UHR-participants had sought help for psychological or emotional problem in the 12-months prior to assessment. The authors argue that this highlights a substantial number of individuals in the general population who meet UHR criteria but are not being seen by clinical services. However, it is important to be aware that UHR-individuals who were not referred through clinical services were not necessarily non-help seeking. Half of these individuals had already sought help, although, not always from specialised services.

4.3.2 Neurocognition as predictors of functioning

Literature on the association of neurocognition and functioning in CHR-populations is sparse. Carrión et al. (2011) found that processing speed predicted both social and role functioning at baseline. Global neurocognitive performance was also found to predict both social and role functioning. Niendam et al. (2006) found levels of social functioning to be predicted by measures of verbal learning and memory as well as negative symptoms. Our results support the findings of Carrión et al. (2011) in relation to global neurocognitive performance being predictive of role functioning at baseline. However, our results do not support the findings that processing speed is an important factor for both social and role functioning in CHR as well as the relationship between social functioning and verbal learning.

However, our findings do partially support data from the NAPLS-2 cohort. They found composite neurocognition was associated with both social and role functioning at baseline. Composite neurocognition at baseline was associated with role functioning, but not social functioning, at 12-month follow up (Meyer, Carrión, Cornblatt, Addington, Cadenhead & Cannon, et al., 2014).

Our regression analysis found emotion recognition RT to be a significant predictor of GAF scores and social functioning at baseline. In addition, the BACS global score was a significant predictor of role functioning. However, these predictors explained only 7%, 9% and 9% of the data respectively. These findings support existing evidence that functional impairments and their relationship to neurocognition exist before the onset of psychosis and are not outcomes of chronic illness (Carrión, Goldberg, McLaughlin, Auther, Correll & Cornblatt, 2011; Niendam, Bearden, Johnson, McKinley, Loewy, & O'Brien et al., 2006). Functional impairment is also an important factor for CHR-groups regardless of transition to psychosis (Ruhrmann, Schultze-Lutter, Salokangas, Heinimaa, Linszen & Dingemans, et al., 2010; Addington, Cornblatt, Cadenhead, Cannon, McGlashan & Perkins, et al., 2011). Our findings extend this to highlight that such functional impairments are evident in a high-functioning sample of CHR-participants.

The variance in the data for our regression models are low. This is similar to other studies investigating neurocognitive predictors of functioning. Carrión et al. (2011) found that processing speed predicted both social and role functioning at baseline explaining 10% of variance for social functioning and 7% of variance for role functioning. Global neurocognitive performance was also found to predict both social and role functioning

explaining 8% and 5% of variance in the data respectively. The most likely explanation for this is that there are additional factors which could help explain poorer functioning in CHR samples, such as stigma and lack of social support. Negative symptoms have also been found to be an important factor in functional outcomes in CHR-participants (Niendam, Bearden, Johnson, McKinley, Loewy, & O'Brien et al., 2006) and in schizophrenia (Rabinowitz, Levine, Garibaldi, Bugarski-Kirola, Berardo & Kapur, 2012). Meyer et al. (2014) found negative symptoms to account for most of the variance in their data followed by composite neurocognition. Moreover, negative symptoms were the strongest predictors of social and role functioning at baseline and 12-month follow up with small to medium effects. This was followed by composite neurocognition which had small independent effects. Negative symptoms were also found to mediate the relationship between neurocognition and social and role functioning (Meyer, Carrión, Cornblatt, Addington, Cadenhead & Cannon, et al., 2014).

4.3.2 Social Cognition as predictors of functioning

In an exploratory analysis, we investigated the relationship between emotion specific recognition and functional parameters. We included only RTs to specific emotional categories as predictors in the analyses. To the best of our knowledge, this is the first study to investigate emotion specific recognition and functional outcomes in a CHR-population. We found RTs to sad faces to be a significant predictor of GAF as well as RTs to fearful stimuli being a significant predictor of both social functioning and role functioning. These predictors explained 10% of the variance for each parameter of functioning.

Pelletier et al. (2013) investigated emotion specific recognition in relation to social and role functioning in a group of students with non-clinical psychosis. They found associations between recognition of fear and social functioning in those who scored highest for NCP. Moreover, both social and role functioning were associated with general emotion recognition. These findings, together with the findings of the current study, suggest that emotion recognition may play a role in social and role functioning more specifically that fear plays a role in predicting social and role functioning. These findings are preliminary and existing literature is limited, therefore further research is needed to assess the relationship between specific emotion recognition categories and functional parameters.

4.4 General

It is important to note the difference in our sample in relation to existing literature. The majority of at-risk studies recruit participants who are help seeking and are already within clinical services (Fusar-Poli, Carpenter, Woods & McGlashan, 2014) as well as often including a 30% drop in functioning (Yung, Phillips, Yuen & McGorry, 2004). These criteria were not inclusion criteria for this study and, as a result, the current sample in generally higher functioning than previous CHR-cohorts which can potentially account for some differences in the findings reported.

Consistent with the current findings, previous CHR-studies have reported deficits in only some domains of neurocognition (Wood, Pantelis, Proffitt, Phillips, Stuart & Buchanan, et al., 2003; Kelleher, Murtagh, Clarke, Murphy, Rawdon & Cannon, 2013). However, these studies typically have small sample sizes with the possibility of being statistically underpowered which leads an increased the possibility of Type II errors. Studies involving large sample sizes have more consistently found deficits in all areas of neurocognition (Carrión, Goldberg, McLaughlin, Auther, Correll & Cornblatt, 2011; Seidman, Shapiro, Stone, Woodberry, Ronzio, Cornblatt, et al., 2016) as have meta-analyses (Bora & Murray, 2014; Fusar Poli et al., 2012). Although, this is not the case for emotion recognition where conflicting findings have been reported even in large scale studies (Barbato, Liu, Cadenhead, Cannon, Cornblatt, McGlashan & Woods, 2015). Our lack of findings in some neurocognitive domains may be partly due to a statistical power issue, particularly for the Penn CNB tasks which had a small control group (n = 26).

Multiple comparisons were performed when assessing between group differences in neurocognitive and social-cognitive domains which may have led to inflated error rates and the probability of making at least one Type I error. Conservative post hoc tests, such as Bonferroni, would lead to a lack in statistical power and a high probability of a Type II error. More liberal post hoc tests typically become unreliable when sample sizes are different. Given the sample size and differences in group sizes, post hoc tests were not performed. Thus, the reported differences between groups in neuro- and social cognitive factors should be interpreted with caution.

These findings are the first to show neuro- and social cognitive and functional impairments in a predominantly high functioning group of CHR-individuals. A relationship between neurocognition, emotion recognition RTs and functional parameters was observed. These findings highlight possible treatment targets for CHR-individuals. This is important as CHR

status has been associated with significant distress, symptomology and functional impairment (Fusar-Poli, Carpenter, Woods & McGlashan, 2014).

We investigated clinical characteristics between CHR-participants meeting differing CHR-criteria as well as differences between those recruited via clinical services and those who were not. Investigation of individuals meeting differing CHR-criteria is important because these represent different stages of CHR progression and are associated with different outcomes and transition rates (Ruhrmann, Schultze-Lutter, Salokangas, Heinimaa, Linszen & Dingemans, et al., 2010). The CHR group which is the most predictive of transition to psychosis is a combination of basic symptoms plus CHR status (Fusar-Poli et al., 2013). This gives insight as to what may be the most meaningful treatment targets for early intervention. We found the CAARMS+SPI-A group to have significantly poorer global functioning relative to the other CHR-criteria suggesting this as a putative treatment target.

Investigation into CHR-participants who are not necessarily recruited through clinical services is important because this can also help to identify important treatment targets for early intervention. Our findings suggest both social and role functioning along with cognitive deficits as possible treatment targets for early intervention.

Follow up analysis will offer insights into transition rates for this sample of CHR-participants.

4.6 Conclusions

This thesis has highlighted that neuro- cognitive and social cognitive deficits are present in a high functioning sample of individuals who are CHR for psychosis. Global functioning is poorer in those who meet combined basic symptom and CHR criteria. Role functioning, global cognition and to a lesser extent social functioning are poorer in individuals recruited through clinical services. These highlight putative treatment targets for early intervention.

Emotion recognition RTs are associated with GAF and social functioning whilst global cognition is associated with role functioning. More specifically, RTs for sad faces are associated with GAF whilst RTs for fearful faces are associated with social and role functioning. However, these factors only explain a small amount of variance in the data. Future research should focus on emotion specific recognition include other factors, such as negative symptoms, to improve predictive models and highlight further treatment targets.

Appendices removed due to copyright reasons: pages 66-76.

Appendix 1 GAF

Appendix 2 GF: Social

Appendix 3 GF: Role

6. REFERENCES

Aas, I.H.M. (2010) Global Assessment of Functioning (GAF): properties and frontier of current knowledge. *Annals of General Psychiatry.* **9,** 20.

Addington, J., Cornblatt, B. A., Cadenhead, K. S., Cannon, T. D., McGlashan, T. H., Perkins, D. O., ... & Heinssen, R. (2011). At clinical high risk for psychosis: outcome for nonconverters. *American Journal of Psychiatry*, **168** (8) 800-805.

