
*Cognition in First-Episode Psychosis:
Characterisation, Reserve and Relationship to
Functioning*

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SUBMITTED FOR DEGREE OF DOCTOR OF PHILOSOPHY

Declaration

I, Andrew James Watson, confirm that the work presented in this thesis is my own.

Where information has been derived from other sources, I confirm that this has been indicated in the thesis

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Statement of Study Contributions

Studies 1, 2 and 3: I recruited all participants to the North London sites of the BeneMin trial and administered all subsequent assessments used in the analyses. I organised all magnetic resonance imaging scans and uploaded the data to the Redcap database. I took the participants' blood, tested urine samples for drugs of abuse and prepared the blood samples for further analysis. I was responsible for cognitive training of research assistants at the other trial sites and scored all the cognitive assessments. I performed all statistical analyses and thesis writing.

Studies 4 and 5. For the ECLIPSE trial, I set-up all North London recruitment sites and, for the majority of participants, carried out all of the assessments and data scoring used in this thesis. I was responsible for overseeing the set-up and data quality of the CANTAB variables. The design of the social cognition study is the result of my own work. I was responsible for obtaining ethical approval and recruitment to the social cognition study at the North London site. I additionally trained and supervised research assistants in Warwick and South London to carry out these assessments on a small proportion of their participants. I scored all of the social cognition assessments and performed all statistical analyses and thesis writing.

Work in Collaboration: For the BeneMin trial, Professor Paola Dazzan supervised the collection and extraction of blood plasma at the Institute of Psychiatry, Psychology and Neuroscience (IoPPN). Professor John Suckling supervised the MRI setup, data acquisition and processing at the University of Cambridge, with structural values extracted by Dr Annalisa Giordano at the IoPPN. Healthy control data for the BeneMin comparison was collected during the West London First-Episode Study and supervised by Professors Eileen Joyce and Thomas Barnes. Healthy control data for the social cognition comparisons was carried out by MSc students at the IoPPN and supervised by Dr Matteo Cella and by me.

Dedication

For Mum and Dad

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Abstract

Schizophrenia is marked by deficits in cognition and social functioning that present early in the course of illness. A relationship between neurocognitive impairment (e.g. memory and processing speed), and social functioning is reported in the literature, with poorer neurocognition associated with worse social outcomes. There is emerging evidence for the existence of neurocognitive subtypes with different cognitive trajectories, hypothesised to reflect separate etiological processes and risk factors for clinical and social outcomes. Despite neurocognition being considered one of the best predictors of social outcomes, there is still a large amount of variance in outcomes left unexplained. In addition to neurocognitive deficits, processes required for successful social interactions, collectively known as 'social cognition' i.e. theory of mind, attribution bias, social perception and emotion perception, have been shown to be impaired in those with established schizophrenia. There is some evidence that social cognition mediates the relationship between neurocognition and functional outcomes.

Studying individuals with a first-episode psychosis (FEP) allows the examination of the fundamental features of schizophrenia, without the confounding effects of prolonged medication, hospitalisation and social isolation. Using two clinical-trial FEP groups, the studies presented in this thesis examined: the existence and magnitude of global and domain-specific neuro- and social cognitive impairment; the existence of neurocognitive-trajectory based subtypes and their brain volumetric and inflammatory profiles; the relationship between neurocognition and social functioning; and whether social cognition mediates the relationship between neurocognition and social functioning. Three IQ-trajectory based subtypes that were stable over time and distinguished by biological underpinnings were found. Social cognition deficits were

present early in the course of illness and significantly overlapped with neurocognitive impairments, but it could not be concluded that social cognition mediates the relationship between neurocognition and social functioning. The results of the studies enabled recommendations for remedial strategies to improve social functioning and quality of life of individuals early in the course of illness.

Impact Statement

There is a need for increased awareness, understanding and effective treatments for cognitive dysfunction in early schizophrenia to improve social functioning and quality of life in those with the illness. Effective treatments will substantially reduce societal and carer burden. This thesis advances understanding of the relationship between both neuro- and social cognition early in the course of illness and social and occupational functioning and furthermore considers their relationship with biological markers. Cognitive and biological markers are useful for early detection of those at risk of poorest outcomes and understanding potential mechanisms of the development and treatment of the illness. Furthermore, this thesis reveals several methodological considerations which may impact the quality of future research in the area and highlights the need for reliable and valid cognitive testing, as well as potential avenues for the development of new measures. The findings provide implications and recommendations for therapeutic advances with the primary goal of improving the quality of life and outcomes of those who have experienced a first-episode of psychosis.

This research underwent formal ethical review and benefits from the thought placed on the burden on service users from its conception. Recruitment to the studies included in this thesis had the benefit of engaging NHS early intervention services in research, as well as the dissemination of current evidence and research findings. Results of the studies have been disseminated to clinical and academic professionals, as well as the service users and the general public through conference presentations and will be published in peer-reviewed scientific journals. This thesis will therefore have impact by: increasing clinical and academic understanding of cognitive dysfunction and relationship with outcomes in the early psychoses; identifying possible biological markers for

cognitive dysfunction in psychosis; making recommendations for optimising the effectiveness for therapies tackling cognitive and social cognitive difficulties, in particular, cognitive remediation. This not only can lead to improvement of patient quality of life but also highlight methodological considerations to improve the quality of future research in this field; engage NHS early intervention services in clinical research; improve understanding of the characterisation of the illness to general and scientific communities with the aim of reducing stigma in this population.

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List of Abbreviations

AD	Alzheimer's Disease
AIHQ	Ambiguous Intentions and Hostility Questionnaire
AJW	Andrew J Watson
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ARMS	At Risk Mental State
aTBV	Absolute Total Brain Volume
AVLT	Auditory Verbal Learning Test
BDNF	Brain-Derived Neurotrophic Factor
BeneMin	Benefit of Minocycline on Negative Symptoms in Psychosis
BMI	Body Mass Index
BPRS	Brief Psychiatric Rating Scale
CAINS	The Clinical Assessment Interview for Negative Symptoms
CANTAB	Cambridge Neuropsychological Test Automated Battery
CDSS	Calgary Depression Scale for Schizophrenia
CIQ	Compromised Intelligence Quotient
COWAT	Controlled Oral Word Association Test
CPT	Continuous Performance Task
CR	Cognitive Reserve
CRT	Cognitive Remediation Therapy
CVLT	California Verbal Learning Test
DFA	Discriminant Function Analysis
DIQ	Deteriorated Intelligence Quotient
DLPFC	Dorsal Lateral Prefrontal Cortex
DSM	Diagnostic Statistic Manual
ECLIPSE	Building Resilience and Recovery through Enhancing Cognition and quality of Life in the early Psychoses
EIS	Early Intervention Service
EME	Efficacy and Mechanisms Evaluation
EMJ	Eileen M Joyce
EP	Emotion Perception
ES	Effect Side
FDR	False Discovery Rate
FEP	First Episode Psychosis
fMRI	Functional Magnetic Resonance Imaging
FSIQ	Full-Scale Intelligence Quotient
GAF	Global Assessment of Functioning
HC	Healthy Control
HRA	Health Research Authority
hsCRP	High-Sensitivity C-Reactive Protein
HT	The Hinting Task
ICV	Intracranial Volume
IFN-γ	Interferon Gamma
IL	Interleukin
IMP	Investigational Medicinal Product

IPSAQ	The Internal, Personal and Situational Attributions Questionnaire
IQ	Intelligence Quotient
MC	Matteo Cella
MINI	The Mini International Neuropsychiatric Interview
MOT	Motor Screening Task
MRC	Medical Research Council
MTT	Multi-Tasking Test
NART	National Adult Reading
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute of Health Research
OTS	One-Touch Stockings of Cambridge
PAL	Paired Associates Learning
PANSS	Positive and Negative Syndrome Scale
PET	Positron Emission Tomography
PIQ	Preserved Intelligence Quotient
PRS	Psychopathology Rating Scale
RAD	Relationships Across Domains
RCT	Randomised Controlled Trial
RTI	Reaction Time
RVP	Rapid Visual Processing
SAT-MC	Social Attribution Task – Multiple Choice
SCIT	Social Cognition and Interaction Training
SD	Standard Deviation
SE	Standard Error
SEM	Structural Equation Modelling
SFS	Social Functioning Scale
sIL-2R	Soluble Interleukin-2R
SOFAS	Social and Occupational Function Assessment Scale
SP	Social Perception
SPSS	Statistical Package for the Social Sciences
SWM	Spatial Working Memory
TBI	Traumatic Brain Injury
TBV	Total Brain Volume
TNF-α	Tumor Necrosis Factor Alpha
ToM	Theory of Mind
UHR	Ultra-High Risk
VF	Verbal Fluency
WAIS	Wechsler Adult Intelligence Scale
WASI	Wechsler Abbreviated Scale of Intelligence
WRAT-R	Wide Range Achievement Test - Reading
WTAR	Wechsler Test of Adult Reading

1 Introduction

1.1 Schizophrenia

The term 'schizophrenia' was first coined by Bleuler in 1911, an adjunct of the Greek words "*schizein*" (to split) and "*phrēn*" (mind) to describe the disordered thinking of those with the illness. Bleuler wrote "I call *dementia praecox* 'schizophrenia' because, as I hope to show, the splitting of the different psychic functions is one of its most important features. In each case there is a more or less clear splitting of the psychological functions: as the disease becomes distinct, the personality loses its unity" (Bleuler, 1968). His allusion to 'dementia praecox' refers to the nomenclature initially given to the disorder we now associate with schizophrenia, by the German physician Kraepelin. Kraepelin was the first to distinguish what had previously been thought of as "insanity" into individual psychotic disorders. Kraepelin's somatic approach highlighted 'dementia' in association with psychotic phenomena as a primary disturbance of the disorder, due to the observation that cognitive functioning and goal-directed behaviour are disrupted in those with the illness.

Schizophrenia is now considered to be a severe mental disorder, which affects thinking, feelings and behaviour. Despite cognitive dysfunction being considered a core impairment of the disorder (van Os and Kapur, 2009, Elvevag and Goldberg, 2000) the current classification system for schizophrenia (DSM-V) (American Psychiatric, 2013) (Table 1.1) focuses predominantly on "positive symptoms" (i.e. delusions, hallucinations or disorganised thought and behaviour) and "negative symptoms" (i.e. alogia, affective flattening or avolition) in association with disruption to social and occupational functioning.

Table 1.1: DSM IV Criteria for Schizophrenia and Other Psychotic Disorders (American Psychiatric, 2013)

A. Characteristic symptoms: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

1. Delusions
2. Hallucinations
3. Disorganized speech (e.g., frequent derailment or incoherence)
4. Grossly disorganized or catatonic behaviour
5. Negative symptoms (i.e., affective flattening, alogia, or avolition)

Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices conversing with each other.

B. Social/occupational dysfunction: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. Duration: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. Schizoaffective and Mood Disorder exclusion: Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no Major Depressive, Manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. Substance/general medical condition exclusion: The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

F. Relationship to a Pervasive Developmental Disorder: If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

1.2 First - Episode Psychosis

The early phase of psychosis is hypothesised to be a critical period in which deterioration can be aggressive and predictive of poor long-term outcome (Birchwood et al., 1998, Leeson et al., 2009). Research in first-episode psychosis cohorts allows the examination of the fundamental features of schizophrenia, whilst avoiding potentially confounding effects of psychosocial influences, continued deterioration, prolonged hospitalisation and antipsychotic medication. Research early in the course of illness is vital in order to identify predictors of functional outcomes following onset of psychosis. Whilst first-episode psychosis (FEP) should not be conflated with schizophrenia, this thesis consists of studies which recruited participants meeting criteria, at presentation, of either schizophrenia or schizophrenia-like FEP. This allows us a way of studying symptoms and functioning of individuals who show early fundamental features of schizophrenia.

1.3 Functional Outcomes

Schizophrenia affects between 0.5 and 1% of the population (Goldner et al., 2002, Perälä et al., 2007), with some variation in prevalence worldwide (Saha et al., 2005) and is one of the leading causes of disability in developed countries (Murray and Lopez, 1996). There is a higher prevalence in men, with onset most commonly occurring in early adulthood (Hafner et al., 1994). Experiencing a first-episode of psychosis is associated with deterioration in everyday functioning, loss of independence and ability to maintain employment (Bowie et al., 2006, Green, 1996, Green et al., 2000), societal and clinical burden (Jenkins, 2013) and increased mortality (Oakley et al., 2018, McGrath et al., 2008). Outcomes following a FEP remain heterogeneous and are influenced by cognitive

functioning (Green et al., 2004), negative symptoms (Kirkpatrick et al., 2001), age of onset (Immonen et al., 2017) and societal factors (Tibber et al., 2019).

In the UK, early intervention services (EIS) were introduced to reduce the duration of untreated psychosis and has led to improved outcomes and decreased societal burden, with many individuals now able to achieve better health and social outcomes (Correll et al., 2018, Tsiachristas et al., 2016). The recovery model of schizophrenia values the importance of individual functioning and empowerment, including independence and ability to access employment (Rose, 2014). This is a move away from symptom remission as the defining outcome of treatment, and has led to increased interest in functional outcomes, with justified optimism that a proportion of people do go on to recover completely or regain good social functioning (O'Keeffe, 2019). The discovery that functional impairment commonly remains even after the remission of positive symptoms and that functional outcomes are central to recovery (Harvey, 2009) has led to a shift in remediation targets; with cognitive remediation being considered key for improving functional outcomes (Wykes et al., 2011).

1.4 Neurocognition in Schizophrenia

1.4.1 Neurocognitive Deficits in First-Episode Psychosis

Studies have shown that cognitive impairments are the best predictor of functional outcome in schizophrenia (Green et al., 2000, Green, 2006) and that deficits persist even with optimal medication strategies (Keefe and Harvey, 2012) and the alleviation of florid psychosis symptoms (Brissos et al., 2011). The neurocognitive deficit profile in schizophrenia is broad and severe, with patient groups having a general IQ deficit,

approximately one standard deviation below that of healthy controls (Reichenberg and Harvey, 2007, Bilder et al., 2000, Keefe et al., 2006a). Cognitive impairment is present in most patients (Dickinson et al., 2007b) and broadly occurs in all cognitive domains (verbal memory, visual memory, executive functions, attention/processing speed, language, sensory-motor function, general verbal ability) with the exception of visual processing (Reichenberg et al., 2009), with well replicated findings that memory, executive functions and processing speed domains are the most compromised in this population (Nuechterlein et al., 2004).

Neurocognitive deficits in first-episode cohorts are similar to those seen in chronic patients, approximately 1 standard deviation below those of the healthy population (Mesholam-Gately et al., 2009), appear before the onset of clinical symptoms (Bilder et al., 2006, Woodberry et al., 2008) by as much as a decade, and are present even in medication-naïve patients (Fatouros-Bergman et al., 2014a).

Despite most patients showing cognitive impairments, Heinrichs and Zakzanis (1998) found that approximately 25% have normal neuropsychological profiles when compared to standardised normative data, whilst other studies show this to vary between 20% – 57% (Carruthers et al., 2019). Despite this, there is evidence that patients still show disparity in comparison to their predicted levels of intelligence, with support for this coming from studies of monozygotic twins discordant for schizophrenia (Goldberg et al., 1990).

1.4.1.1 IQ

Intelligence quotient (IQ) is a measure of global intelligence or “g” (Spearman et al., 1904). The most commonly used test of intelligence was developed by Wechsler, first established in 1955, with updated versions still in clinical and research practice today. The Wechsler Adult Intelligence Scale III (WAIS-III consists) of 14 subtests thought to test different domains of intelligence which are then standardised by age and averaged to give an IQ score. These tests can be time consuming and various short-forms have been validated, including those suitable for individuals with schizophrenia (Blyler et al., 2000). Other commonly used measures of global intelligence include the composite scores of subtests from batteries measuring multiple cognitive domains.

Due to a lack of ability to predict those who are likely to go on to develop schizophrenia, few studies have measures of premorbid general intelligence. Where measures of premorbid intelligence are not available, “hold-tests” are often used to estimate likely premorbid IQ based on function of processes thought to be intact following symptom onset. In the case of schizophrenia, word recognition is thought to be unaffected and performance on tests which involve pronouncing a list of grapheme-phoneme irregular words of increasing difficulty can give us an estimated premorbid IQ value (Holdnack, 2001). The most commonly used in English-speaking populations with schizophrenia are the Wechsler Test of Adult Reading (WTAR) and the National Adult Reading Test (NART) (Holdnack, 2001, Nelson, 1982), with increasing preference for the WTAR due to it being validated against the WAIS-III.