Addington, J., Epstein, I., Liu, L., French, P., Boydell, K. M., & Zipursky, R. B. (2011). A randomized controlled trial of cognitive behavioral therapy for individuals at clinical high risk of psychosis. *Schizophrenia research*, **125** (1) 54-61.

Addington, J., Penn, D., Woods, S.W., Addington, D., Perkins, D.O., (2008a). Facial affect recognition in individuals at clinical high risk for psychosis. *The British Journal of Psychiatry.* **192** (1), 67–68.

Addington, J., Penn, D., Woods, S.W., Addington, D., Perkins, D.O., (2008b). Social functioning in individuals at clinical high risk for psychosis. *Schizophrenia Research.* **99**, 119-124.

Addington, J., Saeedi, H., & Addington, D. (2006). Facial affect recognition: a mediator between cognitive and social functioning in psychosis?. *Schizophrenia research*, **85** (1) 142-150.

Adolphs, R., & Tranel, D. (2004). Impaired judgments of sadness but not happiness following bilateral amygdala damage. *Journal of cognitive neuroscience*, **16** (3) 453-462.

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. R. (1995). Fear and the human amygdala. *Journal of Neuroscience*, **15** (9) 5879-5891.

Aleman, A., Hijman, R., de Haan, E. H., & Kahn, R. S. (1999). Memory impairment in schizophrenia: a meta-analysis. *American Journal of Psychiatry*, **156** (9) 1358-1366.

Aleman, A., Kahn, R.S. (2005). Strange feelings: do amygdala abnormalities dysregulate the emotional brain in schizophrenia? *Progress in Neurobiology.* **77**, 283–298.

Allott, K.A., Rice, S., Bartholomeusz, C.F., Klier, C., Schlögelhofer, M., Schäfer, M.R., Amminger, G.P. (2015). Emotion recognition in unaffected first-degree relatives of individuals with first-episode schizophrenia. *Schizophrenia Research.* **161,** 322-328.

Allott, K.A., Schäfer, M.A., Thompson, A., Nelson, B., Bendall, S., Bartholomeusz, K.F., Yuen, H.P., McGorry, P.D., Schlögelhofer, M., Bechdolf, A., Amminger, G.P. (2014) Emotion recognition as a predictor of transition to a psychotic disorder in ultra-high risk participants. *Schizophrenia Research.* **153**, 25-31.

Amminger, G.P., Schäfer, M.R., Klier, C.M., Schlögelhofer, M., Mossaheb, N., Thompson, A., Bechdolf, A., Allott, K., McGorry, P.D., Nelson, B. (2012). Facial and vocal affect perception in people at ultra-high risk of psychosis, first-episode schizophrenia and healthy controls. *Early Innervation in Psychiatry.* **6** (4), 450–454.

Amminger, G.P., Schafer, M.R., Papageorgiou, K., Klier, C.M., Schlogelhofer, M., Mossaheb, N., Werneck-Rohrer, S., Nelson, B., McGorry, P.D. (2011). Emotion recognition in individuals at clinical high-risk for schizophrenia. *Schizophrenia Bulletin*. **38** (5) 1030–1039.

Baddeley A (1992) Working memory. In Keefe, R. S., & Harvey, P. D. (2012). Cognitive impairment in schizophrenia. In *Novel antischizophrenia treatments* (pp. 11-37). Springer Berlin Heidelberg

Ballon., J.S., Kaur, T., Marks, I.I., Cadenhead, K.S. (2007). Social functioning in young people at risk for schizophrenia. *Psychiatry Research.* **151,** 29-35.

Barbato, M., Liu, L., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., McGlashan, T. H., ... & Woods, S. W. (2015). Theory of mind, emotion recognition and social perception in individuals at clinical high risk for psychosis: Findings from the NAPLS-2 cohort. *Schizophrenia Research: Cognition*, **2** (3) 133-139.

Barbee, J. G., Clark, P. D., Crapanzano, M. S., Heintz, G. C., & Kehoe, C. E. (1989). Alcohol and substance abuse among schizophrenic patients presenting to an emergency psychiatric service. *The Journal of nervous and mental disease*, **177** (7) 400-407.

Bebbington, P., Wilkins, S., Jones, P., Foerster, A., Murray, R., Toone, B., & Lewis, S. (1993). Life events and psychosis. Initial results from the Camberwell Collaborative Psychosis Study. *The British Journal of Psychiatry*, **162** (1) 72-79.

Beiser, M., Erickson, D., Fleming, J.A., Iacono, W.G. (1993). Establishing the onset of psychotic illness. *The American Journal of Psychiatry.* **150,** 1349-1354.

Bilder, R. M., Goldman, R. S., Robinson, D., Reiter, G., Bell, L., Bates, J. A., ... & Geisler, S. (2000). Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. *American Journal of Psychiatry*, **157** (4) 549-559.

Bleuler, E. (1911) *Dementia Praecox oder Gruppe der Schizophrenien*. Leipzig, Germany: Deuticke.

Bora, E., Lin, A., Wood, S.J., Yung, A.R., McGorry, P.D., Pantelis, C. (2014). Cognitive deficits in youth with familial and clinical high risk to psychosis: a systematic review and meta-analysis. Acta Psychiatrica Scandinavia. 130, 1-15.

Bourque, F., van der Ven, E., & Malla, A. (2011). A meta-analysis of the risk for psychotic disorders among first-and second-generation immigrants. *Psychological medicine*, **41** (05) 897-910.

Boyer, P., Phillips, J. L., Rousseau, F. L., & Ilivitsky, S. (2007). Hippocampal abnormalities and memory deficits: new evidence of a strong pathophysiological link in schizophrenia. *Brain research reviews*, **54** (1) 92-112.

Brekke, J. S., Long, J. D., Nesbitt, N., & Sobel, E. (1997). The impact of service characteristics on functional outcomes from community support programs for persons with schizophrenia: A growth curve analysis. *Journal of consulting and clinical psychology*, *65*(3), 464.

Bresnahan, M., Begg, M. D., Brown, A., Schaefer, C., Sohler, N., Insel, B., ... & Susser, E. (2007). Race and risk of schizophrenia in a US birth cohort: another example of health disparity?. *International journal of epidemiology*, **36** (4) 751-758.

Brewer, W.J., Wood, S.J., Phillips, L.J., Francey, S.M., Pantelis, C., Yung, A.R., Cornblatt. B., McGorry, P.D. (2006) Generalized and specific cognitive performance in clinical highrisk cohorts: a review highlighting potential vulnerability markers for psychosis. Schizophrenia Bulletin. **32** (3) 538-555.

Brewer, W. J., Francey, S. M., Wood, S. J., Jackson, H. J., Pantelis, C., Phillips, L. J., ... & McGorry, P. D. (2005). Memory impairments identified in people at ultra-high risk for psychosis who later develop first-episode psychosis. *American Journal of Psychiatry*, **162** (1) 71-78.

Brown, A. S., & Derkits, E. J. (2009). Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. *American Journal of Psychiatry*, **167** (3) 261-280.

Bruijnzeel, D., & Tandon, R. (2011). The concept of schizophrenia: From the 1850s to the DSM-5. *Psychiatric Annals*, **41** (5) 289-295.

Cannon, T. D., Cadenhead, K., Cornblatt, B., Woods, S. W., Addington, J., Walker, E., ... & Heinssen, R. (2008). Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Archives of general psychiatry*, **65** (1) 28-37.

Cannon, M., Jones, P. B., & Murray, R. M. (2002). Obstetric complications and schizophrenia: historical and meta-analytic review. *American Journal of Psychiatry*, **159** (7), 1080-1092.

Cantor-Graae, E., & Selten, J. P. (2005). Schizophrenia and migration: a meta-analysis and review. *American Journal of Psychiatry*, **162** (1) 12-24.

Callicott, J. H., Mattay, V. S., Bertolino, A., Finn, K., Coppola, R., Frank, J. A., ... & Weinberger, D. R. (1999). Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. *Cerebral cortex*, **9** (1) 20-26.

Carlsson, A. (1988). The current status of the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology.*

Cannon, T. D., Bearden, C. E., Hollister, J. M., Rosso, I. M., Sanchez, L. E., & Hadley, T. (2000). Childhood cognitive functioning in schizophrenia patients and their unaffected siblings: a prospective cohort study. *Schizophrenia Bulletin*, **26** (2) 379.

Cannon, T. D., Rosso, I. M., Hollister, J. M., Bearden, C. E., Sanchez, L. E., & Hadley, T. (2000). A prospective cohort study of genetic and perinatal influences in the etiology of schizophrenia. *Schizophrenia Bulletin*, **26** (2) 351-366.

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

Chang, W.C. (2011) Rational and the local development of early intervention in psychosis. *The Hong Kong Medical Diary*. **16** (5) 4-5.

Chapman, L. J., & Chapman, J. P. (1973). Disordered thought in schizophrenia. In Pomarol-Clotet, E., Hynes, F., Ashwin, C., Bullmore, E. T., McKenna, P. J., & Laws, K. R. (2010). Facial emotion processing in schizophrenia: a non-specific neuropsychological deficit?. *Psychological medicine*, **40** (6) 911-919.