As stated, impairment in schizophrenia is considered broad and severe, with longitudinal studies using the global cognitive measures showing people with schizophrenia have premorbid IQ deficit 8 points below those of healthy controls (Woodberry et al., 2008)

and post-onset IQ deficits of 14 points after a first-episode (Mesholam-Gately et al., 2009). There is still debate as to whether cognitive impairment increases throughout adulthood, with some longitudinal studies finding evidence of this (Meier et al., 2014, Zanelli et al., 2019). Low IQ is implicated in risk for developing the schizophrenia (Zammit et al., 2004) as well as earlier onset and poorer outcomes thereafter (Kremen et al., 2001). In a longitudinal birth cohort study, Mollon et al (Mollon et al., 2018) were able to further separate IQ deficits into verbal and nonverbal deficits, finding that verbal deficits appear in early childhood, remaining static thereafter, whereas nonverbal and full-scale IQ deficits continue to decline through adolescence and early adulthood. These findings support that a dynamic process during development may be the cause of cognitive dysfunction, with increasing cognitive lags being present during critical periods of development. There is evidence that high premorbid IQ may counteract genetic risk (Barnett et al., 2006, Watson and Joyce, 2015) or lead to improved outcomes following illness onset (David et al., 1997, Kremen et al., 2001, Leeson et al., 2011). The potential impact and mechanisms of this “cognitive reserve” are detailed later in this chapter.

1.4.1.2 Processing Speed

Processing speed is the speed with which an individual can execute any cognitive operation (Salthouse, 1996). Processes measured by this domain are usually straightforward, include motor and perceptual components and are always timed. In some cases, separate measures of motor speed are partialled out giving separate motor and perceptual components of processing speed. Processing speed is most commonly measured using a paper and pencil digit-symbol coding task (Wechsler, 2011a) or the Trail Making Test part A (Reitan, 1958), with the digit-symbol task shown to be the most

sensitive to detecting processing speed deficits in individuals with schizophrenia as well as a range of other illnesses (Dickinson et al., 2007a, Gonzalez-Blanch et al., 2011). This digit symbol task involves matching a set of number-coded symbols to their corresponding numbers as quickly as possible. Performance is calculated by the number of correct responses in a set amount of time.

Processing speed performance declines as a function of normal aging (Kaufman et al., 1989) and has been shown to be the most impaired cognitive construct in those with schizophrenia (Dickinson et al., 2007a, Schatz, 1998, Krieger et al., 2001). The processing speed hypothesis (Rodriguez-Sanchez et al., 2007) attributes deficits in processing speed to being at the core of impairments in other cognitive domains in schizophrenia and FEP. Many studies support this view (Dickinson et al., 2007a, Dickinson and Harvey, 2009, Leeson et al., 2009) whilst others have identified alternative core deficits (Fioravanti et al., 2005) which, along with processing speed, correspond to the most impaired compared to healthy controls in meta-analyses (Mesholam-Gately et al., 2009).

Understanding the neurobiological constructs and circuits underlying performance on processing speed tasks may improve understanding of the aetiology of the schizophrenia. This has evolved from attempts to localise processing speed to specific brain structures (such as the prefrontal cortex, hippocampus and left superior temporal gyrus) to the understanding of the role of grey and white matter integrity and complex neural circuit dysfunction (Sanfilippo et al., 2002, Dickinson et al., 2007a).

1.4.1.3 Working Memory

Memory is a multi-component construct with a long history of speculation over the conceptualisation and distinction of different memory systems. Memory can be divided

into long- and short-term memory, declarative and procedural memory as well as their various subcomponents (Baddeley, 2010). Working memory is an updated concept of short-term memory, a “store” where memory can be temporarily held or manipulated. Baddeley (Baddeley, 1995) conceptualised working memory as an active process necessary for the completion of a range of neurocognitive tasks such as comprehension, learning and reasoning. Baddeley’s more recent conceptualisation of working memory includes the central executive system which manipulates and guides information within the storage buffers, and the phonological loop and visuospatial sketchpad which assist with the rehearsal of auditory and visual inputs respectively (Baddeley, 2010). There was also the addition of the episodic buffer necessary for the integration of semantic and long-term memory in working memory (Repovs and Baddeley, 2006).

Working memory (and the central executive in particular) is thought to rely upon the successful convergence of multiple cognitive factors (such as attention and cognitive control). Effective working memory capacity tasks rely on effective encoding, storage and retrieval as well as the additional effective manipulation of information.

Working memory tasks can differ in their assessment modality. Examples of early auditory working memory tasks include digit span (Richardson, 2007) and reading span (Daneman and Carpenter, 1980) tasks. However, Gold et al (1997) argued that simple recall of a series of digits did not require cognitive manipulation of stored information hypothesised by the existence of the central executive. Tasks such as the digit-span reversal and letter-number span task which require the reordering of information were therefore created to increase central executive demand characteristics in working memory tasks. Assessments examining visual working memory include the visual n-back (Kirchner, 1958) and visual span tasks (McCarthy and Warrington, 2014).

Large deficits in working memory performance have been shown across almost all studies in schizophrenia and FEP populations (Forbes et al., 2009, Lee and Park, 2005, Mesholam-Gately et al., 2009) including those naïve to antipsychotic medication (Fatouros-Bergman et al., 2014b) and in first-degree relatives of those with schizophrenia (Park, 1995, Seidman et al., 2012).

1.4.1.4 Verbal Learning and Memory

The function of memory is the learning and storing of new information. Verbal memory is a verbal component of declarative memory and is most commonly assessed using verbal word list learning tasks such as the auditory verbal learning test (AVLT) (Schmidt, 1996) and the California verbal learning test (CVLT) (Delis et al., 1988). These measures assess both immediate and delayed recall, with immediate recall likely being a measure of encoding, and delayed recall being a measure of encoding and retrieval (Vakil and Blachstein, 1993, Delis et al., 1991). It is well established that the hippocampus is important in the acquisition and storage of new information (Preston and Eichenbaum, 2013), but verbal learning and memory are thought to rely on an interaction between the prefrontal cortex and the medial temporal lobe structures including the hippocampus (Kennedy and Shapiro, 2004, Hasselmo and Eichenbaum, 2005, Preston and Eichenbaum, 2013).

Verbal memory deficits are well documented and severely impaired in patients with schizophrenia (Goldberg et al., 1989, Hill et al., 2004, Cirillo and Seidman, 2003, Aleman et al., 1999, Heinrichs and Zakzanis, 1998), and present at first-episode (Bilder et al., 2000) and antipsychotic naïve patients (Fatouros-Bergman et al., 2014b). Verbal memory impairments are one of the strongest predictors of functional outcomes,

quality of life and poor performance of daily life skills (Green et al., 2000, Verdoux et al., 2002, Fujii and Wylie, 2003).

1.4.1.5 Executive Functions

Executive functions were first characterised as the ‘central executive’ by Baddeley and Hitch (1995) and later defined by Lezak (2004) as having four components: goal formations, planning, goal-directed behaviours and effective performance. The concepts and components of executive functions have since been broadened with low agreement on the exact constructs falling into the executive function category (Jurado and Rosselli, 2007) These are generally processes that optimise performance in the face of uncertainty and have included: activity initiation, inhibition of irrelevant information and flexibility, evaluation and regulation of thinking, and action. The terms “reasoning and problem-solving”, “frontal-lobe functions” and “cognitive control” have sometimes been used to delineate from the central executive processes of working memory (Nuechterlein et al., 2004). There is general agreement that executive functions include high-level cognitive functions responsible for behaviours necessary to live an independent and productive adult life (Lezak, 2004) and that executive functions are primarily mediated by the frontal lobes (Otero and Barker, 2014) although more recently there is the view that a broad range of cortical areas and distributed networks are involved in executive processes (Reichenberg et al., 2009).

Executive function is measured using a wide range of neuropsychological tests which include the Wisconsin Card Sorting Test (Heaton et al., 1993), the Towers of Hanoi (Hinz et al., 2013) tasks and the Controlled Oral Word Association Test (COWAT). Meta-

analyses have found that executive function is severely impaired in those with schizophrenia (Heinrichs and Zakzanis, 1998) and soon after a FEP (Mesholam-Gately et al., 2009) regardless of the test used.

1.4.1.6 Attention

Definitions of attention (and vigilance) vary widely, with some including it within the category of processing of information and others believing it functions entirely independently of information processing (Lezak, 2004). Broadly speaking, attentional resources are finite and encompass both automatic attention (or reflex) and controlled, voluntary attention. Attentional deficits are considered a core feature of schizophrenia (Keefe and Harvey, 2012, Braff, 1993, Nuechterlein et al., 2015) and deficits span sustained attention, attentional control and selective attention. The most commonly studied area is sustained attention. Sustained attention tasks are separable from attentional control and selective attention, which may have heavy reliance on working memory. Sustained attention tasks are most commonly continuous performance tasks (CPT) which require the participant to respond to a target over a sustained period. Such tasks are able to evaluate focussed readiness. An example of a CPT task is the Cambridge Neuropsychological Test Automated Battery (CANTAB) rapid visual information processing (RVP) CPT (CANTAB®, 2017) which requires participants to focus on the centre of a screen where numbers are presented quasi-randomly at a rate of 100 per minute. Participants are asked to respond by pressing a button when seeing a particular sequence of numbers (3-5-7). Deficits in sustained attention are generally thought to be large, present in first episode groups, in those at high-risk for psychosis and in first-degree relatives of those with schizophrenia (Cornblatt and Keilp, 1994,

Agnew-Blais and Seidman, 2013, Caspi et al., 2003, Appels et al., 2003, Mesholam-Gately et al., 2009)

1.4.1.7 Visual Learning and Memory

As with verbal memory, visuospatial learning and memory involves encoding and subsequent recall, but of non-verbal material. Tasks assessing this involve either the recognition of faces, (Ezzyat and Olson, 2008) or objects, such as the Rey Osterreith Complex Figure [(Shin et al., 2006). Most of these tasks involve a period of learning, a delay and then a recall period after a set amount of time. A computerised task measuring visual learning is the CANTAB paired associates learning (PAL) task (CANTAB®, 2017), which asks participants to identify in which boxes they saw a particular unfamiliar pattern. Visual memory has been shown to partially, rather than wholly separate from verbal memory and found to be severely impaired, albeit not quite as impaired as verbal memory, in those with schizophrenia and schizoaffective disorder (Reichenberg et al., 2009, Heinrichs and Zakzanis, 1998). Visuospatial impairment as marked by failure on the PAL task has been shown to a potentially promising marker of clinical severity at onset in FEP patients (Barnett et al., 2005).

1.4.2 General vs Specific

Some studies support variability in specificity and magnitude of cognitive impairment in schizophrenia, including in first-episode groups (Fioravanti et al., 2005, Mesholam-Gately et al., 2009, Kravariti et al., 2009). Others support a multifactor structure of neuropsychological test performance indicating deficits observed in episodic memory, processing speed, attention, working memory, and reasoning and problem solving

ability (Nuechterlein et al., 2004). Relative to healthy controls, some patients show impairments in the majority of, or all cognitive domains, whereas others show deficits in only a proportion of domains. Regardless, there remains significant heterogeneity in the extent of domain impairments. This variation may result from the effects of individual differences in underlying pathophysiology of the illness or may reflect differential neuronal dysfunction resulting from genetic subtypes (Palmer et al., 2009, Dickinson and Harvey, 2009, Joyce and Roiser, 2007).

However, it is important to note that cognitive domains have been shown to be strongly positively correlated with one another (known as the positive manifold), sharing a general cognitive ability factor (Dickinson et al., 2004, Dickinson et al., 2006, Dickinson and Gold, 2008) referred to as “g” (Jensen, 1998) as well as a general factor of cognitive decline (Tucker-Drob et al., 2019). Using structural equation modelling, Dickinson et al (2008a) examined the structure of “between-group” cognitive deficits (comparing schizophrenia patients and healthy controls) and found a generalised impairment across cognitive domains, indicating a deficit at the level of g. The same research group offer two possible explanations for this loading on a general cognitive ability factor: lack of orthogonal cognitive tests, meaning that neuropsychological measures rely on several cognitive domains for successful completion; or that groups with schizophrenia have generalised cognitive impairment (Dickinson et al., 2008a).

1.4.3 Developmental, Deteriorating or Both?

The basis of the neurodevelopmental hypothesis of schizophrenia can be dated as far back as 1891 to what Thomas Clouston referred to as “developmental insanity”. This view was replaced with the view that schizophrenia was a deteriorating illness with adult onset: “dementia praecox” implying a worsening trajectory of cognitive functioning over

time. Many felt that the observation of cognitive deficits and enlarged ventricles was support for a neurodegenerative view of the illness (Johnstone et al., 1976).

In the 1980's, evidence that people with schizophrenia were more likely to be born during winter and spring months indicated a potential role of prenatal exposure to infections (Torrey et al., 1997), and that affected monozygotic-twin discordant for schizophrenia were exposed to more pre- and perinatal hazards than unaffected twins. These "epiphenomena" (Murray et al., 2017) led to a resurgence of interest in the neurodevelopmental hypothesis of schizophrenia which was officially proposed by Weinberger and Marcenko (2003). Due to a lack of longitudinal cohort studies, the course of cognitive impairment in schizophrenia has remained unclear (Mollon et al., 2018). Most studies suggest that cognitive deficits are present long before illness onset (Cornblatt et al., 1999, Mollon et al., 2018, Kahn and Keefe, 2013) with some worsening during the prodromal stage (Simon et al., 2007). Studies have shown that there appears to be no post-onset decline beyond that of benign aging affecting IQ and gross cognitive status (Kurtz, 2005, Szoke et al., 2008, Bozikas and Andreou, 2011, Hoff et al., 1999, Leeson et al., 2009, Rund, 1998) but few studies have researched schizophrenia in older adults and those which have suggest there may be slow and gradual cognitive decline (Fucetola et al., 2000, Harvey et al., 1999).

Meta-analyses of premorbid IQ in schizophrenia detect a medium-sized (8 IQ-point) impairment in premorbid IQ in those who go on to develop schizophrenia (Woodberry et al., 2008) and an even larger impairment following onset of symptoms (Mesholam-Gately et al., 2009). Findings from longitudinal studies support this, showing that individuals experience decline in cognitive functioning from pre-morbid levels detectable at illness onset, with stability thereafter (Heaton et al., 2001, Hoff et al.,

2005). Relatively few studies have charted the course of cognitive functioning from pre-morbid to post-onset of psychosis. Meier et al., (2014) assessed participants at ages 7, 9, 11, 13 and 38 and found a differential progression of deficits across cognitive domains in those who went on to develop schizophrenia; verbal deficits appeared early and remained stable thereafter but processing speed deficits gradually increased from childhood to early adolescence. Consistent with findings from meta-analyses, they found a 9-point IQ deficit in childhood in those who were later diagnosed with schizophrenia (relative to a healthy control group) and a 15-point IQ deficit in adulthood. Similarly, a recent longitudinal prospective cohort study of parents and children found that a group who went on to develop a psychotic disorder showed continuing IQ deficits from 18-months to 20 years (Mollon et al., 2018). In this group, full-scale and nonverbal IQ deficits progressed through adolescence whereas verbal IQ declined in the early childhood period and remained stable thereafter. Reichenberg et al (Reichenberg et al., 2010) had postulated that cognitive deficits may be the result of two differential processes but these more recent findings (Mollon et al., 2018) support that a single dynamic process during development may be the cause of cognitive dysfunction, with increasing lags following critical periods of development (Pantelis et al., 2009). These studies support a progressive neurodevelopmental view of the illness.

The observation that cognitive deficits predate clinical presentation, remain relatively stable following symptom onset and do not fluctuate with symptoms is important in understanding the aetiology and neurophysiology of the disorder. The supposed stability of cognitive deficits brings into question Kraepelin's hypothesis that schizophrenia is a neurodegenerative disorder and gives weight to the role of abnormal neurodevelopment as a putative risk factor for the illness. A model of progressive

neurodevelopmental impairment (or developmental lag) is thought to account for the discrepancy between premorbid and post-onset cognition, though longitudinal studies over several decades such as that by Zanelli et al., (2019) continue to raise the question of whether the cognitive impairment in schizophrenia results from both abnormal development and later deterioration (Figure 1.1).

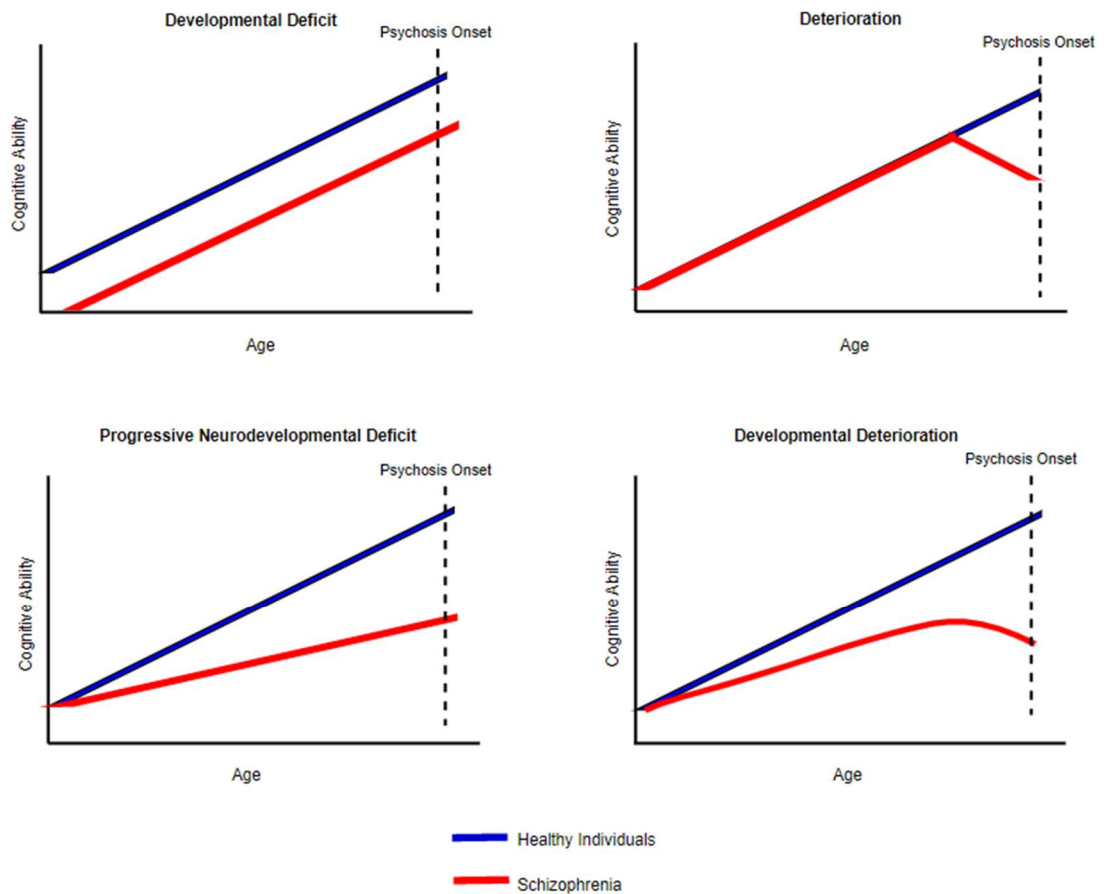


Figure 1.1 – Schematic of proposed models of cognitive impairment in schizophrenia

1.4.4 Neuropsychological Normality

Despite cognitive impairment being considered a core component of schizophrenia and FEP, there remains a proportion of patients with schizophrenia who have putatively intact neuropsychological functioning. Palmer et al (Palmer et al., 1997) found 27% of

their group of patients with schizophrenia to be without cognitive impairment and posed the question “is it possible to be schizophrenic and yet neuropsychologically normal?” and suggested that that pathophysiology underlying cognitive impairment might be distinct from the core symptoms of the illness. In 2005, Wilk et al., (2005) responded to Palmer et al., (1997), with an article titled “No, it is not possible to be schizophrenic and yet neuropsychologically normal”. This conclusion came after comparing 64 patients with schizophrenia, matched within 3 IQ points to 64 healthy controls, and finding markedly different cognitive profiles. They found that those with schizophrenia had comparative deficits in visual processing and memory, but superior perceptual organisation and verbal comprehension. Other studies have found neuropsychologically normal patients with schizophrenia to perform less well than healthy controls on at least one cognitive domain, including learning (Heinrichs and Awad, 1993, Wilk et al., 2005, Palmer et al., 1997), processing speed (Wilk et al., 2005, Heinrichs et al., 2015) and abstraction-executive function and perceptual motor speed (Kremen et al., 2000). Allen et al., (2003) also found evidence that neuropsychologically normal patients with schizophrenia perform worse on a number of neuropsychological measures and would be better described as “high-functioning” (Allen et al., 2003). The question of whether some patients have intact cognitive function remains, along with whether those with putatively preserved cognitive function represent an etiologically different subgroup. Following this, questions have emerged regarding whether intact cognitive functioning is the result of a less severe illness, different genetic and environmental triggers, or simply greater cognitive or brain “reserve”.

1.4.5 Neurocognition and Symptoms

One might expect cognitive deficits to be closely related to psychotic symptoms, but both cross-sectional and longitudinal studies show symptomatology and neurocognitive performance to be, for the most part, independent (Nieuwenstein et al., 2001). One way of testing the association between neurocognition and symptoms is to assess patients during acutely symptomatic phases of the illness and again during periods of symptom remission. Such studies have found cognitive performance does not improve during remission periods (Heaton et al., 2001). Indeed, much evidence for the separation of neural systems involved in mediating cognitive performance and symptomatology comes from robust evidence that clinical response to neither first, nor second-generation antipsychotics has a profound effect on cognitive performance, on either specific cognitive domains or global cognition (Brissos et al., 2011). Rather than being state related, cognition appears to be a stable trait marker for schizophrenia, found to be present long before the onset of illness (Mollon et al., 2018), present in those deemed to be at high-risk for developing the disorder (ARMS) (de Paula et al., 2015) and present (albeit to a lesser extent) in first-degree relatives of those with schizophrenia (Snitz et al., 2006). Correlational studies have found some associations between certain cognitive functions and symptom severity, primarily in relation to negative and disorganised symptoms. These are best explained as a result of overlap between the processes being assessed. For example, poverty of speech is a negative symptom frequently present in schizophrenia and may inversely correlate with performance on a test of verbal fluency (VF) such as the (COWAT).

1.4.6 Neurocognitive Deficits and Outcome

Research into outcomes following an episode of psychosis has been hampered by the lack of consensus in defining the term 'outcomes'. Broadly, the term can be split into two categories: clinical outcomes and functional outcomes. The lack of consensus in defining these terms, along with variability in outcome measures used in clinical studies has made it difficult to draw cross-study comparisons of markers of good and poor prognosis (Allott et al., 2011). Cognition has been shown to be a more reliable predictor of functional outcomes in schizophrenia than symptom severity in both cross-sectional (Green et al., 2000, Fett et al., 2011) and longitudinal studies (Green et al., 2004, Leeson et al., 2009). This association has been highlighted by the formation of consensus groups aimed at targeting the remediation of cognitive deficits in an effort to improve functional outcomes in schizophrenia (Marder and Fenton, 2004, Carter and Barch, 2007).

A major limitation in establishing the association between cognition and outcomes is the scarcity of longitudinal studies investigating this relationship. Cross-sectional studies do not allow causal conclusions to be made (Smith et al., 2002), and many of the longitudinal studies have assessed outcome measures within a year of neurocognitive testing (Fujii and Wylie, 2003). This being said, both cross-sectional (Fett et al., 2011, Green et al., 2000, Ventura et al., 2009) and longitudinal studies have consistently shown cognition to be related to functional outcomes. In 2004, a review by Green et al., (2004) of 18 longitudinal studies with a minimum 6-month follow-up period, shows that cognition reliably predicts community functioning at a later point.

Relationships between specific cognitive deficits and specific functional outcomes have been observed in numerous studies (Green, 2006, Green et al., 2000). Declarative

memory has been shown to correlate with social and occupational functioning and independent living, whilst working memory and executive functions are thought to be closely related to independent living and occupational functioning (McGurk and Meltzer, 2000). Sustained attention is also shown to be particularly important for social and occupational functioning (Green, 1996, Green et al., 2000).

Despite the importance of individual cognitive domains for successful functioning, measures of global cognition, such as IQ, account for the largest amount of variance in functional outcomes (Green et al., 2000). This is to be expected, given that schizophrenia is associated with multiple cognitive impairments, as opposed to deficits in isolated cognitive domains. The relative stability of cognitive impairments following onset of psychosis, mean they are a good candidate as predictors of subsequent outcome. Indeed, cognitive therapies aimed at remediating cognitive impairment in schizophrenia have shown durable effects on cognition are related to improvements in functioning (Wykes et al., 2011).

The association between neurocognition and clinical outcomes is not equally well documented. Examining individual cognitive domains, there is some evidence that those with poorer clinical outcomes perform more poorly on verbal memory tasks (Bodnar et al., 2008) but evidence of a relationship between other cognitive domains and clinical outcomes remains ambiguous (Lepage et al., 2014). Research looking at remission as a clinical outcome measure has shown higher neurocognitive ability is associated with a greater likelihood of achieving remission (Kopelowicz et al., 2005, Helldin et al., 2006), whilst other studies have found no relationship between cognitive functioning and clinical outcome (Buckley et al., 2007, Li et al., 2010a)

1.4.7 Neurocognition and Neuroimaging

Evolutionary increasing brain size is associated with increased intelligence (Potts, 1998). Advances in brain imaging techniques have meant that researchers are now better able to not only accurately measure the size of whole and sub-regional brain volumes and cortical thickness, but to also establish relationships between brain function and cognitive performance. There is a large literature investigating neural correlates of general intelligence. Using positron emission tomography (PET), Duncan et al., (2000) found that rather than diffuse employment of multiple brain regions, both high-g and low-g tasks were associated with activation of lateral frontal regions. These findings suggest that general intelligence may hinge on specific frontal systems which are important for behavioural control. The importance of the frontal lobes (particularly the prefrontal cortex) in general intelligence has been supported by numerous other imaging studies (Duncan, 2005, Duncan, 1996, Prabhakaran et al., 1997), as well as the observation that global intelligence can become greatly impaired in those who suffer frontal lobe lesions (Duncan et al., 1995).

An alternative view suggests that general intelligence is the average performance of independent cognitive functions which are separable, as evidenced by test specific performance variance over and above confounders such as motivation and fatigue (Bartholomew et al., 2009). The view that intelligence is the average or combined activity of specific cognitive domains mediated by specialised brain areas (Jung and Haier, 2007) has led to neuroimaging work identifying brain regions necessary for different cognitive modalities. In a review of 37 modern neuroimaging studies examining intelligence and its correlates, (Jung and Haier, 2007) concluded that differences in a “parieto-frontal” network of frontal and posterior brain regions explain individual

differences in intelligence. Functional MRI (fMRI) studies have reported a plethora of brain regions involved in cognitive processes, although these can vary slightly depending on the exact task employed. These regions include: frontal areas for executive functions (Kane and Engle, 2002); the dorsal lateral prefrontal cortex (DLPFC) and posterior parietal cortex for working memory (Hahn et al., 2018) the anterior cingulate for inhibition and response selection (Turken and Swick., 1999); parietal regions for sensory integration and abstraction (Prabhakaran et al., 1997); medial temporal regions (including the hippocampus, dorsolateral and ventrolateral prefrontal cortex) for long-term memory (Ragland et al., 2009) and temporal and occipital regions for the processing of sensory information (Jung and Haier, 2007). In schizophrenia, the majority of studies report hypoactivation, compared with healthy controls, though some report hyperactivation in areas such as the dorsolateral prefrontal cortex during working memory tasks (Karlsgodt et al., 2009). Hyperactivation is usually thought to be due to inefficient recruitment of neural resources (Green et al., 2019). When activation is found in regions not typically associated with task performance, this is viewed as evidence of compensatory recruitment (Tan et al., 2007).

1.4.8 Neurocognition and Inflammation

In recent years there has been increased interest in the complex interactions between the immune system and the brain (Khandaker et al., 2015). A plethora of hypotheses have been put forward linking the immune system with the aetiology of mental health problems and is supported by curious epiphenomena (Murray et al., 2017) surrounding risk for schizophrenia (such as prenatal exposure to viral infections). Amongst these have been the implication of innate and adaptive immune responses in both

neurodevelopmental and neurodegenerative models of the pathogenesis of schizophrenia. There is growing evidence that immune and inflammatory mechanisms may also play an important role in cognitive functioning (Roberts et al., 2009) and in schizophrenia (Fond et al., 2018, Ribeiro-Santos et al., 2014), with evidence that low grade systemic inflammation increases risk for schizophrenia even when controlling for potential confounders (Khandaker et al., 2014, Kappelmann et al., 2019). Studies looking at markers of innate inflammatory response, have shown that schizophrenia is associated with disruption to levels of pro-inflammatory cytokines (released by microglia) in both those with long-standing (Potvin et al., 2008) and first-episode populations (Upthegrove et al., 2014). A meta-analysis by Miller et al., (2014) examining cytokine levels in both acute-relapse and FEP patients suggests several cytokines as potential state-markers, due to being increased during acute exacerbations and normalised with antipsychotic treatment (Interleukin (IL)-1 β , IL-6, and Tumor Growth Factor (TGF)- β) whilst others may be trait markers due to being elevated and remaining so even after antipsychotic intervention (IL-12, IFN- γ , TNF- α , and sIL-2R). In a meta-analysis of medication-naive FEP patients, Upthegrove et al., (2014) found significant effect sizes for elevated levels of IL-1 β , sIL-2r, IL-6, and TNF- α but non-significant effect size estimates for IL-2, IL-4, and Interferon- γ (IFN- γ).

A reliable marker of subclinical and systemic inflammation is the level of CRP found in blood. It is most commonly shown in high-sensitivity assays (hs-CRP) (Windgassen et al., 2011). Many studies (Bulzacka et al., 2016, Dickerson et al., 2007, Dickerson et al., 2013, Frydecka et al., 2015, Joseph et al., 2015, Micoulaud-Franchi et al., 2015) have found elevated CRP levels in people with schizophrenia compared to healthy controls. Fan et al., (2007) found increased CRP to be associated with severity of symptoms in people

with psychosis, but in a notably small sample which was not replicated by other investigations (Bulzacka et al., 2016, Dickerson et al., 2007, Johnsen et al., 2016). A meta-analysis, however, found CRP was associated with positive, but not negative symptoms and was not altered by antipsychotics (Fernandes et al., 2016). Although still uncertainty about the nature of the relationship, support from Mendelian randomisation studies suggests associations between CRP and IL-6 and schizophrenia are likely to be causal (Upthegrove and Khandaker, 2019)

Pathways between systemic and inflammation and cognitive dysfunction have been hypothesised in both human and animal studies. In animal studies, cytokines have been found to have a role in cognitive functioning via neurogenesis (Borsini et al., 2015), synaptic plasticity (McAfoose and Baune, 2009), synaptic pruning (Mottahedin et al., 2017), memory consolidation (Alboni et al., 2014) and hypothalamic pituitary adrenal axis response (Wang and Dunn, 1998). In human studies, there is evidence that systemic inflammation mediates age-related cognitive deficits and in particular processing speed (Bettcher et al., 2014), memory (Teunissen et al., 2003) and executive function (Heringa et al., 2014) with the view that microglia may be a key mechanism for neuropsychological impairment via the propagation of pro-inflammatory cytokines (Lin et al., 2018). The microglia hypothesis of schizophrenia postulates that microglia activation can lead to impairments in neurogenesis, white matter abnormalities and neurodegeneration resulting from the activation of pro-inflammatory cytokines (Monji et al., 2009). Neuroinflammation can therefore result in structural and functional impairments in areas such as the hippocampus (Sankowski et al., 2015, Varatharaj and Galea, 2017) and substantia nigra (Brydon et al., 2008), which have been associated with cognitive impairments. Lin et al., (2018) suggest that since microglial cells are

widespread throughout the brain (van Horssen et al., 2019), cognitive processes which rely on the coordination and integration of multiple areas of the brain (such as processing speed) may be more vulnerable to impairment resulting from neuroinflammation.