Chen, W. J., & Faraone, S. V. (2000). Sustained attention deficits as markers of genetic susceptibility to schizophrenia. *American journal of medical genetics*. **97** (1) 52-57.

Couture, S.M., Penn, D.L., Roberts, D.L. (2006). The functional significance of social cognition in schizophrenia: a review. *Schizophrenia Bulletin*. **32** (2006) S44–S63.

Corcoran, R., Mercer, G., & Frith, C. D. (1995). Schizophrenia, symptomatology and social inference: investigating "theory of mind" in people with schizophrenia. *Schizophrenia research*, **17** (1) 5-13.

Cornblatt, B.A., Auther, A.N., Niendam, T., Smith, C.W., Zinberg, J., Bearden, C.E., Cannon, T.D. (2007). Preliminary findings for two new measures of social and role functioning in the prodromal phase of schizophrenia. *Schizophrenia Bulletin.* **33,** 688-702.

Cornblatt, B. A., & Keilp, J. G. (1994). Impaired attention, genetics, and the pathophysiology of schizophrenia. *Schizophrenia Bulletin*, **20** (1) 31-46.

Davidson, M., Reichenberg, A., Rabinowitz, J., Weiser, M., Kaplan, Z., Mordehai, M. (1999). Behavioural and intellectual markers for schizophrenia in apparently healthy male adolescents. *American Journal of Psychiatry.* **156,** 1328-1335.

Dickinson, D. (2008). Digit symbol coding and general cognitive ability in schizophrenia: worth another look?. *The British Journal of Psychiatry*, **193** (5) 354-356.

Dickson, H., Laurens, K. R., Cullen, A. E., & Hodgins, S. (2012). Meta-analyses of cognitive and motor function in youth aged 16 years and younger who subsequently develop schizophrenia. *Psychological medicine*, **42** (04), 743-755.

Dickinson, D., Ramsey, M. E., & Gold, J. M. (2007). Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Archives of general psychiatry*, **64** (5) 532-542.

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013

D'Souza, D. C., Abi-Saab, W. M., Madonick, S., Forselius-Bielen, K., Doersch, A., Braley, G., ... & Krystal, J. H. (2005). Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biological psychiatry*, **57** (6) 594-608.

Eack, S.M., Mermon, D.E., Montrose, D.M., Miewald, J., Gur, R.E., Gur, R.C., Sweeney, J.A., Keshavan, M.S. (2010). Social cognition deficits among individuals at familial high risk for schizophrenia. *Schizophrenia Bulletin*. Published online: 25 March 2010. doi:10.1093/schbul/sbp026.

Edwards, J., Jackson, H. J., & Pattison, P. E. (2002). Emotion recognition via facial expression and affective prosody in schizophrenia: a methodological review. *Clinical psychology review*, **22** (6) 789-832.

Erhart, S. M., Marder, S. R., & Carpenter, W. T. (2006). Treatment of schizophrenia negative symptoms: future prospects. *Schizophrenia Bulletin*, **32** (2) 234-237.

Evans, J. D., Heaton, R. K., Paulsen, J. S., Palmer, B. W., Patterson, T., & Jeste, D. V. (2003). The relationship of neuropsychological abilities to specific domains of functional capacity in older schizophrenia patients. *Biological psychiatry*, **53** (5) 422-430.

Ferdinand, R. F., Sondeijker, F., Van Der Ende, J., Selten, J. P., Huizink, A., & Verhulst, F. C. (2005). Cannabis use predicts future psychotic symptoms, and vice versa. *Addiction*, **100** (5) 612-618.

Fett, A.K., Viechtbauer, W., Dominguez, M.G., Penn, J.L., van Os, J., Krabbendam, L. (2011). The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis. *Neuroscience & Biobehavioral Reviews.* **35** (3) 573-588.

Fleischhaker, C., Schulz, E., Tepper, K., Martin, M., Hennighausen, K., & Remschmidt, H. (2005). Long-term course of adolescent schizophrenia. *Schizophrenia bulletin*, **31** (3) 769-780.

Fonnum, F. (1984). Glutamate: a neurotransmitter in mammalian brain. *Journal of neurochemistry*, **42** (1) 1-11.

Francey, S. M., Jackson, H. J., Phillips, L. J., Wood, S. J., Yung, A. R., & McGorry, P. D. (2005). Sustained attention in young people at high risk of psychosis does not predict transition to psychosis. *Schizophrenia research*, **79** (1) 127-136.

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

Fusar-Poli, P., Borgwardt, S., Crescini, A., Deste, G., Kempton, M. J., Lawrie, S., ... & Sacchetti, E. (2011). Neuroanatomy of vulnerability to psychosis: a voxel-based meta-analysis. *Neuroscience & Biobehavioral Reviews*, **35** (5) 1175-1185.

Fusar-Poli, P., Carpenter, W. T., Woods, S. W., & McGlashan, T. H. (2014). Attenuated psychosis syndrome: ready for DSM-5.1?. *Annual review of clinical psychology*, **10**, 155-192.

Fusar-Poli, P., Deste, G., Smieskova, R., Barlati, S., Yung, A.R., Howes, H., Stieglitz, R.D., Vita, A. (2012). Cognitive Functioning in Prodromal Psychosis. A meta-analysis. *Archives of General Psychiatry.* **69** (6) 562-571.

Fusar-Poli, P., Placentino, A., Carletti, F., Landi, P., Allen, P., Surguladze, S., ... & Perez, J. (2009). Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *Journal of psychiatry & neuroscience: JPN*, **34** (6) 418.

Fusar-Poli, P., Rocchetti, M., Sardella, A., Avila, A., Brandizzi, M., Caverzasi, E., ... & McGuire, P. (2015). Disorder, not just state of risk: meta-analysis of functioning and quality of life in people at high risk of psychosis. *The British Journal of Psychiatry*, **207** (3) 198-206.

Gaebel, W., & Wölwer, W. (1992). Facial expression and emotional face recognition in schizophrenia and depression. *European archives of psychiatry and clinical neuroscience*, **242** (1) 46-52.

Gee, D. G., Karlsgodt, K. H., van Erp, T. G., Bearden, C. E., Lieberman, M. D., Belger, A., ... & Woods, S. W. (2012). Altered age-related trajectories of amygdala-prefrontal circuitry in adolescents at clinical high risk for psychosis: a preliminary study. *Schizophrenia research*, **134** (1) 1-9.

Genetic, R. (2011). Evidence that familial liability for psychosis is expressed as differential sensitivity to cannabis: an analysis of patient-sibling and sibling-control pairs. *Archives of general psychiatry*, **68** (2) 138.

Giusti-Rodríguez, P., & Sullivan, P. F. (2013). The genomics of schizophrenia: update and implications. *The Journal of Clinical Investigation*, **123** (11) 4557–4563. http://doi.org/10.1172/JCI66031

Green, M. F. (1996). What are the functional consequences of neurocognitive deficits in schizophrenia? *The American journal of psychiatry*, **153** (3) 321.

Green, M.F., Bearden, C.E., Cannon, T.D., Fiske, A.P., Hellemann, G.S., Horan, W.P., Kee, K., Kern, R.S., Lee, J., Sergi, M.J., Subotnik, K.L., Sugar, C.A., Ventura, J., Yee, C.M., Nuechterlein, K.H. (2012). Social cognition in schizophrenia, part 1: performance across phase of illness. *Schizophrenia Bulletin*. **38** (4) 854–864.

Green, M. F., & Harvey, P. D. (2014). Cognition in schizophrenia: Past, present, and future. *Schizophrenia Research: Cognition*, **1** (1), e1-e9.

Green, M. F., Kern, R. S., Braff, D. L., & Mintz, J. (2000). Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the" right stuff"?.

Green, M. F., Nuechterlein, K. H., Gold, J. M., Barch, D. M., Cohen, J., Essock, S., ... & Keefe, R. S. (2004). Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICS conference to select cognitive domains and test criteria. *Biological psychiatry*, **56** (5) 301-307.

Gold, J. M. (2004). Cognitive deficits as treatment targets in schizophrenia. *Schizophrenia research*, **72** (1) 21-28.

Gold, J. M., Goldberg, R. W., McNary, S. W., Dixon, L. B., & Lehman, A. F. (2002). Cognitive correlates of job tenure among patients with severe mental illness. *American Journal of Psychiatry*, **159** (8) 1395-1402.

Goldberg, T. E., Ragland, J. D., Torrey, E. F., Gold, J. M., Bigelow, L. B., & Weinberger, D. R. (1990). Neuropsychological assessment of monozygotic twins discordant for schizophrenia. *Archives of General Psychiatry*, **47** (11) 1066-1072.

Goldman-Rakic, P. S. (1994). Working memory dysfunction in schizophrenia. *The Journal of neuropsychiatry and clinical neurosciences*.

Goldman-Rakic, P. S. (1987). Circuitry of the frontal association cortex and its relevance to dementia. *Archives of gerontology and geriatrics*, **6** (3) 299-309.

Gonzalez-Burgos, G., Hashimoto, T., & Lewis, D. A. (2010). Alterations of cortical GABA neurons and network oscillations in schizophrenia. *Current psychiatry reports*, **12** (4) 335-344.