Studies looking at the relationship between cytokine levels and cognition in populations with schizophrenia have yielded mixed results (Misiak et al., 2018). Associations have been found between IL2 and the positive and negative syndrome scale (PANSS) cognitive factor (Tan et al., 2007), digit span and non-verbal cognition (Asevedo et al., 2014) but other studies have found no significant associations (Fillman et al., 2016, Zhang et al., 2016). Similarly, associations have been found between increased cytokine IL-6 levels and poorer visuomotor processing speed, visual attention, semantic memory, working memory, task-switching and a measure of executive control (Frydecka et al., 2015). Some studies have found IL6 is associated with an index of cognitive deterioration e.g. (Frydecka et al., 2015), but others have found no relationship between IL-6 and any cognitive measure (Hori et al., 2017). The case of TNF-a is slightly more complex. Several studies have assessed TNF-a and its receptors in schizophrenia (Hori et al., 2017, Lv et al., 2015, Zhang et al., 2002, Zhang et al., 2016). Lv et al 2015 (Lv et al., 2015) found a significant negative correlation between TNF-a and PANSS cognitive factor score, and Yang et al., (2016) found a negative effect of interaction between levels of brain derived neurotrophic (BDNF) factor and TNF-a on the same measure. Other studies have found relationships between other cytokines and cognitive functioning, including IL-18 (Wu et al., 2016, Fillman et al., 2016), IL-1B (Fillman et al., 2016), IL-10 (Xiu et al., 2014) and IL1RA (Lotrich et al., 2014).

Despite various cognition-cytokine relationships, the most consistent finding is that cognitive functioning is poorer in those with elevated serum levels of inflammatory biomarker C-reactive protein (CRP) (Dickerson et al., 2007, Johnsen et al., 2016, Bulzacka et al., 2016, Misiak et al., 2018) with some evidence that this may be explained by an inverse relationship between CRP levels and cortical thickness (Jacomb et al., 2018). Elevated CRP has been associated with worse performance on a range of cognitive tasks including global cognition (Misiak et al., 2018, Dickerson et al., 2007, Bulzacka et al., 2016), memory and attention (Johnsen et al., 2016, Bulzacka et al., 2016), processing speed and learning (Bulzacka et al., 2016) in populations with schizophrenia. Longitudinal studies have not shown CRP at baseline to be predictive of risk for later development of psychiatric disorders, with the exception of a study by Wium-Anderson et al., (2014) which showed higher baseline CRP to be predictive of late or very-late onset schizophrenia. Longitudinal studies indicating a causal relationship of immune markers in the pathophysiology of cognitive deficits in schizophrenia and psychosis are rare. One study by Dickerson et al., (2013) found that CRP levels at baseline did not predict change in cognitive performance over time.

Studies so far have been limited and often confounded by not controlling for additional variables which affect inflammatory profiles, such as smoking status and body mass index (BMI). Interestingly though, CRP does not appear to be altered by antipsychotic medication (Fernandes et al., 2016). Findings of elevated inflammatory profiles in those experiencing psychosis have led to an interest in the anti-inflammatory properties of antipsychotic medication and the trialling and development of anti-inflammatory interventions with the aim of treating symptoms and improving cognition, although success thus far has been limited (Deakin et al., 2018, Cho et al., 2019). Establishing the

relationship between cognitive dysfunction (a core component of schizophrenia) and systemic inflammation is important if we are to have a better understanding of the aetiology of the illness, factors underlying poor outcomes, as well as remedial approaches.

1.4.9 Neurocognition Remediation Strategies

Remediation of neurocognitive impairment is a key target for improving outcomes and quality in life of people with schizophrenia (Wykes and Huddy, 2009). Major efforts have been made to develop and test both psychological and pharmacological interventions. Cognitive remediation therapy (CRT) has shown most promise. CRT interventions generally involve either drill and practice or drill and strategy modalities, with drill and strategy forms of therapy thought to show the most improvement as it can be translated to functional gains (Wykes et al., 2011). A meta-analysis of different forms of CRT for schizophrenia has shown a medium effect on cognitive gains which are durable at follow-up periods and translate into functional gains (Wykes et al., 2011). In the UK, CRT is now recommended in Scotland (Scottish Intercollegiate Guidelines et al., 2013), but at last review, the National Institute for Care and Excellence (NICE), 2014) which makes evidence-based guidelines for healthcare in England requested further evidence of effectiveness for inclusion in their guidelines.

A meta-analysis examining the evidence for the effectiveness of pharmacological interventions (combined across all neurotransmitter systems) for cognitive enhancement in schizophrenia revealed a small significant effect on overall cognition (Sinkeviciute et al., 2018). Many different neurotransmitter targets have been put forward, including GABA, dopamine, serotonin, acetylcholine, glutamate and

noradrenaline, with the greatest evidence for a positive effect on overall cognition coming from studies investigating drugs targeting the glutamate system. Studies investigating pharmacological interventions for many of the other systems were too few to provide adequate power and many contained relatively small numbers of participants. This meta-analysis (Sinkeviciute et al., 2018) included a 'miscellaneous' or 'Modafinil/Armodafinil' subgroup. Modafinil has been shown to selectively enhance working memory in FEP (Scoriels et al., 2012) and reviews of single-dose studies of Modafinil have reported benefits on cognition in schizophrenia (Scoriels et al., 2013). However, the majority of studies with longer treatment duration included in the meta-analysis, did not. Inconsistent results highlight the need to select appropriately sensitive cognitive tests when assessing interventions for remediating neurocognition in schizophrenia (Lees et al., 2017).

1.5 Cognitive Reserve

1.5.1 The Concept of Cognitive Reserve

The observation that the degree of brain pathology is not always indicative of symptom severity, as seen in dementia (Liu et al., 2012, Pernecky et al., 2009), led to the proposal that some people may have greater protection, or coping ability than others in the face of similar brain pathology (Stern, 2012). This led to the concept of "brain reserve" (Katzman, 1993) which hypothesised that it is the quantifiable inter-individual differences in brain "hardware" one has in reserve, which accounts for the amount of pathology necessary for the manifestation of clinical symptoms. This "hardware" may relate to intracranial volume, dendritic branching or neuronal or synapse count (Stern, 2002, Sole-Padulles et al., 2009, Mortimer et al., 2005). Stern (Stern, 2002) proposed the

idea that this quantifiable brain “hardware” is a “passive” model of reserve, with functional impairment being inevitable once a critical ratio of pathology to residual hardware (i.e. reserve) is exceeded.

An alternative explanation is that the clinical expression of cognitive impairment is not mediated by quantitative measures of brain “hardware”, but rather that active engagement of cognitive processes or compensatory mechanisms accounts for individual differences in the ratio of brain pathology to functioning. This active model is termed “cognitive reserve” (CR). The concept of CR suggests the cognitive processes which are important in mediating the degree of clinical expression of an illness, are altered based on life experiences. Having “high” CR generally means that a greater level of pathology is necessary in order to reach the threshold for clinical loss of function, i.e. someone with high CR would be more resilient to showing clinical symptoms than someone with low CR with equivalent neuropathology.

Active engagement of cognitive processes has been shown to result in structural and neural changes, demonstrating the capacity for local plastic change in the adult brain (Maguire et al., 2000). This blurs the distinction between “active” and “passive” reserve with Barulli and Stern (2013) introducing the terms “neural reserve” (addressing the way in which neural networks have developed over the course of the lifespan in response to cognitive experiences as well as innate capacity) and ‘neural compensation’ (referring to the adoption of compensatory neural networks to accomplish tasks which have been affected by pathological or age-related changes). Differences in performance between healthy controls are explained by the concept of neural reserve, which posits that these differences may account for differential susceptibility to pathology. Someone with high neural reserve may have more efficient cognitive networks, requiring less increase in

neural activity than someone with poorer neural reserve in order to perform an equivalent task. Alternatively, neural reserve may come in the form of higher capacity networks, which are able to activate to a greater degree when facing more difficult tasks, or greater flexibility in network selection when choosing which network to employ to successfully complete a task. The concept of neural reserve is supported by intelligence research, which has related higher intelligence to higher neural efficiency (Neubauer et al., 2002, Neubauer and Fink, 2008, Neubauer and Fink, 2009, Vitouch et al., 1997, Jausovec, 2000). Neural compensation refers to the adoption of compensatory neural networks to complete a task, in situations where primary task-related networks are disrupted due to neuropathological or age-related disruption. Those with higher CR relating to neural compensation may have superior ability to appropriate compensatory neural networks than those with lower CR.

Brain reserve and CR initially began as distinct concepts, but changes in the understanding of brain plasticity indicate that this boundary should be softened (Barulli and Stern, 2013) with changes to the brain's hardware increasingly being considered the result of changes in behaviour and exposure to cognitive experiences (Penades et al., 2017).

The concept of CR has been used to explain differential symptom expression and functional outcomes in dementia (Stern, 2012), traumatic brain injury (TBI) (Barbey et al., 2014) and multiple sclerosis (MS) (Sumowski et al., 2013, Nunnari et al., 2016). Studies of TBI offer a more simplified model of CR than other disorders, since factors traditionally associated with both brain reserve and CR are independent of risk of experiencing a TBI. This makes it possible to infer reserve by establishing the

discrepancy between pathology and symptom expression. In dementia, the picture is not so divergent. In Alzheimer's disease (AD) the neurodegenerative nature suggests that cognitive reserve may act only as a protective factor, delaying illness onset. The concept of reserve is also muddied by the role of environmental factors (such as diet and exposure to toxins) in the risk for developing the illness, and the interaction between environment and CR (such as measured by educational attainment) in the risk for symptom expression. Longitudinal studies have found that the risk for developing AD is modified by educational years and premorbid IQ, but that following symptom onset, decline is faster in those with higher CR. This indicates that CR operates as a protective factor delaying clinical expression, until this is eventually overcome by sheer neuropathological load (Rolstad et al., 2009).

Barnett et al., (2006) were the first to hypothesise that cognitive reserve may play an important role in the risk for developing neuropsychiatric disorders and may bear a relationship to the clinical expression and functional outcomes in these disorders. This is of particular interest in schizophrenia, where low intelligence is well established as a risk factor for developing the disorder.

1.5.2 Cognitive Reserve in Schizophrenia

The concept of CR is complicated further in schizophrenia, with the neurodevelopmental nature of the disorder likely to impact the degree to which reserve can be accumulated. CR has been implicitly studied in schizophrenia using premorbid intelligence as a proxy measure of the risk for development of the disorder and the relationship to outcome. An inverse relationship between premorbid IQ and risk for development of non-affective

psychosis is well established (David et al., 1997, Crow et al., 1995, Kremen et al., 2008, Cannon et al., 2002). Lower premorbid IQ is understood to have a negative effect on functional outcomes in this population (Leeson et al., 2011), with this relationship being stronger in schizophrenia than in other forms of mental illness (Koenen et al., 2009, Gale et al., 2010).

In order to establish whether CR is an active process in schizophrenia, it is important to establish whether the inverse linear relationship between IQ and risk for developing schizophrenia exists across the entire IQ range. If cognitive reserve actively protects against the risk for reaching the criteria for a diagnosis of schizophrenia, one would expect this effect to operate across the IQ range. Examining methodologically rigorous cohort studies, Khandaker et al., (2011) showed a robust linear relationship between pre-morbid IQ and the risk for development of schizophrenia, which operated across the entire range of intellectual ability with each IQ point decrement conferring a 3.7% increased risk for developing schizophrenia. This finding was recently replicated in a large army conscript study (Kendler et al., 2015), finding that high IQ also counteracts the impact of genetic liability on risk for schizophrenia. This same study showed that the effect of IQ on schizophrenia risk was stronger in the lower IQ range. In contrast, a large British cohort study found a similar effect of low IQ on risk for schizophrenia but that this relationship only existed in the learning disability range (Schulz et al., 2014).

Cognitive reserve may have influence not only on the likelihood of reaching the clinical threshold for schizophrenia, but also for delaying onset and moderating outcome. Evidence that high CR delays the onset of psychosis comes from studies finding that lower pre-morbid IQ is associated with a lower age of schizophrenia onset (Khandaker et al., 2011). One caveat to this comes from research into cannabis use in schizophrenia.

Cannabis users have been shown to have an earlier age of onset of psychosis than non-cannabis users, but concurrently show higher premorbid IQs (Leeson et al., 2012, Cunha et al., 2013, Ferraro et al., 2013, de la Serna et al., 2010, Schnell et al., 2009, Ferraro et al., 2019). This implicates cannabis use as a trigger for the onset of psychosis which counteracts the protective effect of high cognitive reserve in delaying onset of symptoms (Sami and Bhattacharyya, 2018, Leeson et al., 2012). Evidence for CR as a moderator of functional outcomes comes from longitudinal studies which have shown IQ at psychosis onset is the best predictor of functional outcome at follow-up (Leeson et al., 2009). In contrast, others have shown premorbid IQ to be the best predictor of functioning (van Winkel et al., 2007), raising the question of whether CR deteriorates due to a neurodegenerative process, or whether once established, high CR can continue to contribute to improved outcomes for those with the illness. One method of addressing this question is through studying the cognitive trajectories of patients.

1.5.3 IQ Trajectory in Schizophrenia

There is evidence that CR declines from premorbid estimates in a large subgroup of patients but remains preserved in others (Weickert et al., 2000). Several cross-sectional studies have examined the relationship between IQ trajectories and functioning in schizophrenia. These studies have generally found that there are three main cognitive courses: those with premorbid IQ in the normal range who have similar current IQ when measured following illness onset; those with a normal premorbid IQ which is significantly decreased when measured following illness onset; and those with a premorbid and post-onset IQ below the normal range. Weickert et al., (2000) have since

labelled these cognitive subgroups 'preserved', 'deteriorated' and 'compromised' respectively.

Despite these cognitive groupings being well replicated, they have been arrived at using differing methods. Earlier studies categorised patients using a predefined discrepancy between premorbid and current IQ. 'Preserved' denoted those with a premorbid IQ score of >90 and a current IQ with less than a 10-point reduction; 'deteriorated' denoted patients with a decline of 10 IQ points or more from a pre-morbid IQ >90; and 'compromised' were those with a pre-morbid IQ and current IQ of <90 and no evidence of IQ decline greater than 10 IQ (Weickert et al., 2000, Kremen et al., 2008, Badcock et al., 2005, Joyce et al., 2005). Other studies have categorised patients on the basis of a pre-morbid IQ above the 10th percentile of the distribution of healthy controls and a current IQ being consistent (preserved) or inconsistent (deteriorated) with that expected by their pre-morbid intellect; or with a premorbid and current IQ below the 10th percentile (compromised) (Woodward and Heckers, 2015, Czepielewski et al., 2017). In order to remove any bias in categorising patients, researchers have more recently begun to use mathematical clustering methods to identify true categories within the data (Uren et al., 2017, Reser et al., 2015, Weinberg et al., 2016, Van Rheenen et al., 2017, Lewandowski et al., 2014, Wells et al., 2015). This method allows the number of clusters to be identified computationally and ensure maximum proximity to cluster centres (Lo Siou et al., 2011). Using empirical cluster techniques, most studies in schizophrenia populations with long-standing illness, have identified the same three IQ clusters (preserved, deteriorated and compromised).

Establishing cognitive subtypes could improve diagnostic and prognostic accuracy and may reflect etiological differences with implications for treatment. Few studies to date

have examined IQ cluster trajectory longitudinally, and only one to date has done this in a first-episode cohort (Leeson et al., 2011). However, this used the clinical method of categorisation and to my knowledge, no longitudinal study to date has used an empirical clustering method to identify IQ subtypes and their trajectory in a first-episode population. As a proxy measure of CR, it is important to establish whether these same cognitive subtypes can be empirically detected in a first-episode cohort, their clinical usefulness and relationship to functional outcomes.

1.5.4 Cognitive Subtypes and Relationship to Clinical and Functional Outcomes

Several cross-sectional studies examining the relationship between general intelligence derived cognitive subtypes and outcomes have identified a relationship with clinical symptoms. In a large sample of chronically ill patients (Wells et al., 2015) more negative symptoms were observed in compromised and deteriorated groups than those with preserved cognitive function. The compromised group also reported significantly more severe current hallucinations than the preserved group, whereas the preserved group reported more lifetime delusions. The authors note that these effect sizes represent small to medium effects and may therefore not be clinically relevant. Other studies have similarly found negative symptoms to be greater in compromised than preserved groups in chronically ill patients (Van Rheenen et al., 2017, Czepielewski et al., 2017) whereas another found negative symptoms to be greater in a deteriorated group (Weinberg et al., 2016).

In a longitudinal study of first-episode patients, Leeson et al., (2011) found that at presentation, preserved patients showed lower negative and disorganisation syndrome

scores than the compromised and deteriorated groups. Examining the trajectory of symptoms over time, they found that compromised, deteriorated and preserved groups all improved over a 3-year period on positive and negative symptoms, depression, mania and disorganisation scores, with the exception of the preserved group whose negative symptoms scores did not improve.

Examining the relationship between cognitive subtypes and functional outcomes, Wells et al., (2015) found that outcomes did not differ between those with preserved, and those with deteriorated cognitive function, but that the compromised group were more likely to be unemployed, have fewer friends, and a chronic course without periods of recovery between episodes. Van Rheenen et al., (2017) also found the compromised group to have worse global functioning than the preserved and deteriorated groups. In the only longitudinal study in a first-episode cohort, at 3-year follow-up Leeson et al., (2011) showed the deteriorated group were less likely to be employed than the preserved group, and that the preserved group were likely to have shorter admissions than the compromised group, but found no differences between groups in a global social function score. Longitudinal studies using a data driven approach to examine this relationship early in the course of illness are necessary to elucidate the relationship between CR and clinical and functional outcomes.

1.5.5 Neurocognitive Subtypes and Neuroimaging

Given that cognitive subtypes of schizophrenia are hypothesised to reflect etiological differences, there has been some research into whether changes in brain structure differentiate cognitive subtypes. Categorising patients based on 10th percentile deviation from healthy controls in a mixed schizophrenia and psychotic bipolar group,

Woodward and Heckers (2015) were the first to examine brain volumetric differences between groups. They observed smaller mean intra-cranial volumes (ICV) in their compromised group and, relatively normal ICV but smaller absolute total brain volume (once adjusted for ICV) in their deteriorated group. They argue that this validates the cognitive profile subtypes, indicating a neurodevelopmental deficit resulting in cerebral hypoplasia in the compromised group, and normal development followed by subsequent global cerebral atrophy or dysmaturation in the deteriorated group. In comparison with healthy controls, they also found smaller total brain volumes in the preserved group after adjusting for ICV. This finding indicates that even those with putatively preserved cognition may have some degree of cerebral atrophy.

There has been subsequent support for this argument, with a similar study observing neurodevelopmental and neurodegenerative profiles which mapped on to cognitive subtypes (Czepielewski et al., 2017). Unlike Woodward and Heckers (2015), when accounting for ICV, they found no difference between healthy controls and deteriorated patients in total brain volumes but did find significantly smaller total cortical and gray matter volumes and cortical thicknesses. They also found this in compromised groups but found little evidence of global brain volumetric reductions in preserved cognition groups. These brain abnormalities are evidence for developmental abnormalities in those with low premorbid cognitive function, and of cortical alterations reflecting neurodegeneration in those with normal range premorbid cognition; but latter deterioration. The authors also suggest that there is evidence of additional atrophy in the developmental group indicating this group may have a progressive neurodevelopmental profile. Another, larger study (Van Rheenen et al., 2017) employing a cluster analysis to determine groups found similar evidence of progressive

neurodevelopmental structural abnormalities in the group with the most marked cognitive impairments, but did not find between group differences in ICV. Instead, they found reduced absolute TBV (aTBV) across all groups compared to healthy controls, suggesting deterioration in all groups. Weinberg et al., (2016) also assessed global brain volumes in empirically derived cognitive subtypes. Unfortunately, due to low numbers they were unable to include their compromised group in their analysis. They found no differences between preserved, moderately deteriorated and severely deteriorated groups in ICV but found their severely deteriorated group to have reduced total grey matter, cortex and cortical white matter volumes relative to healthy controls.

Van Rheenen et al., (2017), Czepielewski et al (2017) and Weinberg et al (2016) also examined additional brain subregions and cortical thickness to assess the extent to which cognitive subtypes might correspond to distinct cortical reductions. Results from such studies have found a range of abnormalities in the compromised groups relative to healthy controls, including mean reductions in: cortical thickness and insular volume (Czepielewski et al., 2017); smaller left anterior, middle and superior temporal and occipital lobe areas; right lateral medial and interior frontal areas; and left superior and middle frontal areas (Van Rheenen et al., 2017). In the study, which was unable to include the compromised group for comparison, Weinberg et al., (2016) found preserved and deteriorated subtypes had smaller inferior parietal volumes than controls. When compared to preserved groups, severely deteriorated patients had smaller mean hippocampal, superior temporal sulcus and lingual gyrus volumes.

Other groups have classified cognitive subtypes based on cluster analyses of current cognitive function alone (Geisler et al., 2015) and are beyond the scope of this literature review.

1.5.6 Cognitive Subtypes and Inflammation

Studies have examined high vs low inflammatory subtypes of schizophrenia and psychosis. As previously mentioned, there is growing evidence that those with increased levels of CRP have a range of cognitive deficits. Fillman et al., (2016) found that an elevated-cytokine subgroup performed significantly worse than a low-cytokine subgroup on verbal fluency and that this corresponded with a volume reduction in the left pars opercularis. In contrast, despite growing interest in cluster analytic techniques to identify cognitive subtypes with meaningful clinical and brain structural differences, no studies have examined the relationship between cognitive subtypes and their inflammatory profiles.

1.6 Social Cognition in Schizophrenia

Although successful social interactions depend on adequate cognitive function, there are other important and necessary psychological processes not captured by neurocognitive tests known collectively as 'social cognition'. Social cognition can be defined as "the psychological processes that are involved in the perception, encoding, storage, retrieval and regulation of information about other people and ourselves" (Green et al., 2015). These are: mentalising or 'theory of mind' (the ability to infer correctly the thoughts of others); social perception (the ability to recognise and identify social rules and context); attributional bias (the interpretation of social situations); and emotion perception (perceiving and employing emotions) (Pinkham et al., 2014, Mancuso et al., 2011). Impaired social cognition has a negative impact on social function

and may be an important predictor of poor outcome in schizophrenia (Fett et al., 2011). Growing evidence suggests that at least some social cognitive domains are core impairments of schizophrenia, independent of medication effects and unrelated to clinical symptoms (Savla et al., 2013, Lee et al., 2015, McCleery et al., 2014).

1.6.1 Social Cognitive Deficits in First-Episode Psychosis

With neurocognitive deficits explaining 20% - 60% of the variance in functional outcomes in schizophrenia (Green et al., 2004), there is still a large proportion of unexplained variance. Included in the MATRICS consensus battery (Marder, 2006) developed to measure cognitive deficits in schizophrenia is the domain of social cognition. Social cognition has been less extensively studied in schizophrenia than neurocognitive deficits, but recent evidence has shown it to account for a greater proportion of the variance in functional outcomes than neurocognitive impairments (Fett et al., 2011, Pinkham and Penn, 2006). Social cognitive sub-domains thought to play an important role in functional outcomes, particularly social functioning, have been identified but research into each domain, particularly in FEP cohorts is still in its infancy. Many studies have only small sample sizes, variability in sub-domain assessment measures, poor measure reliability and few studies examining all domains in the same cohort (Pinkham et al., 2016b, Pinkham et al., 2014). The limited research to date suggests that social cognitive impairments are present in the early phase of psychosis and may constitute a core impairment of the disorder (McCleery et al., 2014).

Few studies have assessed social cognition at psychosis onset and how it relates to social function and most studies have focussed on only one domain (Healey et al., 2016). Two studies have found stable impairments in social cognition that were an important

determinant of functional outcome 12 months later (Horan et al., 2012, Addington et al., 2006b). These studies examined only a proportion of social cognitive domains in a relatively small sample. If we are to develop targeted and practical interventions to improve outcomes, a greater understanding is needed of: the social cognitive impairments experienced by those presenting with a first episode of psychosis; which sub-domains of social cognition have a relationship with social functioning; the relationship of social cognition domains to one another; and how social and non-social cognition relate to one another.

1.6.1.1 Theory of Mind

Theory of Mind (ToM) is the ability to infer and represent the thoughts, feelings and intentions of others, including the understanding that others may hold false beliefs (Baron-Cohen et al., 1985). There is some evidence of different processes for affective ToM (concerning emotions and feelings of others) and affect neutral (or cognitive) ToM (Kalbe et al., 2010). ToM is sometimes additionally separated into two types: 'first' and 'second' order. First order is the ability to understand that others may hold beliefs, and second order is understanding that it is possible to hold a false belief about someone else's belief (Miller, 2009). Many different theory of mind tests have been developed, often for use in studies of children and autism, including visual (Wimmer and Perner, 1983) and verbal false-belief tasks, hinting tasks (Corcoran et al., 1995) and tasks involving the understanding of visual jokes (Marjoram et al., 2005).

ToM or 'mentalizing' is well documented in schizophrenia (Savla et al., 2013). In 1992, Frith proposed that ToM impairments due to functional or structural impairment of neural mechanisms may play a role in contributing to the symptomatology of

schizophrenia (Frith and Corcoran, 1996). Two meta-analyses have since compared ToM impairments in people with schizophrenia to healthy controls, both concluding that there is evidence of large effect sizes in ToM performance and that ToM impairment may represent a trait marker in schizophrenia (Sprong et al., 2007, Bora et al., 2009).

A review of social cognitive deficits in first-episode patients found that, along with emotional perception, ToM deficits are the most pronounced in this population and comparable to those with an established diagnosis of schizophrenia (Healey et al., 2016).

1.6.1.2 Emotion Perception (EP)

Facial emotion perception (EP) is the most studied domain of social cognition in schizophrenia. The terms ‘emotion perception’, ‘emotion recognition’ and ‘emotion processing’ are often used interchangeably. These refer to the individual’s ability to perceive emotions, though some emotion processing tasks also assess an individual’s ability to regulate emotions adaptively. Commonly used emotion recognition tasks include the Bell-Lysaker Emotion Recognition Task (Bryson et al., 1997) and the Penn Emotion Recognition Task (Kohler et al., 2010) which use videos and static images respectively of individuals displaying facial emotional expressions. A variation of facial emotion recognition tasks is the ToM “reading the mind from the eyes test” which uses only static images of “emotional eyes” and is supported by evidence that the reading of emotions from eyes is an effective assessment of the emotional states of others (Baron-Cohen et al., 2015). More recently, CANTAB (CANTAB®, 2017) have included a computerised assessment of emotion recognition using morphed images derived from emotion expressions of real people developed to display different intensities. Unlike many of the other tasks, the image is displayed for only a short time.

Meta-analyses have consistently found large deficits in emotion perception in schizophrenia populations (Kohler et al., 2010, Savla et al., 2013) irrespective of the type of task used, and that the impairment in schizophrenia is larger than in other psychiatric groups (Addington et al., 2008, Gaebel and Wolwer, 1992).

In first-episode psychosis, the majority of studies have shown emotion perception to be significantly impaired in comparison to healthy controls with large effect sizes (Thompson et al., 2012, Amminger et al., 2012, Bediou et al., 2007, Comparelli et al., 2013, Edwards et al., 2001, Herbener et al., 2005). In contrast, a small number of studies have found there to be no significant differences between healthy control and first-episode groups. When comparing FEP and established schizophrenia groups, the majority of studies have found no difference in performance on emotion recognition tasks, with the exception of two (Comparelli et al., 2011, Kucharska-Pietura et al., 2005) who found that FEP groups performed significantly better than the established schizophrenia group. Furthermore, some studies have examined whether impairments exist in identifying certain emotions, with well-replicated evidence that schizophrenia patients exhibit deficits in the recognition of negative emotions, particularly fear and sadness, and two studies with large sample sizes found that this extends to disgust and anger (Kucharska-Pietura et al., 2005, Comparelli et al., 2011). In studies comparing specific emotions recognition deficits between FEP and multi-episode schizophrenia, two found evidence of significantly worse emotion recognition in the established schizophrenia patients of disgust and fear (Kucharska-Pietura et al., 2005), neutral (Romero-Ferreiro et al., 2016) and anger (Kucharska-Pietura et al., 2005) emotions.

1.6.1.3 Social Perception (SP)

Social perception (SP) is concerned with one's ability to perceive social contexts, roles and rules using non-verbal information (Green et al., 2019) and although reported to be strongly correlated with community functioning (Fett et al., 2011) has seldom been studied in schizophrenia. Tasks for measuring social perception are limited and have often been more widely used in other neurological or psychiatric conditions (McDonald et al., 2003, Bell et al., 2010). One of the most commonly used is the Relationships Across Domains (RAD) task which utilises vignettes to measure perception of proposed relational models (Sergi et al., 2009) but concerns have been raised over suitability for use in schizophrenia due to assessment length, difficulty and tolerability (Pinkham et al., 2016b). A meta-analysis by Savla et al., (2013) demonstrated that when comparing healthy controls with schizophrenia samples, social perception had a large effect size, with some of the variability accounted for by inpatient status (inpatients showed poorer performance than outpatients). This effect size was larger than in any other domain of social cognition, highlighting the need for further research in this domain.

Most studies in first-episode psychosis found social perception to be impaired when compared to healthy controls (Addington et al., 2006b, Bertrand et al., 2007, Green et al., 2012a, Montreuil et al., 2010), with only one finding no significant difference (Achim et al., 2012). A paucity of studies to date have assessed the differences in social perception abilities between FEP individuals and individuals with established schizophrenia, finding impairments to be comparable (Addington et al., 2006b, Green et al., 2012a). Interestingly, Green et al., (2012a) found a FEP group were more impaired than a schizophrenia group on measures of social perception. Given poor measurement validity and reliability in this domain (Pinkham et al., 2016b) there is a need for

development of new measures of social perception, or the repurposing of measures previously used for other diagnoses. For example, the Social Attribution Task - Multiple Choice (SAT-MC), developed for use in autism shows promise for use in schizophrenia populations (Bell et al., 2010).

1.6.1.4 Attribution Bias

Attribution bias (AB) is another domain rarely studied in schizophrenia. AB is considered a measure of cognitive bias, measuring tendencies in ways of interpreting the actions of others and subsequent anger, blame or intentions as a result. A meta-analysis evaluating attributional bias in schizophrenia included only a small number of studies (Savla et al., 2013), all using the Internal, Personal and Situational Attributions Questionnaire (IPSAQ) (Kinderman and Bentall, 1996). Findings using this measure were negligible (Savla et al., 2013). This measure, however, received expert panel ratings for suitability that were substantially below those of other attribution bias measures (Pinkham et al., 2014). A more recent study using the Ambiguous Intentions and Hostility Questionnaire (AIHQ) has found more hostile social cognitive biases than healthy controls (HC) (Lahera et al., 2015). Buck et al., (2016) found that the blame score component of the AIHQ was valid in providing information on cognition, symptoms and functioning in those with schizophrenia and supports the need for continued assessment of cognitive biases in order to improve outcomes in those with psychosis.

Studies in first episode cohorts found mixed results, some finding FEP individuals to perceive greater hostility than HCs but no greater sense of intentionality, anger or blame (An et al., 2010). Fornells-Ambrojo and Garety., (2009) found that FEP patients were

more likely to attribute negative events to others, whereas So et al., (2015) found that they were more likely to attribute positive events to themselves.

1.6.2 Are Neurocognition and Social Cognition Distinct Constructs?

Neurocognition and social cognition are generally thought to be modestly related, but to represent separate constructs with separable neural systems (Fanning et al., 2012, Pinkham et al., 2003, Green et al., 2015, Allen et al., 2007). This separation of social and neurocognition is supported by research into “hot” (personally relevant) and “cold” (affect neutral) cognition (Roiser and Sahakian, 2013), which shows that social or emotionally relevant and non-emotional cognition are differentially affected in neuropsychiatric disorders and underpinned by differential neural networks (Stange et al., 2018). Studies using structural equation modelling and factor analytical approaches have also found models with social cognition as a separate construct provide the best model fit (Allen et al., 2007, Sergi et al., 2007), though these studies have been limited in the number of social cognitive domains they have been able to incorporate. There is a distinct need for further research to establish the relationship between social cognitive and neurocognitive tasks in order to determine discriminant validity of social cognition in this population and to identify effective treatments to targets.