Gottesman, I. I., & Shields, J. (1972). A polygenic theory of schizophrenia. *International Journal of Mental Health*, **1** (1-2) 107-115.

Grozeva, D., Kirov, G., Ivanov, D., Jones, I. R., Jones, L., Green, E. K., … Craddock, N. (2010). Rare Copy Number Variants: A Point of Rarity in Genetic Risk for Bipolar Disorder and Schizophrenia. *Archives of General Psychiatry*, **67** (4) 318–327. http://doi.org/10.1001/archgenpsychiatry.2010.25

Gur, R. E., March, M., Calkins, M. E., Weittenhiller, L., Wolf, D. H., Turetsky, B. I., & Gur, R. C. (2015). Negative symptoms in youths with psychosis spectrum features: complementary scales in relation to neurocognitive performance and function. *Schizophrenia research*, **166** (1) 322-327.

Gur, R. C., Sara, R., Hagendoorn, M., Marom, O., Hughett, P., Macy, L., ... & Gur, R. E. (2002). A method for obtaining 3-dimensional facial expressions and its standardization for use in neurocognitive studies. *Journal of neuroscience methods*. **115** (2) 137-143.

Häfner, H. (2014). The concept of schizophrenia: From unity to diversity. *Advances in Psychiatry*, *2014*.

Häfner, H., Maurer, K., Ruhrmann, S., Bechdolf, A., Klosterkötter, J., Wagner, M., ... & Wölwer, W. (2004). Early detection and secondary prevention of psychosis: facts and visions. *European archives of psychiatry and clinical neuroscience*. **254** (2) 117-128.

Hall, W., & Degenhardt, L. (2008). Cannabis use and the risk of developing a psychotic disorder. *World Psychiatry*, **7** (2) 68-71.

Hall, W., & Degenhardt, L. (2009). Adverse health effects of non-medical cannabis use. *The Lancet*, **374** (9698) 1383-1391.

Harrison, P. J. (2008). Neuropathology of schizophrenia. *Psychiatry*, **7** (10) 421-424.

Harrison, P. J., & Weinberger, D. R. (2005). Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Molecular psychiatry*, **10** (1) 40.

Harvey, P. D. (2013). Assessment of everyday functioning in schizophrenia: implications for treatments aimed at negative symptoms. *Schizophrenia research*, **150** (2) 353-355.

Harvey, P. D., & Keefe, R. S. (1997). Cognitive impairment in schizophrenia and implications of atypical neuroleptic treatment. *CNS spectrums*, **2** (8) 41-55.

Hawkins, K.A., Addington, J., Keefe, R.S., Christensen, B., Perkins, D.O., Zipurksy, R., Woods, S.W., Miller, T.J., Marquez, E., Breier, A., McGlashan, T.H. (2004). Neuropsychological status of subjects at high risk for a first episode of psychosis. *Schizophrenia. Research*. **67**, 115– 122.

Hawkins, K. A., Keefe, R. S., Christensen, B. K., Addington, J., Woods, S. W., Callahan, J., ... & McGlashan, T. H. (2008). Neuropsychological course in the prodrome and first episode of psychosis: findings from the PRIME North America Double Blind Treatment Study. *Schizophrenia research*, **105** (1) 1-9.

Heinrichs, R. W., & Zakzanis, K. K. (1998). Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology*, **12** (3) 426.

Hoenig, J. (1983). The concept of Schizophrenia. Kraepelin-Bleuler-Schneider. *The British Journal of Psychiatry*, **142** (6) 547-556.

Hoff, A. L., Harris, D., Faustman, W. O., Beal, M., DeVilliers, D., Mone, R. D., ... & Csernansky, J. G. (1996). A neuropsychological study of early onset schizophrenia. *Schizophrenia research*, **20** (1) 21-28.

Howes, O.D., Fusar-Poli, P., Bloomfield, M., Selvaraj, S., McGuire, P (2012) From prodrome to chronic schizophrenia: the neurobiology underlying psychotic symptoms and cognitive impairments. *Current Pharmaceutical Design.* **18,** 459-465.

Hooker, C., Park, S. (2002). Emotion processing and its relationship to social functioning in schizophrenia patients. *Psychiatry Research*. **112**, 41–50.

Horan, W. P., Subotnik, K. L., Snyder, K. S., & Nuechterlein, K. H. (2006). Do recent-onset schizophrenia patients experience a "social network crisis"?. *Psychiatry: Interpersonal and Biological Processes*, **69** (2) 115-129.

Hou, C, Xiang, Y., Wang, Z., Everall, I., Tang, Y., Yang, C., Xu, M., Correll, C.U., Jia, F. (2016). Cognitive functioning in individuals at ultra-high risk for psychosis, first degree relatives of patients with psychosis and patients with first-episode schizophrenia. *Schizophrenia Research*. http://dx.doi.org/10.1016/j.schres.2016.04.034

Huber, G. (1955). The pneumoencephalogram at the onset of schizophrenic disease. In *MRI in Psychiatry* (pp. 87-116). Springer Berlin Heidelberg.

Huber G (1961) Clinical and neuroradiological research on chronic schizophrenics. In *MRI in Psychiatry* (pp. 87-116). Springer Berlin Heidelberg.

Huber G, Gross G. (1989) The concept of basic symptoms in schizophrenic and schizoaffective psychoses. In: Schultze-Lutter, F., Addington, J., Ruhrmann, S., Klosterko¨tter, J. (2007) Schizophrenia Proneness Instrument, Adult Version (SPI-A). Rome, Italy: *Giovanni Fiorito Editore*.

Hutchinson, G., Bhugra, D., Mallett, R., Burnett, R., Corridan, B., & Leff, J. (1999). Fertility and marital rates in first-onset schizophrenia. *Social psychiatry and psychiatric epidemiology*, **34** (12) 617-621.

Ikebuchi, E. (2007). Social skills and social and nonsocial cognitive functioning in schizophrenia. *Journal of Mental Health.* **16**, 581–594.

Insel, T. R. (2010). Rethinking schizophrenia. *Nature*, **468** (7321) 187-193.

Ising, H. K., Veling, W., Loewy, R. L., Rietveld, M. W., Rietdijk, J., Dragt, S., ... & van der Gaag, M. (2012). The validity of the 16-item version of the Prodromal Questionnaire (PQ-16) to screen for ultra high risk of developing psychosis in the general help-seeking population. *Schizophrenia bulletin*. **38** (6) 1288-1296.

Jahshan, C., Heaton, R. K., Golshan, S., & Cadenhead, K. S. (2010). Course of neurocognitive deficits in the prodrome and first episode of schizophrenia. *Neuropsychology*, **24** (1) 109.

Jarskog, L. F., Gilmore, J. H., Glantz, L. A., Gable, K. L., German, T. T., Tong, R. I., & Lieberman, J. A. (2007). Caspase-3 activation in rat frontal cortex following treatment with typical and atypical antipsychotics. *Neuropsychopharmacology*, **32** (1) 95-102.

Javitt, D. C., & Zukin, S. R. (1991). Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry*, **148** (10) 1301-1308.

Johnstone, E. C., Ebmeier, K. P., Miller, P., Owens, D. G., & Lawrie, S. M. (2005). Predicting schizophrenia: findings from the Edinburgh high-risk study. *The British Journal of Psychiatry*, **186** (1), 18-25.

Johnstone, E., Frith, C. D., Crow, T. J., Husband, J., & Kreel, L. (1976). Cerebral ventricular size and cognitive impairment in chronic schizophrenia. *The Lancet*, **308** (7992) 924-926.

Jungbauer, J., Wittmund, B., Dietrich, S., & Angermeyer, M. C. (2004). The disregarded caregivers: subjective burden in spouses of schizophrenia patients. *Schizophrenia bulletin*, **30** (3) 665-675.

Karayiorgou, M., Simon, T. J., & Gogos, J. A. (2010). 2q11. 2 microdeletions: linking DNA structural variation to brain dysfunction and schizophrenia. *Nature reviews. Neuroscience*, **11** (6) 402.

Karlsgodt, K. H., Niendam, T. A., Bearden, C. E., & Cannon, T. D. (2009). White matter integrity and prediction of social and role functioning in subjects at ultra-high risk for psychosis. *Biological psychiatry*, **66** (6) 562-569.

Karpouzian, T. M., Alden, E. C., Reilly, J. L., & Smith, M. J. (2016). High functioning individuals with schizophrenia have preserved social perception but not mentalizing abilities. *Schizophrenia research*, **171** (1) 137-139.

Katschnig, H. (1990). Vulnerability models for schizophrenia: discussion. In Insel, T. R. (2010). Rethinking schizophrenia. *Nature*, **468** (7321) 187-193.

Keefe, R. S. (1995). The contribution of neuropsychology to psychiatry. *American Journal of Psychiatry*, **152** (1) 6-15.

Keefe, R. S. (2000). Working memory dysfunction and its relevance to schizophrenia. *Cognition in schizophrenia*, 16-50.

Keefe, R. S., Bilder, R. M., Davis, S. M., Harvey, P. D., Palmer, B. W., Gold, J. M., ... & McEvoy, J. P. (2007). Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. *Archives of general psychiatry*, **64** (6) 633-647.

Keefe, R. S., Eesley, C. E., & Poe, M. P. (2005). Defining a cognitive function decrement in schizophrenia. *Biological psychiatry*, **57** (6) 688-691.

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

Keefe, R. S., & Harvey, P. D. (2012). Cognitive impairment in schizophrenia. In *Novel antischizophrenia treatments* (pp. 11-37). Springer Berlin Heidelberg.

Keefe, R. S., Fox, K. H., Harvey, P. D., Cucchiaro, J., Siu, C., & Loebel, A. (2011). Characteristics of the MATRICS Consensus Cognitive Battery in a 29-site antipsychotic schizophrenia clinical trial. *Schizophrenia research*, **125** (2) 161-168.

Keefe, R. S., Perkins, D. O., Gu, H., Zipursky, R. B., Christensen, B. K., & Lieberman, J. A. (2006). A longitudinal study of neurocognitive function in individuals at-risk for psychosis. *Schizophrenia research*, **88** (1) 26-35.

Kelleher, I., Devlin, N., Wigman, J. T., Kehoe, A., Murtagh, A., Fitzpatrick, C., & Cannon, M. (2014). Psychotic experiences in a mental health clinic sample: implications for suicidality, multimorbidity and functioning. *Psychological medicine*, **44** (08) 1615-1624.

Kelleher, I., Murtagh, A., Clarke, M. C., Murphy, J., Rawdon, C., & Cannon, M. (2013). Neurocognitive performance of a community-based sample of young people at putative ultra high risk for psychosis: support for the processing speed hypothesis. *Cognitive neuropsychiatry*, **18** (1-2) 9-25.

Kelleher, I., Clarke, M.C., Rawdon, C., Murphy, J., Cannon, M. (2013). Neurocognition in the extended psychosis phenotype: performance of a community sample of adolescents with psychotic symptoms on the MATRICS neurocognitive battery. *Schizophrenia Bulletin*. **39**, 1018-1026.

Kelly, B. D., O'Callaghan, E., Waddington, J. L., Feeney, L., Browne, S., Scully, P. J., ... & Kinsella, A. (2010). Schizophrenia and the city: A review of literature and prospective study of psychosis and urbanicity in Ireland. *Schizophrenia research*, **116** (1) 75-89.

Kim, H.S., Shin, N.Y., Jang, J.H., Kim, K.E., Shim, G., Park, H.Y., Hong, K.S., Kwon, J.S. (2011) Social cognition and neurocognition as predictors of conversion to psychosis in individuals at ultra-high risk. *Schizophrenia Research.* **130**, 170–175.

Knapp, M., Mangalore, R., Simon, J. (2004). The global costs of schizophrenia. *Schizophrenia Bulletin*. **30**, 279-293

Knowles, E. E., David, A. S., & Reichenberg, A. (2010). Processing speed deficits in schizophrenia: reexamining the evidence. *American Journal of Psychiatry*, **167** (7) 828-835.

KlosterKotter, J., Hellmich, M., Steinmeyer, E.M., Schultze-Lutter, F. (2001) Disgnosing schizophrenia in the initial prodromal phase. *Archives in General Psychiaty.* **58**, 158-164.

Kochunov, P., & Hong, L. E. (2014). Neurodevelopmental and neurodegenerative models of schizophrenia: white matter at the center stage. *Schizophrenia bulletin*, **40** (4), 721-728.

Kohler, C. G., Bilker, W., Hagendoorn, M., Gur, R. E., & Gur, R. C. (2000). Emotion recognition deficit in schizophrenia: association with symptomatology and cognition. *Biological psychiatry*, **48** (2) 127-136.

Kohler, C. G., Turner, T. H., Bilker, W. B., Brensinger, C. M., Siegel, S. J., Kanes, S. J., ... & Gur, R. C. (2003). Facial emotion recognition in schizophrenia: intensity effects and error pattern. *American Journal of Psychiatry*, **160** (10) 1768-1774.

Kohler, C. G., Walker, J. B., Martin, E. A., Healey, K. M., & Moberg, P. J. (2009). Facial emotion perception in schizophrenia: a meta-analytic review. *Schizophrenia bulletin*, **36** (5) 1009-1019.

Koutsouleris, N., Meisenzahl, E. M., Davatzikos, C., Bottlender, R., Frodl, T., Scheuerecker, J., ... & Möller, H. J. (2009). Use of neuroanatomical pattern classification to identify subjects in at-risk mental states of psychosis and predict disease transition. *Archives of general psychiatry*, **66** (7) 700-712.

Krabbendam, L., & Van Os, J. (2005). Schizophrenia and urbanicity: a major environmental influence—conditional on genetic risk. *Schizophrenia bulletin*, *31*(4), 795-799.

Kremen, W. S., Seidman, L. J., Faraone, S. V., Toomey, R., & Tsuang, M. T. (2000). The paradox of normal neuropsychological function in schizophrenia. *Journal of abnormal psychology*, **109** (4) 743.

Kurtz, M. M., Ragland, J. D., Bilker, W., Gur, R. C., & Gur, R. E. (2001). Comparison of the continuous performance test with and without working memory demands in healthy controls and patients with schizophrenia. *Schizophrenia research*. **48** (2) 307-316.

Lawrie, S. M., Olabi, B., Hall, J., & Mcintosh, A. M. (2011). Do we have any solid evidence of clinical utility about the pathophysiology of schizophrenia? *World Psychiatry*, **10** (1), 19-31.

Lencz, T., Smith, C. W., McLaughlin, D., Auther, A., Nakayama, E., Hovey, L., & Cornblatt, B. A. (2006). Generalized and specific neurocognitive deficits in prodromal schizophrenia. *Biological psychiatry*, **59** (9) 863-871.

Lieberman, J. A., Stroup, T. S., McEvoy, J. P., Swartz, M. S., Rosenheck, R. A., Perkins, D. O., ... & Severe, J. (2005). Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal of Medicine*, **353** (12) 1209-1223.

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

Lin, A., Yung, A. R., Nelson, B., Brewer, W. J., Riley, R., Simmons, M., ... & Wood, S. J. (2013). Neurocognitive predictors of transition to psychosis: medium-to long-term findings from a sample at ultra-high risk for psychosis. *Psychological medicine*, **43** (11) 2349-2360.

Lysaker, P., & Bell, M. (1995). Work rehabilitation and improvements in insight in schizophrenia. *The Journal of nervous and mental disease*, **183** (2) 103-106.

Lewis, D. A., & Levitt, P. (2002). Schizophrenia as a disorder of neurodevelopment. *Annual review of neuroscience*, **25** (1), 409-432.

Loewy, R. L., Bearden, C. E., Johnson, J. K., Raine, A., & Cannon, T. D. (2005). The prodromal questionnaire (PQ): preliminary validation of a self-report screening measure for prodromal and psychotic syndromes. *Schizophrenia research*, **79** (1) 117-125.

Lukoff, D., Snyder, K., Ventura, J., & Nuechterlein, K. H. (1984). Life events, familial stress, and coping in the developmental course of schizophrenia. *Schizophrenia bulletin*, **10** (2) 258-292.

Lumey, L. H., Stein, A. D., & Susser, E. (2011). Prenatal famine and adult health. *Annual review of public health*, **32**, 237-262.

Magaña, S. M., Ramírez García, J. I., Hernández, M. G., & Cortez, R. (2007). Psychological distress among Latino family caregivers of adults with schizophrenia: The roles of burden and stigma. *Psychiatric Services*, **58** (3) 378-384.

Mandal, M.K., Pandey, R., Prasad, A.B. (1998). emotions and schizophrenia: a review. *Schizophrenia Bulletin*. **24**, 399–412.

March, D., Hatch, S. L., Morgan, C., Kirkbride, J. B., Bresnahan, M., Fearon, P., & Susser, E. (2008). Psychosis and place. *Epidemiologic reviews*, **30** (1), 84-100.

Marenco, S., Weinberger, D.R. (2000). The neurodevelopmental hypothesis of schizophrenia: following a trail of evidence from cradle to grave. *Developmental Psychopathology*. **12** (3) 501–527.

Marsman, A., Mandl, R. C., Klomp, D. W., Bohlken, M. M., Boer, V. O., Andreychenko, A., ... & Pol, H. E. H. (2014). GABA and glutamate in schizophrenia: a 7 T 1 H-MRS study. *NeuroImage: Clinical*, **6**, 398-407.

Marsman, A., van den Heuvel, M. P., Klomp, D. W., Kahn, R. S., Luijten, P. R., & Hulshoff Pol, H. E. (2011). Glutamate in schizophrenia: a focused review and meta-analysis of 1H-MRS studies. *Schizophrenia bulletin*, **39** (1) 120-129.

Mayer-Gross, W. (1939) Die Klinik der Schizophrenie. In: Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rössler, A., Schultze-Lutter, F., ... & Valmaggia, L. (2013). The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA psychiatry*, **70** (1) 107-120.

McAllister A.K. (2014) Major histocompatibility complex I in brain development and schizophrenia. Biological Psychiatry. **75** (4) 262–268

McClure, M. M., Bowie, C. R., Patterson, T. L., Heaton, R. K., Weaver, C., Anderson, H., & Harvey, P. D. (2007). Correlations of functional capacity and neuropsychological performance in older patients with schizophrenia: evidence for specificity of relationships?. *Schizophrenia research*, **89** (1) 330-338.