1.6.3 General vs Specific

At an NIMH workshop on definitions, assessment, and research opportunities in social cognition (Green et al., 2008) it was considered unlikely that social cognition could be represented as a single construct. Factor structure studies are limited, with the

workshop identifying a paucity of research in this area. Most studies employed only one measure of social cognition and many studies had small sample sizes. In recent years, there has been increased research in this area. In a systematic review of distinct cognitive factors in schizophrenia, Mehta et al., (2013) identified 11 studies exploring the factor structure of social cognition, concluding there is a lack of consensus in the findings. Six studies found social cognition to best load onto one factor (Bell et al., 2009, Bell et al., 2013, Addington, 2011, Lysaker et al., 2013, Green et al., 2012b, Reise et al., 2011) four showed a two-factor model (Mehta and Thirthalli, 2013, Lin et al., 2012, Eack et al., 2009, Williams et al., 2008) and one a three-factor model (Mancuso et al., 2011). The authors note that only two of these studies assessed all the social cognition domains recommended by the NIMH workshop (Mancuso et al., 2011, Mehta et al., 2013) and that the studies are hindered by the lack of validation of social cognitive assessments. More recently, Green et al., (2015) suggested that empathy may be a good example of a complex social cognitive function which incorporates several sub domains of social cognition, and may serve as a good global measure of social cognitive functioning in schizophrenia. This factor structure of social cognition requires further research.

1.6.4 Stable or Deteriorating?

Since social cognition is an area of more recent interest, there have been no prospective cohort studies investigating the longitudinal development of social cognitive function in those who go on to later develop schizophrenia. Whether social cognition is stable or deteriorates after illness onset is still unclear, though investigators have begun to examine this. Evidence from a limited number of studies, including one with a 5-year follow-up period (McCleery et al., 2016) has found social cognition to be stable over

time, regardless of whether or not patients were in the early phase of illness at the time of first assessment. Longitudinal studies have been hampered by lack of control groups for comparison. Addington et al., (2006a and 2006b) found that FEP patients had stable performance on emotion and social perception tasks, but that HCs improved. To interpret these results, it is important to establish not only whether performance is stable, but also whether the slope of improvement differs between patients and HCs to determine whether any lag behind healthy controls remains stable or increases following illness onset.

1.6.5 Social Cognition and Symptoms

Social cognition has been linked to both positive and negative symptoms of schizophrenia. ToM deficits have been hypothesised to underlie delusions and paranoia resulting from aberrant inferences about the mental states of others (Frith and Corcoran, 1996). Some studies provide empirical support for this theory (Corcoran et al., 1995, Pickup and Frith, 2001), whilst others find no relationship between ToM and delusions (Harrington et al., 2005) or paranoia (Drury et al., 1998). Similarly, the misattribution of positive and negative outcomes is thought to be linked to positive symptoms, with Bentall et al., (2001) suggesting that persecutory delusions may be underpinned by an exaggerated self-serving bias, that is, inflated internal attribution of positive and external attribution of negative events. Evidence for this relationship comes from several studies (Martin and Penn, 2002, Fraguas et al., 2008, Candido and Romney, 1990).

Similarly, there is justification for the theory that abnormal, social perception or facial recognition may underlie hostility, paranoia and delusions resulting from the

misinterpretation of social situations and facial cues, but research in these areas is limited.

Social cognition and negative symptoms are considered to be separate constructs (Bell et al., 2013) though there is some evidence of a relationship, with reduced emotional/affective states and expressions common to both symptom sets. Lincoln et al (Lincoln et al., 2011) found that social cognitive variables, including attribution bias and ToM, explained 39% of the variance in negative symptoms, and other studies have shown evidence of a relationship between negative symptoms and ToM (Mehta et al., 2014, Bora et al., 2008, Shean and Meyer, 2009); emotion recognition; (Johnston et al., 2010) and social perception (Sergi et al., 2007). Other studies have found no relationship (Mancuso et al., 2011, Kalin et al., 2015).

1.6.6 Social Cognitive Deficits and Outcome

As previously detailed, neurocognition is a stronger predictor of functional outcomes in schizophrenia than symptomatology. Social cognition and its relationship to function has been far less studied (Pinkham et al., 2003). A comprehensive meta-analysis examining the cross-sectional associations between neurocognitive and social cognitive functioning and social and functional outcomes, found both neurocognition and social cognition are consistently associated with functional outcomes, but that social cognition was more strongly associated with community functioning than neurocognition (Fett et al., 2011). The largest effects were for ToM (0.48), social perception (0.24) and emotional processing (0.22). This study noted an underreporting of potential moderator variables, and intercorrelations between individual neurocognitive, social cognitive and

functional outcome measures in the literature. There is the further limitation that all studies were cross-sectional.

There is also recent evidence that social cognition mediates the relationship between neurocognition and functional outcome (Schmidt et al., 2011). Due to most studies examining only one or two social cognitive domains and using composite neurocognitive scores, it remains unclear which social cognitive domains are the most effective mediators of functional outcomes. More research is necessary, using validated social cognitive assessments across several domains, to distinguish the differential relationships between neurocognitive domains and functional outcome, as well as including additional potential mediators in the model. To date, in mediation models, social perception and emotion processing have been shown to have a significant relationship with almost all measures of function. Few studies have examined the relationship between ToM or attribution bias and functional outcomes in psychotic populations, making it difficult to draw conclusions about the relationship between these domains and functional outcomes, as well as their relationship to other cognitive domains (Couture et al., 2006).

1.6.7 Social Cognition and Neuroimaging

Fewer neuroimaging studies have focussed on social cognition compared to non-social cognition. Research into personally relevant vs affect neutral cognitive tasks has identified differential neural networks involved in different task types, with the DLPFC important in “cold” decision making tasks; and the orbitofrontal cortex playing a role in “hot” decision-making tasks (Roiser and Sahakian, 2013). Patients with schizophrenia show abnormal neural activation in areas thought to be necessary for ToM, including

hypoactivation in areas of the prefrontal cortex, temporoparietal junction, anterior temporal cortex and posterior cingulate cortex and hyperactivation in areas of temporoparietal junction (Kronbichler et al., 2017, Amodio and Frith, 2006, Bahnemann et al., 2010). On emotion perception tasks, which have been the most studied, hypoactivation has been shown in areas associated with facial recognition and emotion processing, such as the fusiform gyrus, amygdala, and ventro-lateral prefrontal cortex, along with hyperactivation in some areas not typically associated with facial affect recognition (Taylor et al., 2012, Li et al., 2010b, Pinkham et al., 2008)

1.6.8 Social Cognition Remediation Strategies

The relationship between social cognition impairment and functional outcomes (Fett et al., 2011, Couture et al., 2006, Pinkham and Penn, 2006) has led to the development of interventions. Many of these interventions target only one social cognitive domain (ToM or emotion recognition) (Grant et al., 2017, Frommann et al., 2003, Penn and Combs, 2000, Wolwer and Frommann, 2011, Kayser et al., 2006, Russell et al., 2008). Social Cognitive and Interaction Training (SCIT) is a “comprehensive treatment” targeting all four of the aforementioned social cognitive domains (Penn et al., 2007). This comprehensive treatment is generally carried out in a group format and includes emotion recognition training and reduction of the use of maladaptive heuristics in social decision making and judgements, using integration of client-specific social difficulties. The majority of group interventions targeting all social cognition domains are based on the SCIT template.

Social cognitive interventions were found to produce significant improvements in emotion perception and theory of mind, but there is limited evidence of this translating

to improvements in functional outcomes (Kurtz et al., 2016, Grant et al., 2017). Smaller effect sizes have been found for attribution bias and social perception. There are wide variations in duration, modality and delivery of social cognitive interventions and more research is needed to disentangle the elements which may lead to social cognition domain improvements and to increase their transfer to functional outcomes. A review by Grant et al., (2017) found that the quality of evidence to date is limited by heterogeneity of measures used, poor study methodology and short follow-up periods. Pharmacological approaches have largely focussed on the neuropeptide oxytocin, thought to enhance the notability of social information including perception and processing of facial expressions, trusting behaviour and cooperation (Ebert and Brüne, 2018). The current understanding is that oxytocin may modulate activity in the amygdala, known to be important in our understanding of social cognitive function. A recent meta-analysis, however, found no significant effect of intranasal oxytocin on social cognitive performance (Burkner et al., 2017). More recently efforts have been made to combine administration of oxytocin with social cognitive training, but research into the effectiveness of this is still in its infancy (Davis et al., 2014, Cacciotti-Saija et al., 2015). There is some evidence for the effectiveness of Modafinil in improving the analysis of emotional face expressions in individuals who have experienced a FEP (Scoriels et al., 2011). These findings require further research but may have implications for improving social function in this group.

1.7 Background Summary

Neurocognition is impaired in individuals with a FEP; but significant heterogeneity exists. General intelligence or 'g', a construct derived from all neurocognitive measures, and

estimated by IQ, is one of the best predictors of long-term outcomes in this population. Neurocognition is thought to be the result of progressive developmental impairment which remains stable after illness onset, but recent studies have questioned whether some neurocognitive functions show further deterioration over longer follow-up periods. In keeping with the cognitive reserve hypothesis, studies examining the relationship between neurocognition and functional outcomes have found that those with better neurocognitive function at illness-onset have better global and social outcomes, but significant variance in outcomes remains unexplained. Studies characterising the structure of heterogeneity in established schizophrenia have identified 3 cognitive subtypes: those with preserved cognition, those with deterioration from premorbid levels of cognition and those with below average (or compromised) premorbid and post-onset intelligence. Those with deteriorated and compromised cognition are found to have worse functional outcomes than those with preserved cognition. However significant heterogeneity exists in the methods used to classify cognitive subtypes and only one study to date has examined global neurocognition trajectories early in the course of illness. Studies have sought to examine neuroimaging markers of cognitive subtypes, with heterogeneity of findings. Recent studies have found smaller intracranial volumes, a marker of cerebral hypoplasia, in compromised subgroups whereas deteriorated groups showed evidence of neurodeterioration marked by smaller total brain volumes after adjusting for intracranial volume. Neuroimaging findings in preserved groups have been mixed with some evidence of abnormalities compared to healthy controls. Early indications suggest that inflammatory markers may have a relationship with cognition in schizophrenia, but the direction and

strength of this relationship is currently poorly characterised, and confounders are frequently not controlled for.

Other important psychological processes known as 'social cognition' are thought to be necessary for successful adaptive social functioning and are not captured by traditional neuropsychological tests. Social cognition encompasses the processes underlying successful understanding, interpretation and response to the behaviours of others and is thought to be related to, but somewhat distinct from, neurocognition with distinct neural substrates. Social cognition is impaired in those with established schizophrenia and most studies suggest impairment of a similar magnitude in FEP. Whether impairments are the result of 'state or trait' and whether impairments remain stable over time, remain unanswered. Recent meta-analyses suggest social cognition may have a stronger relationship with functional outcomes than neurocognition, but studies are mostly limited to those with established schizophrenia. Furthermore, domains of social cognition have been identified as potential mediators of the relationship between neurocognition and functional outcomes, but few studies have examined multiple domains of social cognition in schizophrenia and even fewer in FEP groups. Social cognition research has been further hampered by a lack of consistency in the use valid and reliable measures for each domain. A recent validation study led to the identification of the most valid, reliable and acceptable measures for the established social cognition domains of attribution bias, social perception, emotion recognition and theory of mind.

Neuro- and social cognition interventions are in development. There is also evidence of significant and durable effects of computerised cognitive remediation therapies targeting neurocognition which translate to functional outcomes. There is some

evidence for the success of social cognition interventions, but many studies have methodological issues and there is less evidence that effects translate to functioning in populations with schizophrenia.

1.8 Study Aims and Objectives

The review of cognitive function at illness onset suggests that establishing and characterising the presence of cognitive subtypes would improve diagnostic and prognostic accuracy in patients with schizophrenia. Longitudinal studies using a data driven approach early in the course of illness are necessary to elucidate the relationship between cognitive reserve and clinical and functional outcomes. Study 1 will therefore address these questions.

1.8.1 Study 1 - Cognitive Reserve: Relationship with neurocognitive, clinical and functional outcomes

Aim: To determine whether previously identified cognitive sub-groups in schizophrenia are clinically valid.

Objectives:

a) To apply empirical methods of cluster analysis to cognitive data from a new cohort of patients who had recently developed a first episode of psychosis and were attending National Health Service Early Intervention Services.

b) To determine whether cognitive subtyping, based on IQ, applies also to other more specific neuropsychological functions

c) To determine the relationship between cognitive subtypes, symptoms, social function and biological markers.

Longitudinal trajectories of those assigned to cognitive clusters have not been examined in first-episode cohorts. This will be addressed in study 2.

1.8.2 Study 2 - Longitudinal Cognitive and Functional Trajectories of Neurocognitive Subtypes

Aim: To determine trajectory of cognitive, clinical and social functioning over time in the entire patient group and IQ-based cognitive subtypes.

Objectives:

- a)** To determine whether cognitive function remains stable over time following the early illness phase, relative to healthy control comparison group.
- b)** To elucidate whether cognitive trajectory is an important long-term determinant of course of illness and functioning.
- c)** To assess stability of clinical symptoms, social functioning and biological markers 12-months after initial assessment.

1.8.3 Study 3 - Neurocognitive Predictors of Global and Social Functional Outcomes in First-Episode Psychosis

Aim: To determine cross-sectional and longitudinal cognitive predictors of social and functional outcomes using global and domain specific measures of neurocognition in a large FEP group.

Objectives:

- a)* To assess the predictive validity of neurocognitive measures both cross-sectionally and longitudinally in an FEP cohort
- b)* To determine discriminant validity of neurocognitive measures

Social cognition has not been characterised at illness onset and it remains to be seen whether findings from patients with long-standing illness pertain to the early stages of schizophrenia. This will be addressed in Study 4.

1.8.4 Study 4 - Social Cognitive Deficits in a First-episode Cohort

Aim: To determine the degree to which social cognition is affected at illness onset in schizophrenia and profile of impairment.

Objectives:

- a)* To characterise social cognition in patients with psychosis presenting to NHS Early Intervention Services and healthy volunteers using a short social cognition battery comprising tests previously shown be sensitive to patients with long-standing schizophrenia.

- b)** To determine whether social cognitive impairment is global or domain specific at illness onset
- c)** To compare social cognitive functioning in a FEP group with a healthy control group
- d)** To examine the discriminant validity of social cognitive tests in healthy controls and the patient group

The relationship between social cognition and neurocognition at illness onset is unknown. This is important because cognitive remediation (CR) aims to improve neurocognition with the ultimate aim of better functional outcomes. If social cognition is a factor in determining outcome, this would indicate the need to supplement CR programmes with social cognition training. Study 5 will address this question.

1.8.5 Study 5 - Does Social Cognition Mediate the Relationship Between Neurocognition and Social Functioning?

Aim: To assess the relationship between neurocognition, social cognition and functional outcomes in first-episode psychosis using structural equation modelling (SEM).

Objectives:

- a)** To determine the strength of the relationship between measures of neurocognition and social cognition.
- b)** To determine whether social cognition mediates the relationship between neurocognition and functional outcomes.

2 Methods

This thesis incorporates neurocognitive and clinical data collected as part of two multi-site clinical trials performed in UK Early Intervention Services: ‘The ‘BeneMin study’ and ‘The ECLIPSE study’ (described below). Social cognition assessments were performed during the ECLIPSE study separately from the trial protocol.

2.1 The BeneMin Study

Participants were recruited as part of a study entitled “The Benefit of Minocycline on Negative Symptoms in Early-Phase Psychosis in Addition to Standard Care”. This study was funded by a National Institute for Health Research (NIHR)/Medical Research Council (MRC) partnership: The Efficacy and Mechanisms (EME) evaluation programme. The study took place in 8 research centres across the UK. Minocycline was found to have no effect, compared to placebo, on any measure and data were therefore pooled.