McGorry, P.D, Yung A.R., Phillips, L.J. (2001). Ethics and early intervention in psychosis: keeping up the pace and staying in step. *Schizophrenia Research*. **51,** 17-29.

McGorry, P. D., Yung, A. R., Phillips, L. J., Yuen, H. P., Francey, S., Cosgrave, E. M., ... & Adlard, S. (2002). Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Archives of general psychiatry*, **59** (10) 921-928.

McGrath, J., Saha, S., Chant, D., & Welham, J. (2008). Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiologic reviews*, **30** (1) 67-76.

McGurk, S & Meltzer, H.Y. (2000) The role of cognition in vocational functioning in schizophrenia. *Schizophrenia Research.* **45,** 175-184.

McKenna, P.J. (2007). *Schizophrenia and Related Syndromes*. In Pomarol-Clotet, E., Hynes, F., Ashwin, C., Bullmore, E. T., McKenna, P. J., & Laws, K. R. (2010). Facial emotion processing in schizophrenia: a non-specific neuropsychological deficit?. *Psychological medicine*, **40** (6) 911-919.

Merugumala, S., Ramadan, S., Keenan, W., Liao, H., Wang, L. Y., & Lin, A. (2014). Magnetic Resonance Spectroscopy. In *MRI in Psychiatry* (pp. 87-116). Springer Berlin Heidelberg.

Meyer, E. C., Carrión, R. E., Cornblatt, B. A., Addington, J., Cadenhead, K. S., Cannon, T. D., ... & Woods, S. W. (2014). The relationship of neurocognition and negative symptoms to social and role functioning over time in individuals at clinical high risk in the first phase of the North American Prodrome Longitudinal Study. *Schizophrenia bulletin*, **40** (6) 1452-1461.

Miller, T.J., McGlashan, T.H., Rosen, J.L., Cadenhead, K., Cannon, T., Ventura, J., McFarlane, W., Perkins, D.O., Pearlson, G.D., Woods, S.W. (2003). Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophrenia Bulletin.* **29** (4) 703-715.

Mills, J. G., Fusar-Poli, P., Morgan, C., Azis, M., & McGuire, P. (2017). People meeting ultra high risk for psychosis criteria in the community. *World Psychiatry*, **16** (3) 322-323.

Moore, T. H., Zammit, S., Lingford-Hughes, A., Barnes, T. R., Jones, P. B., Burke, M., & Lewis, G. (2007). Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *The Lancet*, **370** (9584) 319-328.

Moosmang, S., Haider, N., Klugbauer, N., Adelsberger, H., Langwieser, N., Müller, J., Stiess, M…Kleppisch. T. (2005) Role of hippocampal Cav1.2 Ca2+ channels in NMDA receptor-independent synaptic plasticity spatial memory. Journal of Neuroscience **25** (43) 9883–9892.

Morgan, C., Charalambides, M., Hutchinson, G., & Murray, R. M. (2010). Migration, ethnicity, and psychosis: toward a sociodevelopmental model. *Schizophrenia bulletin*, sbq051.

Morgan, C., & Fisher, H. (2007). Environment and schizophrenia: environmental factors in schizophrenia: childhood trauma—a critical review. *Schizophrenia bulletin*, **33** (1) 3-10.

Morrison, A. P., French, P., Parker, S., Roberts, M., Stevens, H., Bentall, R. P., & Lewis, S. W. (2006). Three-year follow-up of a randomized controlled trial of cognitive therapy for the prevention of psychosis in people at ultrahigh risk. *Schizophrenia bulletin*, **33** (3) 682-687.

Morrison, A. P., French, P., Walford, L., Lewis, S. W., Kilcommons, A., Green, J., ... & Bentall, R. P. (2004). Cognitive therapy for the prevention of psychosis in people at ultra-high risk. *The British Journal of Psychiatry*, **185** (4) 291-297.

Morrison, A. P., Stewart, S. L., French, P., Bentall, R. P., Birchwood, M., Byrne, R., ... & Lewis, S. W. (2011). Early detection and intervention evaluation for people at high-risk of psychosis-2 (EDIE-2): trial rationale, design and baseline characteristics. *Early Intervention in Psychiatry*, **5** (1) 24-32.

Morrison, P. D., Zois, V., McKeown, D. A., Lee, T. D., Holt, D. W., Powell, J. F., ... & Murray, R. M. (2009). The acute effects of synthetic intravenous Δ 9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. *Psychological medicine*, **39** (10) 1607-1616.

Mortensen, P. B., Nørgaard-Pedersen, B., Waltoft, B. L., Sørensen, T. L., Hougaard, D., Torrey, E. F., & Yolken, R. H. (2007). Toxoplasma gondii as a risk factor for early-onset schizophrenia: analysis of filter paper blood samples obtained at birth. *Biological psychiatry*, **61** (5) 688-693.

Moskowitz, A., & Heim, G. (2011). Eugen Bleuler's dementia praecox or the group of schizophrenias (1911): a centenary appreciation and reconsideration. *Schizophrenia Bulletin*, **37** (3) 471-479.

Myin-Germeys, I., van Os, J., Schwartz, J. E., Stone, A. A., & Delespaul, P. A. (2001). Emotional reactivity to daily life stress in psychosis. *Archives of general psychiatry*, **58** (12) 1137-1144.

Nanko, S., & Moridaira, J. (1993). Reproductive rates in schizophrenic outpatients. *Acta Psychiatrica Scandinavica*, **87** (6) 400-404.

Nelson, H. E., & Willison, J. (1991). *National Adult Reading Test (NART)*. Windsor: Nfer-Nelson.

Niendam, T.A., Bearden, C.E., Johnson, J.k. McKinley, M., Loewy, R,, O'Brien, M., Nuechterlein, K.H., Green, M.F., Cannon, T.D. (2006) Neurocognitive performance and functional disability in the psychosis prodrome. *Schizophrenia Research.* **84,** 100-110.

Niendam, T. A., Bearden, C. E., Zinberg, J., Johnson, J. K., O'brien, M., & Cannon, T. D. (2007). The course of neurocognition and social functioning in individuals at ultra high risk for psychosis. *Schizophrenia bulletin*, **33** (3) 772-781.

Nuechterlein, K. H., & Dawson, M. E. (1984). A heuristic vulnerability/stress model of schizophrenic episodes. *Schizophrenia bulletin*, **10** (2) 300.

Ohaeri, J. U. (2003). The burden of caregiving in families with a mental illness: a review of 2002. *Current Opinion in Psychiatry*, **16** (4) 457-465.

Park, S., & Gooding, D. C. (2014). Working memory impairment as an endophenotypic marker of a schizophrenia diathesis. *Schizophrenia Research: Cognition*, **1** (3) 127-136.

Palmer, B. W., Heaton, R. K., Paulsen, J. S., Kuck, J., Braff, D., Harris, M. J., ... & Jeste, D. V. (1997). Is it possible to be schizophrenic yet neuropsychologically normal?. *Neuropsychology*, **11** (3) 437.

Pantelis, C., Velakoulis, D., McGorry, P. D., Wood, S. J., Suckling, J., Phillips, L. J., ... & Desmond, P. (2003). Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *The Lancet*, **361** (9354) 281-288.

Pedersen, C. B., & Mortensen, P. B. (2001). Evidence of a dose-response relationship between urbanicity during upbringing and schizophrenia risk. *Archives of general psychiatry*, **58** (11) 1039-1046.

Pedersen, M. G., Stevens, H., Pedersen, C. B., Nørgaard-Pedersen, B., & Mortensen, P. B. (2011). Toxoplasma infection and later development of schizophrenia in mothers. *American Journal of Psychiatry*, **168** (8) 814-821.

Pelletier, A. L., Dean, D. J., Lunsford-Avery, J. R., Smith, A. K., Orr, J. M., Gupta, T., ... & Mittal, V. A. (2013). Emotion recognition and social/role dysfunction in non-clinical psychosis. *Schizophrenia research*, **143** (1) 70-73.

Perlick, D. A., Rosenheck, R. A., Kaczynski, R., Swartz, M. S., Cañive, J. M., & Lieberman, J. A. (2006). Special section on CATIE baseline data: components and correlates of family burden in schizophrenia. *Psychiatric services*, **57** (8) 1117-1125.

Pinkham, A.E., Penn, D.L. (2006). Neurocognitive and social cognitive predictors of interpersonal skill in schizophrenia. *Psychiatry Research*. **143**, 167–178.

Pinkham, A.E., Penn, D.L., Perkins, D.O., Graham, K.A., Siegel, M. (2007). Emotion perception and social skill over the course of psychosis: a comparison of individuals 'at-risk' for psychosis and individuals with early and chronic schizophrenia spectrum illness. *Cognitive Neuropsychiatry*. **12**, 198–212.

Pinkham, A. E., Penn, D. L., Perkins, D. O., & Lieberman, J. (2003). Implications for the neural basis of social cognition for the study of schizophrenia. *American Journal of Psychiatry*, **160** (5) 815-824.

Poels, E. M., Kegeles, L. S., Kantrowitz, J. T., Javitt, D. C., Lieberman, J. A., Abi-Dargham, A., & Girgis, R. R. (2014). Glutamatergic abnormalities in schizophrenia: a review of proton MRS findings. *Schizophrenia research*, **152** (2), 325-332.

Polanczyk, G., Moffitt, T. E., Arseneault, L., Cannon, M., Ambler, A., Keefe, R. S., ... & Caspi, A. (2010). Etiological and clinical features of childhood psychotic symptoms: results from a birth cohort. *Archives of general psychiatry*, **67** (4), 328-338.

Pomarol-Clotet, E., Hynes, F., Ashwin, C., Bullmore, E. T., McKenna, P. J., & Laws, K. R. (2010). Facial emotion processing in schizophrenia: a non-specific neuropsychological deficit?. *Psychological medicine*, **40** (6) 911-919.

Port, J. D., & Agarwal, N. (2011). MR spectroscopy in schizophrenia. *Journal of Magnetic Resonance Imaging*, **34** (6) 1251-1261.

Rabinowitz, J., Levine, S. Z., Garibaldi, G., Bugarski-Kirola, D., Berardo, C. G., & Kapur, S. (2012). Negative symptoms have greater impact on functioning than positive symptoms in schizophrenia: analysis of CATIE data. *Schizophrenia research*, **137** (1) 147-150.

Ragland, J. D., Turetsky, B. I., Gur, R. C., Gunning-Dixon, F., Turner, T., Schroeder, L., ... & Gur, R. E. (2002). Working memory for complex figures: an fMRI comparison of letter and fractal n-back tasks. *Neuropsychology*. **16** (3) 370.

Rajji, T. K., Miranda, D., & Mulsant, B. H. (2014). Cognition, function, and disability in patients with schizophrenia: a review of longitudinal studies. *The Canadian Journal of Psychiatry*, **59** (1) 13-17.

Rapoport, J. L., Giedd, J. N., & Gogtay, N. (2012). Neurodevelopmental model of schizophrenia: update 2012. *Molecular psychiatry*, **17** (12), 1228-1238.

Read, J., Os, J. V., Morrison, A. P., & Ross, C. A. (2005). Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. *Acta Psychiatrica Scandinavica*, **112** (5) 330-350.

Reichenberg, A., Harvey, P.D. (2007). Neuropsychological impairments in schizophrenia: integration of performance-based and brain imaging findings. *Psychological Bulletin* **133**, 833–858.

Renard, S. B., Huntjens, R. J., Lysaker, P. H., Moskowitz, A., Aleman, A., & Pijnenborg, G. H. (2017). Unique and overlapping symptoms in schizophrenia spectrum and dissociative disorders in relation to models of psychopathology: a systematic review. *Schizophrenia bulletin*, **43** (1) 108-121.

Remington J, Klein J, Wilson C, Baker, DJ. *Infectious Diseases of the Fetus and Newborn Infant, 6th edn*. In Rapoport, J. L., Giedd, J. N., & Gogtay, N. (2012). Neurodevelopmental model of schizophrenia: update 2012. *Molecular psychiatry*, **17** (12), 1228-1238.

Riley, E. M., McGovern, D., Mockler, D., Doku, V. C., ÓCeallaigh, S., Fannon, D. G., ... & Sharma, T. (2000). Neuropsychological functioning in first-episode psychosis—evidence of specific deficits. *Schizophrenia research*, **43** (1) 47-55.

Ripke, S., O'Dushlaine, C., Chambert, K., Moran, J. L., Kähler, A. K., Akterin, S., … Sullivan, P. F. (2013). Genome-wide Association Analysis Identifies 14 New Risk Loci for Schizophrenia. *Nature Genetics*, **45** (10) 1150–1159.

Rowland, L. M., Kontson, K., West, J., Edden, R. A., Zhu, H., Wijtenburg, S. A., ... & Barker, P. B. (2012). In vivo measurements of glutamate, GABA, and NAAG in schizophrenia. *Schizophrenia bulletin*, **39** (5) 1096-1104.

Ruhrmann, S., Schultze-Lutter, F., Salokangas, R. K., Heinimaa, M., Linszen, D., Dingemans, P., ... & Morrison, A. (2010). Prediction of psychosis in adolescents and young adults at high risk: results from the prospective European prediction of psychosis study. *Archives of general psychiatry*, **67** (3) 241-251.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological review*, **103** (3) 403.

Schatz, J (1998). Cognitive processing efficiency in schizophrenia: generalized vs domain specific deficits. *Schizophrenia Research,* **30**, 41–49.

Seidman, L. J., Giuliano, A. J., Meyer, E. C., Addington, J., Cadenhead, K. S., Cannon, T. D., ... & Woods, S. W. (2010). Neuropsychology of the prodrome to psychosis in the NAPLS consortium: relationship to family history and conversion to psychosis. *Archives of general psychiatry*, **67** (6) 578-588.

Seidman, L.J., Giuliano, A.J., Smith, C.W., Stone, W.S, Glatt, S.J., Meyer, E., Faraone, S.V., Tsuang, M.T., Cornblatt, B. (2006). Neuropsychological functioning in adolescents and young adults at genetic risk for schizophrenia and affective psychoses: results from the Harvard and Hillside Adolescent High Risk Studies. *Schizophrenia Bulletin*. **32**, 507-524.

Sergi, M. J., Rassovsky, Y., Widmark, C., Reist, C., Erhart, S., Braff, D. L., ... & Green, M. F. (2007). Social cognition in schizophrenia: relationships with neurocognition and negative symptoms. *Schizophrenia research*, **90** (1) 316-324.

Selten, J. P., & Cantor-Graae, E. (2005). Social defeat: risk factor for schizophrenia?. *The British Journal of Psychiatry*, **187** (2) 101-102.

Simon, A.E., Cattapan-Ludewig, K., Zmilacher, S., Arbach, D., Gruber, K., Dvorsky, D.N., Roth, B., Isler, E., Zimmer, A, Umbricht, D. (2007). Cognitive functioning in the schizophrenia prodrome. *Schizophrenia Bulletin*. **33** (3) 761-771.

Schmand, B., Brand, N., & Kuipers, T. (1992). Procedural learning of cognitive and motor skills in psychotic patients. *Schizophrenia research*, **8** (2) 157-170.

Schneider, K. (1959) Clinical Psychopathology, translated by M. W. Hamilton, Grune & Stratton, New York, NY, USA. In Häfner, H. (2014). The concept of schizophrenia: From unity to diversity. *Advances in Psychiatry*, *2014*.

Schroeder, K., Fisher, H. L., & Schäfer, I. (2013). Psychotic symptoms in patients with borderline personality disorder: prevalence and clinical management. *Current opinion in psychiatry*, **26** (1) 113-119.

Schultze-Lutter, F., Addington, J., Ruhrmann, S., Klosterko¨tter, J. (2007) Schizophrenia Proneness Instrument, Adult Version (SPI-A). Rome, Italy: *Giovanni Fiorito Editore*.

Schultze-Lutter, F., Klosterko¨tter, J., Picker, H., Steinmeyer, E., Ruhrmann, S. (2007) Predicting first-episode psychosis by basic symptoms criteria. *Clinical Neuropsychiatry*. **4** (1) 11-22.

Schultze-Lutter, F., Marshall, M., Koch, E. (2012) Schizophrenia Proneness Instrument, Child and Youth Version (SPI-CY), Extended English Translation. Rome, Italy: *Giovanni Fiorito Editore*.

Schultze-Lutter, F. (2009) Subjective symptoms of schizophrenia in research and the clinic: the basic symptom concept. *Schizophrenia Bulletin*. **35** (1) 5-8.

Schultze-Lutter, F., Ruhrmann, S., Klosterkötter, J. (2006) Can schizophrenia be predicted phenomenologically? In: Lam, M (2011). Psychosis high risk research - local scene. *The Hong Kong Medical Diary*. **16** (5) 4-5.

Seidman, L. J., Giuliano, A. J., Meyer, E. C., Addington, J., Cadenhead, K. S., Cannon, T. D., ... & Woods, S. W. (2010). Neuropsychology of the prodrome to psychosis in the NAPLS consortium: relationship to family history and conversion to psychosis. *Archives of general psychiatry*, **67** (6) 578-588.

Seidman, L. J., Shapiro, D. I., Stone, W. S., Woodberry, K. A., Ronzio, A., Cornblatt, B. A., ... & Mathalon, D. H. (2016). Association of neurocognition with transition to psychosis: baseline functioning in the second phase of the North American prodrome longitudinal study. *JAMA psychiatry*, **73** (12) 1239-1248.

Seiferth, N. Y., Pauly, K., Habel, U., Kellermann, T., Shah, N. J., Ruhrmann, S., ... & Kircher, T. (2008). Increased neural response related to neutral faces in individuals at risk for psychosis. *Neuroimage*, **40** (1) 289-297.

Sergi, M.J., Rassovsky, Y., Widmark, C., Reist, C., Erhart, S., Braff, D.L., Marder, S.R., Green, M.F. (2007). Social cognition in schizophrenia: relationships with neurocognition and negative symptoms. *Schizophrenia Research*. **90**, 316–324.