2.1.1 Recruitment

Patients were asked by a member of their clinical team if they would like to hear more about the study. Those who were interested were approached by a member of the research team, who provided information about the study and allowed a minimum of 48 hours to come to a decision. Those who assented, gave written informed consent and were screened to check that they met the full eligibility criteria. Ethical approval for the study was obtained by the North West Research Ethics Committee (ref.11/NW/0218)

and the Health Research Authority (HRA). Participants were given £30 as acknowledgement and thanks for their time completing assessments.

2.1.2 Participants

Participants were recruited from participating 15 NHS trusts across the United Kingdom corresponding to 8 research centres (Table 2.1). AJW recruited and completed assessments for all North London participants at both baseline and follow-up. All participants were currently receiving care from Early Intervention Services (EIS) and were within the first 5 years of their first presentation to mental health services.

Table 2.1: BeneMin Research Centres and corresponding NHS Trusts

Site Number	Site Name	NHS Trusts	MRI Scan Centre
1	University of Manchester	- Manchester Mental Health and Social Care Trust - Great Manchester West Mental Health NHS Foundation Trust - Pennine Care NHS Foundation Trust	MRI facility in Salford Royal NHS Foundation Trust
2	Lancashire Early Intervention Service	- Lancashire Care NHS Foundation Trust	
3	University of Edinburgh	- NHS Lothian - NHS Fife	Clinical Research Imaging Centre Edinburgh
4	University of Cambridge	- Cambridge and Peterborough NHS Foundation Trust - Norfolk and Suffolk NHS Foundation Trust	Wolfson Brain Imaging Centre Cambridge
5	King's College London	- South London and Maudsley NHS Trust	Centre for Neuroimaging Sciences King's College London
6	University College London	- Camden & Islington NHS Foundation Trust - Central and North West London NHS Foundation Trust - Barnet, Enfield and Haringey Mental Health Trust - West London Mental Health NHS Trust	Wellcome Trust Centre for Neuroimaging University College London
7	University of Birmingham	- Birmingham and Solihull Mental Health NHS Foundation Trust	Birmingham University Imaging Centre

2.1.2.1 Inclusion Criteria:

- Aged 16 – 35, inclusive, at onset of psychosis
- Meeting DSM-IV criteria for schizophrenia, schizophreniform or schizo-affective psychosis as assessed by the research team
- Within 5 years of onset of symptoms meeting diagnostic criteria
- Patient is being treated with antipsychotic medication for a psychosis which is not primarily a mood disorder
- At least a mild persisting symptom from: delusions (abnormal beliefs), disorganised thinking, hallucinations, suspiciousness (as defined by a score of >2 on P1, P2, P3, or P6 on the PANSS assessment).
- In contact with early-intervention community of in-patient services for at least 3-months
- Pre-morbid IQ greater than 70
- Able to understand and willing to give written informed consent

2.1.2.2 Exclusion Criteria:

- Alcohol/Substance abuse that seriously affects function
- Inability to communicate sufficiently in English
- Patient poses a current suicidal or violence risk
- Tetracycline use within past 2 months
- Patient is pregnant or intends to become pregnant during course of the study
- Current substance misuse diagnosis which in the opinion of the investigator may interfere with the study

- Relevant current or past haematological, hepatic, renal, neurological or other medical disorder

2.1.3 Healthy Controls

A healthy control (HC) database (n=86) from the West London First-Episode Study (Leeson et al., 2011) was used for comparison on the cognitive measures (premorbid and current IQ, digit symbol, arithmetic, information, block design and auditory verbal learning test (AVLT)). HC data were not available for the verbal fluency task. HCs were recruited from the same London boroughs as those in the West London study (Ealing, Hammersmith and Fulham, Wandsworth, Kingston and Richmond, Merton, Sutton) and were aged between 16 and 60 years. Exclusion criteria were: history of psychiatric illness in either themselves or first-degree relatives, drug or alcohol abuse and head injury or other neurological condition or endocrine disorder affecting brain function (e.g. epilepsy).

2.1.4 Diagnostic Screening

2.1.4.1 *MINI International Neuropsychiatric Interview (MINI)*

Patients were screened using the MINI to assess whether they met criteria for a non-affective psychosis; schizophrenia (lifetime/current), schizophreniform, or schizoaffective disorder.

2.1.5 Follow-Ups

Follow-up assessments were completed on all measures 12-months after baseline, with the exception of the MINI and some demographic variables. Healthy controls were followed up on cognitive measures 12-months after first assessment.

2.1.6 Cognitive Measures

2.1.6.1 Pre-Morbid IQ

Accurately estimating premorbid intelligence is important in order to establish cognitive decline resulting from neurological damage. One approach to attain an estimate is to make sense of an individual's history. "Historical" methods gauge a subjective measure of premorbid IQ based on the review of clinical interviews and records (Vanderploeg, 1994). "Actuarial" methods also use an individual's history, but incorporate objective factors such as age, educational attainment and occupation into a regression formula to produce prediction of premorbid IQ (Wilson et al., 1978, Barona et al., 1984). Although the actuarial method is culturally sensitive and more objective than the "historical" approach, it loses validity in predicting pre-morbid IQ at the extremes of the normal curve.

An alternative approach is to use a "hold" test, which utilises performance on a test deemed unaffected by neurological damage to predict pre-morbid functioning. In the case of IQ, this makes it possible to measure the discrepancy between current IQ and a premorbid predictor to measure the extent of cognitive decline resulting from neurological damage. "Hold" tests frequently use vocabulary knowledge or reading pronunciation ability as their measure, based on the observation that verbal skills tend to be intact long after the decline of other cognitive functions such as memory and

executive functions (Lezak, 2004). Due to the reliance of hold-tests on current performance, hold measures need to be validated for each population for which they are to be used.

Despite cognitive dysfunction in schizophrenia existing across a wide spectrum of domains, as well as IQ, performance on the National Adult Reading Test (NART) (Nelson, 1982) seems to be unaffected, not differing from that of nonclinical populations (Wechsler, 2001). A study by Harvey et al., (2000) showed that performance on the Wide Range Achievement Test – Revised (WRAT-R) reading test remains stable over time in geriatric patients with lifelong chronic schizophrenia, suggesting the preservation of word recognition in this population. Due to preservation of this function, word recognition tests are often considered good measures of pre-morbid IQ in populations with schizophrenia. A word-recognition test validated for this use, with the added benefit of being standardised to the WAIS-III measure of current IQ, is the Wechsler Test of Adult Reading (WTAR) (Holdnack, 2001, Wechsler, 2001).

2.1.6.2 WTAR

The WTAR is a hold-test which uses vocabulary level as a correlate to IQ. The test assesses word recognition and pronunciation and is for use in English-speaking patients aged 16-89.

As mentioned previously, a benefit of using the WTAR rather than the NART is that it has been co-normed against the WAIS-III to allow direct comparisons to be made. In a standardisation sample, the correlations between WTAR score and performance on the WAIS-III are high, ranging between 0.74 – 0.80 in individuals aged 18 - 44. The WTAR has

been shown to be suitable for use in a clinically diverse group, including those with a diagnosis of schizophrenia (Holdnack, 2001).

Participants are shown a list of 50 words with irregular grapheme-to-phoneme translation and are asked to read them out loud. Participants receive a score of one-point for each correct response. The test is discontinued if the participant reaches 12-consecutive incorrect responses. Each word has a list of allowable responses to account for correct but differing pronunciation variants between individuals. Correct responses are totalled to give a raw-score (maximum = 50) which can be converted to a standardised score using a validated conversion table. These conversion tables group participants according to their current age. Once a standardised score has been obtained, look-up tables can then be used to convert this to a full-scale IQ (FSIQ).

A disadvantage of the WTAR is that those with reading-disabilities score lower on the WTAR than on WAIS test measures and this test is therefore not recommended for use with these individuals. For this reason, those known to have dyslexia were excluded from this part of the analysis (Spreen, 2006).

2.1.6.3 Full-Scale IQ

In order to establish a current full-scale IQ (FSIQ) we used a version of the most widely used standard test of intelligence in adults, the WAIS-III (Wechsler 1997). The WAIS-III consists of 14-sub-tests and provides three composite IQ scores; verbal IQ, performance IQ and FSIQ. The full assessment takes approximately 80 minutes in healthy subjects (Wechsler 1997) and longer in many clinical populations (Ryan et al., 1998). Due to the demand on resources of both participants and the researcher, short-form versions of the WAIS-III have been developed for clinical populations to give an accurate estimate

of FSIQ using fewer tasks. Blyler et al., (2000) used regression analyses to calculate the subtests which would provide the most reliable estimate of FSIQ in a population with schizophrenia, whilst reducing burden on the participants and subjectivity in scoring. Before analysis they excluded the four most time-consuming sub-tests (comprehension, picture arrangement, matrix reasoning and vocabulary). When looking at combinations including one sub-test from each of the four WAIS index scores (Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index and Processing Speed Index) the regression analysis produced a four-task solution consisting of the tasks: *block design, arithmetic, digit symbol* and *information*. This solution had an R^2 value of 0.92 in predicting WAIS-III FSIQ of participants with schizophrenia and 0.91 of healthy controls.

2.1.6.4 Digit Symbol Substitution Task

The Digit Symbol Substitution Task is a performance IQ sub-test of the WAIS-III is a measure of processing speed. The Digit Symbol task requires the participant to use a key to copy symbols which are paired with a number (Figure 2.1). The examiner first demonstrates the correct completion of the first three number-symbol pairings, before asking the participant to complete the next four as a practice. The participant is then encouraged to draw the correct symbols below the corresponding numbers as quickly as possible, whilst maintaining accuracy. The participant is then given 120 seconds to follow the response sheet, completing as many as possible in order. The examinee's score is determined by the number of symbols correctly drawn within the 120-second time limit. One point is awarded for each correctly corresponding symbol, with a maximum raw score of 133.

1 —	2 ⊥	3 ⊐	4 L	5 ⊏	6 ○	7 ^	8 ×	9 ≡	SCORE <div style="border: 1px solid black; width: 40px; height: 20px; margin: 0 auto;"></div>
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SAMPLES																									
2	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4	5	6	3	1	4	

Figure 2.1 Screenshot of a sample of the Digit Symbol Substitution Task

2.1.6.5 Information Task

This subtest contributes to the verbal comprehension index of the WAIS-III. Participants are required to respond orally to a series of questions relating to factual information, with 1-point awarded for a correct answer and 0 for an incorrect answer. The questions are read in order and are repeated only if the examinee’s response suggests they misheard or misunderstood the exact meaning of the question. A list of acceptable responses to each question are provided, though this list is not exhaustive. There is no time-limit on this subtest, with the test being discontinued after six consecutive scores of 0. The maximum achievable score is 28.

2.1.6.6 Arithmetic Task

This task contributes to the WAIS-III working memory index. In this subtest the examinee is asked a series of mental arithmetic questions which are time-limited. There are a total of 20 questions, with 1-point awarded for a correct response within the allotted time, and 0 for an incorrect response. Timing begins immediately after the question has been asked and is not stopped even if the participant needs the question to be repeated (which is permissible once for each item). The use of pencil and paper is not allowed for this task. Completion time is recorded on the answer sheet, with two “bonus points”

awarded on the last two questions for quick, correct performance on these items (within ten seconds). This makes a score of 22 the maximum achievable score for this subtest.

2.1.6.7 Block Design Task

This task is considered a test of perceptual organisation. The participant is given four coloured blocks consisting of two red faces, two white faces and two half-red and half-white faces. The participant is asked to replicate designs shown in a booklet using these four-blocks. For the first items, the examiner shows how the blocks can be made to look like the designs, so that the participant understands the task. The items increase in difficulty, before the participant is handed an additional five blocks required to complete the designs in the later items (requiring 9 blocks). Each item has a time-limit and is timed and recorded by the examiner. For the first two items, participants are allowed repeat attempts if their first attempt is incorrect or exceeds the time-limit, but second attempts are awarded fewer marks than attempts which are completed at the first attempt. As the subtest progresses, examinees are allowed only one attempt at each item, which is scored according to how long it took to complete. The subtest is discontinued following three consecutive scores of 0. The maximum raw score for this subtest is 68.

2.1.6.8 Calculation of current FSIQ

To calculate a FSIQ for each participant, raw scores were first converted to scaled score equivalents using norms tables which take into account participant age (ranges: 18-19, 20-24, 25-29, 30-34, 35-44). Blyler *et al.*, (2000) recommend that due to the instability of regression coefficients across samples, the mean of the four sub-scales (rather than weighted scores from the regression coefficient) are used to estimate FSIQ. The scaled

scores for each of the four sub-tests are therefore summed and pro-rated by multiplying the total by the number of scaled score used to calculate FSIQ ($n=11$) and then divided by the number of tests administered in the short-form ($n=4$). This pro-rated score can then be used to find the corresponding FSIQ from the WAIS-III IQ score equivalents table. Using the pro-rated short-form FSIQ, the R^2 values for predicting the FSIQ of the full WAIS-III remained high, 0.90 in participants with schizophrenia and 0.86 for healthy controls (Blyler et al., 2000).

2.1.6.9 Rey Auditory Verbal Learning Test (AVLT)

The AVLT (Schmidt, 1996) is a sensitive test to evaluate verbal learning and memory. The AVLT was administered in standard format, which involves a list of 15 words being read aloud by the examiner at the rate of one word a second. The participant is then asked to recall as many of the words as possible, in any order. The same procedure, using the same word list, is then repeated a further four times. There is no time limit for the task. Each trial is then scored on the number of words correctly recalled. We used recall from the first attempt as a measure of immediate memory span (AVLT immediate) and the sum of all 5 scores (AVLT total) as an index of learning.

2.1.6.10 Verbal Fluency – Controlled Oral Word Association Test (COWAT)

The COWAT is a verbal fluency test belonging to the Halstead-Reitan Neuropsychological Battery (Reitan, 1985), which measures one's ability to produce words beginning with a specified letter, or belonging to a specified category. These are seen as tests of language and executive function domains. Participants are asked to name as many words as they

can beginning with the letter 'F' with a time limit of 60 seconds. The same is then repeated for the letters 'A' and 'S'. In this part of the task, participants are instructed to exclude proper nouns and not to use tense alternatives of words they have already produced. Following this, participants are then asked to name as many words as they can fitting a specified category. Firstly 'fruit and vegetables' then 'animals' then 'household items'. There is a time limit of 60 seconds for each category. In both sections of the task participants are asked to try not to repeat words they have already said. Correct words are scored as correct for each trial and then summer to give participants a total for 'FAS' and a total score for 'categories'.

2.1.7 Clinical Measures

2.1.7.1 Positive and Negative Syndrome Scale (PANSS)

The PANSS (Kay et al., 1987) is an assessment scale used for measuring severity of symptoms in patients with schizophrenia. The scale consists of 30-items (Table 2.2), adapted from the Psychopathology Rating Scale (PRS) and the Brief Psychiatric Rating Scale (BPRS). In the current study, interviewers used the SCI-PANSS, a set of semi-structured interview questions taking approximately 40 – 50 minutes to administer and covering each item on the PANSS. Each item is then rated on a scale of 1 – 7: 1 = absent, 2 = minimal, 3 – mild, 4 = moderate, 5 = moderate-severe, 6 – severe, 7 = extreme. The PANSS guide includes a detailed definition of the criteria for each score within each individual item, including suggested anchor points. The scoring is divided into three subsections, positive symptoms (7 items), negative symptoms (7 items) and general psychopathology (16 items). Each section is summed to give a score for each symptom sub-scale as well as overall PANSS score. The PANSS has been shown to be a valid

measure of psychiatric symptoms, showing good test re-test reliability, inter-rater reliability and a lack of ceiling effects. All those using the PANSS must be adequately trained before administering the assessment.