Schmidt, M. J., & Mirnics, K. (2015). Neurodevelopment, GABA System Dysfunction, and Schizophrenia. *Neuropsychopharmacology*, **40** (1), 190–206. http://doi.org/10.1038/npp.2014.95

Shepherd, A. M., Laurens, K. R., Matheson, S. L., Carr, V. J., & Green, M. J. (2012). Systematic meta-review and quality assessment of the structural brain alterations in schizophrenia. *Neuroscience & Biobehavioral Reviews*, **36** (4) 1342-1356.

Silver, H., Feldman, P., Bilker, W., & Gur, R. C. (2003). Working memory deficit as a core neuropsychological dysfunction in schizophrenia. *American Journal of Psychiatry*, **160** (10) 1809-1816.

Simon, A. E., Cattapan-Ludewig, K., Zmilacher, S., Arbach, D., Gruber, K., Dvorsky, D. N., ... & Umbricht, D. (2007). Cognitive functioning in the schizophrenia prodrome. *Schizophrenia bulletin*, **33** (3) 761-771.

Smith, C. W., Park, S., & Cornblatt, B. (2006). Spatial working memory deficits in adolescents at clinical high risk for schizophrenia. *Schizophrenia research*, **81** (2) 211-215.

St Clair, D., Xu, M., Wang, P., Yu, Y., Fang, Y., Zhang, F., ... & He, L. (2005). Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959-1961. *Jama*, **294** (5) 557-562.

Tabarés-Seisdedos, R., Balanzá-Martínez, V., Sánchez-Moreno, J., Martinez-Aran, A., Salazar-Fraile, J., Selva-Vera, G., ... & Vieta, E. (2008). Neurocognitive and clinical predictors of functional outcome in patients with schizophrenia and bipolar I disorder at one-year follow-up. *Journal of affective disorders*, **109** (3) 286-299.

Tan, H. Y., Choo, W. C., Fones, C. S., & Chee, M. W. (2005). fMRI study of maintenance and manipulation processes within working memory in first-episode schizophrenia. *American Journal of Psychiatry*, **162** (10) 1849-1858.

Tayoshi, S. Y., Nakataki, M., Sumitani, S., Taniguchi, K., Shibuya-Tayoshi, S., Numata, S., ... & Ohmori, T. (2010). GABA concentration in schizophrenia patients and the effects of antipsychotic medication: a proton magnetic resonance spectroscopy study. *Schizophrenia research*, **117** (1) 83-91.

Thompson, A.D., Bartholomeuzs, C., Yung, A. (2011) Social cognition deficits and the 'ultra-high risk' for psychosis population: a review of literature. *Early Intervention in Psychiatry.* **5** (3) 192-202.

Thompson, A., Papas, A., Bartholomeusz, C., Allott, K., Amminger, G. P., Nelson, B., ... & Yung, A. (2012). Social cognition in clinical "at risk" for psychosis and first episode psychosis populations. *Schizophrenia research*, **141** (2) 204-209.

Thompson, A., Papas, A., Bartholomeusz, C., Nelson, B., & Yung, A. (2013). Externalized attributional bias in the Ultra High Risk (UHR) for psychosis population. *Psychiatry research*, **206** (2) 200-205.

Trémeau, F. (2006). A review of emotion deficits in schizophrenia. *Dialogues in Clinical Neuroscience.* **8**, 59–70.

van der Gaag, M., Smit, F., Bechdolf, A., French, P., Linszen, D. H., Yung, A. R., ... & Cuijpers, P. (2013). Preventing a first episode of psychosis: meta-analysis of randomized controlled prevention trials of 12month and longer-term follow-ups. *Schizophrenia research*, **149** (1) 56-62.

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

van Mastrigt, S., & Addington, J. (2002). Assessment of premorbid function in first-episode schizophrenia: modifications to the Premorbid Adjustment Scale. *Journal of Psychiatry and Neuroscience*, **27** (2) 92.

van Os, J., Hanssen, M., Bak, M., Bijl, R. V., & Vollebergh, W. (2003). Do urbanicity and familial liability coparticipate in causing psychosis? *American Journal of Psychiatry*, **160** (3) 477-482.

van Os, J., Hanssen, M., Bijl, R. V., & Ravelli, A. (2000). Strauss (1969) revisited: a psychosis continuum in the general population?. *Schizophrenia research*, **45** (1) 11-20.

van Os, J., Kenis, G., & Rutten, B. P. (2010). The environment and schizophrenia. *Nature*, **468** (7321), 203-212.

van Os, J., Linscott, R. J., Myin-Germeys, I., Delespaul, P., & Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. *Psychological medicine*, **39** (2) 179-195.

van Os, J., Pedersen, C. B., & Mortensen, P. B. (2004). Confirmation of synergy between urbanicity and familial liability in the causation of psychosis. *American Journal of Psychiatry*, **161** (12) 2312-2314.

van Os, J., Rutten, B.P. & Poulton, R. (2008). Gene-environment interaction in schizophrenia: review of epidemiological findings and future directions. *Schizophrenia Bulletin,* **34,** 1066-1082.

van Rijn, S., Aleman, A., de Sonneville, L., Sprong, M., Ziermans, T., Schothorst, P., van Engeland, H., Swaab, H. (2011). Misattribution of facial expressions of emotion in adolescents at increased risk of psychosis: the role of inhibitory control. *Psychological Medicine*. **41** (3), 499–508.

Veling, W., Susser, E., Van Os, J., Mackenbach, J. P., Selten, J. P., & Hoek, H. W. (2008). Ethnic density of neighborhoods and incidence of psychotic disorders among immigrants. *American Journal of Psychiatry*, **165** (1) 66-73.

Velthorst, E., Nieman, D. H., Becker, H. E., van de Fliert, R., Dingemans, P. M., Klaassen, R., ... & Linszen, D. H. (2009). Baseline differences in clinical symptomatology between ultra high risk subjects with and without a transition to psychosis. *Schizophrenia research*, **109** (1) 60-65.

Velthorst, V., Nieman, D.H., Linszen, D., Becker, H., de Haan, L., Dingemans, P.M., Birchwood, M., Patterson, P., Salokangas, R.K.R., Heinimaa, M., Heinz, A., Juckel, G., von Reventlow, H.J., French, P., Stevens, H., Schultze-Lutter, F., Klosterkötter, J., Ruhrmann, S. (2010). Disability in people clinically at high risk of psychosis. *British Journal of Psychiatry.* **197,** 278-284.

Vita, A., De Peri, L., Silenzi, C., Dieci, M. (2006) Brain morphology in first-episode schizophrenia: a metaanalysis of quantitative magnetic resonance imaging studies. Schizophrenia Research, **82** (1) 75–88

Warner, R., & de Girolamo, G. (1995) Schizophrenia, Epidemiology of Mental Disorders and Psychological Problems, World Health Organization, Geneva, Switzerland. In Häfner, H. (2014). The concept of schizophrenia: From unity to diversity. *Advances in Psychiatry*, *2014*.

Weinberger, D. R. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Archives of general psychiatry*, **44** (7) 660-669.

Wheatley, M. (1998). The prevalence and relevance of substance use in detained schizophrenic patients. *The Journal of Forensic Psychiatry*, **9** (1) 114-129.

Wood, S.J., Pantelis, C., Proffitt, T., Phillips, J.L., Stuart, G.W., Buchanan, J.A., Mahony, K., Brewer, W., Smith, D.J., McGorry, P.D. (2003). Spatial working memory ability is a marker of risk-for-psychosis. *Psychological Medicine*. **33**, 1239-1274.

Xu, M. Q., Sun, W. S., Liu, B. X., Feng, G. Y., Yu, L., Yang, L., ... & He, L. (2009). Prenatal malnutrition and adult schizophrenia: further evidence from the 1959-1961 Chinese famine. *Schizophrenia bulletin*, sbn168.

Yung, A.R., McGorry, P.D. (1996a). The initial prodrome in psychosis: descriptive and qualitative aspects. *Australian and New Zealand Journal of Psychiatry*. **30**, 587-599

Yung, A.R., McGorry, P.D. (1996b). The prodromal phase of first episode psychosis: past and current conceptualizations. *Schizophrenia Bulletin.* **22,** 353-370.

Yung, A.R., McGorry, P.D., McFarlane, C.A., Jackson, H.J., Patton, G.C., Rakkar, A. (1996) Monitoring and care of young people at incipient risk of psychosis. *Schizophrenia Bulletin.* **22,** 283-303.

Yung, A., Phillips, L., Simmons, M. B., Ward, J., Thompson, K., French, P., & McGorry, P. (2006). CAARMS: Comprehensive Assessment of At Risk Mental States. *Melbourne, Australia: The PACE Clinic*.

Yung, A.R., Phillips, L.J., Yuen, H.P., McGorry, P.D. (2004). Risk factors for psychosis in an ultra-high-risk group: psychopathology and clinical features. *Schizophrenia Research.* **67,** 131-142.

Zubin, J., & Spring, B. (1977). Vulnerability: A new view of schizophrenia. *Journal of abnormal psychology*, **86** (2) 103.