Table 2.2: Positive and Negative Syndrome Scale categories (PANSS) (Kay et al., 1987)

Positive Scale	Negative Scale
<i>P1. Delusions</i>	<i>N1. Blunted affect</i>
<i>P2. Conceptual disorganisation</i>	<i>N2. Emotional withdrawal</i>
<i>P3. Hallucinatory behaviour</i>	<i>N3. Poor rapport</i>
<i>P4. Excitement</i>	<i>N4. Passive/Apathetic social withdrawal</i>
<i>P5. Grandiosity</i>	<i>N5. Difficulty in abstract thinking</i>
<i>P6. Suspiciousness</i>	<i>N6. Lack of spontaneity and flow of conversation</i>
<i>P7. Hostility</i>	<i>N7. Stereotyped behaviour</i>
General Psychopathology Scale	
<i>G1. Somatic concern</i>	
<i>G2. Anxiety</i>	
<i>G3. Guilt feelings</i>	
<i>G4. Tension</i>	
<i>G5. Mannerisms and posturing</i>	
<i>G6. Depression</i>	
<i>G7. Motor retardation</i>	
<i>G8. Uncooperativeness</i>	
<i>G9. Unusual thought content</i>	
<i>G10. Disorientation</i>	
<i>G11. Poor attention</i>	
<i>G12. Lack of judgement and insight</i>	
<i>G13. Disturbance of volition</i>	
<i>G14. Poor impulse control</i>	
<i>G15. Preoccupation</i>	
<i>G16. Active social avoidance</i>	

2.1.7.2 Calgary Depression Scale for Schizophrenia (CDSS)

The CDSS is a semi-structured interview, developed for the purpose of assessing depression in schizophrenia and addressing the issue of overlap of depression and negative symptoms (Addington et al., 1990a). The scale has become the recommended scale for assessing depression in schizophrenia due to its excellent psychometric properties (Addington et al., 1992, Sarro et al., 2004, Grover et al., 2017) and superiority over other rating scales to distinguish between depression and positive and negative symptoms (Addington et al., 1996, Collins et al., 1996). Another advantage for this study is that this scale can be administered relatively quickly. The scale consists of 9 items, 8 of which are questions asked by the trained assessor, relating to different aspects of depression (depression, hopelessness, self-deprecation, guilty ideas of reference, pathological guilt, morning depression, early awakening, suicide) and one item (observed depression) which is rated based on observation of the participant throughout the interview. Each item is rated from 0 – 3 (0 - Absent, 1 - Mild, 2 - Moderate, 3 - Severe) with guidance given for each rating point on each item. Questions are asked verbatim, with probes and qualifiers asked at the discretion of the administrator. Participants are to refer only to the past two weeks when answering. The scores for each item are summed to give an overall score for the scale (0 – 27).

2.1.7.3 Global Assessment of Functioning (GAF)

The GAF scale is an instrument from the DSM-III-R, used to rate an individual's overall level of functioning on a scale of 0 (poor/dangerous functioning) to 100 (superior functioning). It is used widely both in research and clinically. Psychological, social and occupational functioning impairments are considered, to assign the most accurate score

to an individual, based on descriptions of functioning provided for across ten anchor points in the assessment guidelines. Individuals are scored based on the worst component of their assessment, either symptom severity or level of functioning. As there is a 10-point range for each description, the assessor must choose the number which is most descriptive of the individual's overall functioning.

2.1.7.4 Social Function Scale (SFS)

The Social Function Scale (SFS) is a sensitive, reliable and valid measure of areas of functioning deemed crucial to the community maintenance of people with schizophrenia (Birchwood et al., 1990). Participants complete the self-report questionnaire with questions relating to the domains of social engagement/withdrawal; interpersonal behaviour; pro-social activities; recreation; independence-competence; independence-performance; and employment/occupation. Items were scored according to the validated mark scheme. Raw scores for each section were converted to standardised scores and total standardised scores for analysis, and sub-scores were summed for a total measure of social functioning

2.1.8 Drug-Treatment

Current antipsychotic medication, dose, whether oral or depot and frequency were recorded from medical notes. For analysis, scores were converted to olanzapine equivalents due to olanzapine being the most frequently prescribed antipsychotic in this patient group.

2.1.9 Recreational Drug Use

Past and current recreational cannabis use was recorded using a self-report measure rated as either: daily, weekly, monthly or once/twice. To measure current drug use, participants also underwent a urine drug-screen screen. For analysis, patients were dichotomised as either “yes” or “no” for past cannabis use. Those who reported past cannabis use or had a positive drug screen were dichotomised as ‘having used cannabis’; and those with neither were dichotomised as ‘not’.

2.1.10 Neuroimaging

The MRI sequences were coordinated across imaging centres by Prof J. Suckling based on the previous NeuroPsyGrid multi-centre validation and reliability study comprising three-dimensional T1-weighted magnetization-prepared rapid gradient-echo (MPRAGE/SPGR) as described in Deakin et al., (2018). Whole brain segmentation and cortical reconstruction was carried out by Dr Annalisa Giordano at the IoPPN, using FreeSurfer v5.3.0 (Massachusetts General Hospital, Harvard Medical School; <http://surfer.nmr.mgh.harvard.edu>). The fully automated procedure used has been described by Fishchl et al., (2002). All volumes were visually inspected after segmentation pipeline and no manual edits were necessary. Mean gray matter volumes were extracted from bilateral medial prefrontal cortex defined independently by an atlas. In contrast to the ‘cortex’ measure, ‘total gray volume’ also includes subcortical and cerebellum volumes. Participant sex and age, and MRI acquisition centre were included as covariates in between-group analyses.

2.1.11 Inflammatory Markers

A blood draw was taken from each participant at baseline and 12-month follow-up visits. Samples were collected in a 9ml ethylenediamine tetraacetic acid tube and spun in a centrifuge within four hours of collection for 15 minutes at 20 degrees Celsius and 2000g. Plasma was aliquotted from the tube into 6 x 0.5ml 1.8ml freezer vials and labelled. Samples were stored in two separate freezer boxes (as a safeguard) in alarmed -70 degree freezers. Samples were transported to King's College, London for analysis using high-sensitivity Meso Scale Discovery (MSD) V-PLEX sandwich immunoassays under the supervision of Professor P. Dazzan, trial principal investigator. To assess inflammatory markers of participants assays included, hsCRP, IL-6, TNF- α , and IL1RA.

2.2 The ECLIPSE Study

Participants were recruited as part of a study entitled "Building Resilience and Recovery through Enhancing Cognition and Quality of Life in the Early Psychosis (ECLIPSE)" and a social cognition add-on study. ECLIPSE was funded by an NIHR programme grant and took place across 6 research centres across the UK. Ethical approval for the study was obtained by local research ethics committees (Research Ethics Committee, ref. 15/LO/1960) and the Health Research Authority (HRA). The Social Cognition study took place in 3 of these sites. Ethical approval for this study was obtained by local research ethics committees (North West Research Ethics Committee, ref. 16/WM/0326) and the Health Research Authority (HRA). Patients whom the clinical teams felt would meet the basic eligibility criteria were approached by a member of their care team and asked if they would like to hear more about the study. Those who were interested were then

spoken to by a member of the research team, who provided information about the study and allowed a minimum of 48 hours for the participant to make a decision on whether or not they would like to participate. Those who assented, gave written informed consent and were screened by a researcher to check they met the full eligibility criteria

2.2.1 Recruitment

As in the BeneMin study, patients were asked by a member of their clinical team if they would like to hear more about the study. Those who were interested were approached by a member of the research team, who provided information about the study and allowed a minimum of 48 hours to come to a decision. Those who assented, gave written informed consent and were screened to check they met the full eligibility criteria. At the time of recruitment, participants were asked by AJW if they would like to take part in a social-cognition add-on study.

2.2.2 Participants

Participants were recruited from participating NHS trusts across the United Kingdom, amounting to 3 research centres (Table 2.3). AJW was responsible for the design and assessment of the social cognition battery across all sites, and the assessment of the majority of all other measures in the North London site. All participants were currently receiving care from Early Intervention Services (EIS) and were within the first 5 years of their first presentation to mental health services: Participants were given £28 as acknowledgement and thanks for their time completing assessments.

Table 2.3: ECLIPSE Research Centres and corresponding NHS Trusts

Site Number	Site Name	NHS Trusts
1	University College London	- Camden & Islington NHS Foundation Trust - Barnet, Enfield and Haringey Mental Health Trust - North East London NHS Foundation Trust - East London NHS Foundation Trust
2	King's College London	- South London and Maudsley NHS Trust
3	University of Warwick	- Coventry and Warwickshire Partnership NHS Trust

2.2.2.1 Inclusion Criteria

- Aged 16 – 45
- Attending an early intervention service for at least 3 months from onset of first-episode psychosis.
- Research diagnosis of a non-affective psychosis (schizophrenia, schizophreniform or schizo-affective disorder)
- Able to give informed consent

2.2.2.2 Exclusion Criteria

- Not able to communicate in English sufficiently to complete research assessments
- Suffering from underlying organic or neurological disorder affecting cognition
- A comorbid diagnosis of learning disability

2.2.3 Healthy Controls

For comparisons on social cognition measures, healthy control data were collected for all social cognition measures and the WTAR. Participants were currently living in the UK and between the ages of 16 and 60. Exclusion criteria were: history of psychiatric illness in either themselves or first-degree relatives, drug or alcohol abuse and head injury or other neurological condition or endocrine disorder affecting brain function.

2.2.4 Social Cognition Measures

2.2.4.1 The Hinting Task (HT)

The Hinting Task (HT) (Corcoran et al., 1995) examines the ability to infer the true intent of indirect speech. Ten passages describing an interaction between 2 characters are read out by the researcher. Each passage ends with one of them dropping a “hint” and participants are asked what the character really means. If the correct answer is given, a score of 2 is awarded. If an incorrect answer is given, a further hint is read by the examiner. If the participant then gives the correct answer, a score of 1 is given. If the participant gives an incorrect answer, they are scored 0. The maximum total score for HT is 20. The Hinting Task has been shown to have good test retest reliability and be practical and tolerable for patients with schizophrenia (Pinkham et al., 2017).

2.2.4.2 CANTAB Emotion Recognition Task Short-Form (C-ERT)

The C-ERT (CANTAB®, 2017) assesses the ability to recognise emotions accurately and their response speed. The participant is presented with computer morphed images derived from the facial features of real individuals each showing a specific emotion (happiness, sadness, anger, fear, disgust or surprise), displayed on an iPad, one at a time

(Figure 2.2). Each face is displayed for 200ms and then immediately obscured. The participant must select which emotion the face showed from 6 options. There is a total of 48 trials, 8 of each emotion. Scores are the percentage correct, as well as response latencies. There is a separate score given for each emotion, which is corrected for response guessing or response bias effects.

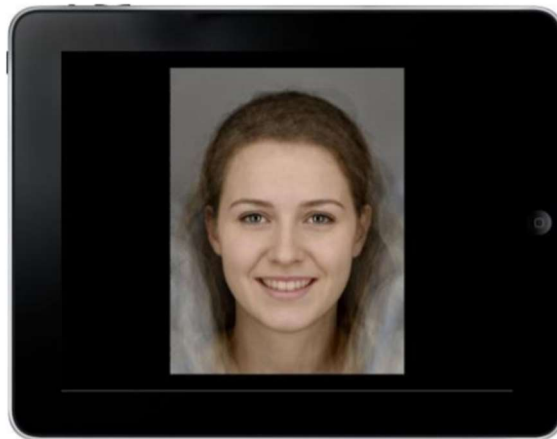


Figure 2.2: Screenshot of the CANTAB Emotion Recognition Task

2.2.4.3 Social Attribution Task- Multiple Choice (SAT-MC)

The SAT-MC consists of a 64-second silent animation showing geometric figures (a small triangle, a large triangle and a small circle) enacting a social drama, with 19 multiple choice questions about the interactions, scored one point for each correct answer and zero for an incorrect answer. It was originally developed for autism research by Heider and Simmel (1994) and has more recently been used in schizophrenia (Bell et al., 2010). The use of silent geometric images, presented monochromatically, means there is no task reliance of auditory processing, facial encoding or verbal comprehension scanning which could confound the task. The SAT-MC has traditionally been classed as measuring the domain of mental state attribution or ToM, but relies heavily on first perceiving and

interpreting of social cues and therefore can be thought of as a hybrid task, also measuring social perception (Pinkham et al., 2017).

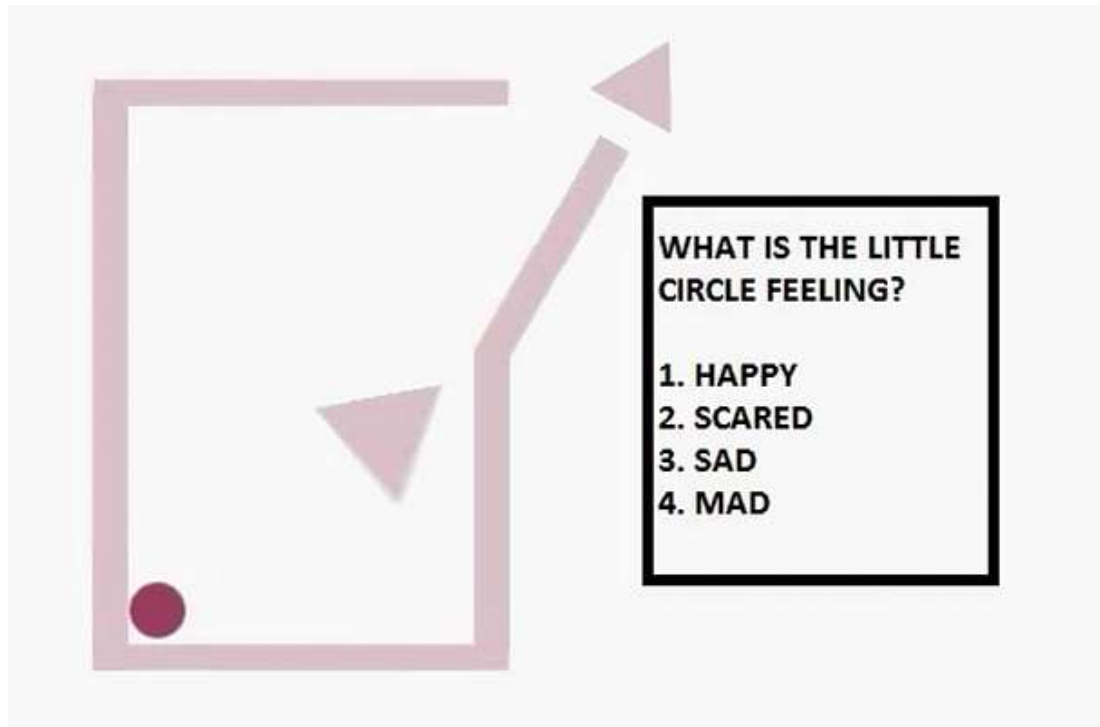


Figure 2.3: Screenshot of the SAT-MC

2.2.4.4 The Ambiguous Intentions and Hostility Questionnaire (AIHQ)

The AIHQ (Combs et al., 2007) assesses hostile social cognitive biases, with a focus on an individual's tendency to over-attribute hostile intentions to others. Five hypothetical, negative situations with ambiguous causes are presented as happening to the participant. Participants use Likert scales to rate whether someone has performed the action deliberately, how angry they feel about this and how much they blame the person. Evaluations of psychometric tests of social cognition have acknowledged the difference between assessing social cognition and assessing social biases, supporting the validity of continued evaluation of social cognitive biases (Buck et al., 2016). Questions have been raised over the incremental validity of the AIHQ and cumbersome rater-based

scoring. However, Buck et al., (2017) found that the full AIHQ, and the composite blame score (as scored by the participant) was sensitive to differences between patients and healthy controls and showed acceptable internal consistency and test retest reliability. Independent-rater items was included and double scored by two independent raters. Results from these items are treated with caution given that they are thought to provide little in the way of additional information above that of self-report items (Buck et al., 2016).

2.2.5 Neurocognitive Measures

2.2.5.1 WTAR

See section 2.1.6.2 (page 91)

2.2.5.2 Wechsler Abbreviated Scale of Intelligence – Second Edition

Similar to the WAIS-short form, the WASI-II (Wechsler, 2011b) is a 4-item test which provides a calculation of a current FSIQ score, normalised for age. These 4 items are:

2.2.5.3 Block Design

See section 2.1.6.7 (page 94)

2.2.5.4 Vocabulary

The vocabulary subtest is a measure of a participant's word knowledge and verbal concept formation. Participants are scored on a total of 28 items, awarded a score of 2 for a correct answer, 1 for a partially correct answer and 0 for an incorrect answer.

2.2.5.5 Matrix Reasoning

A measure of fluid intelligence, spatial intelligence and broad visual intelligence, participants are presented with 30 incomplete matrices or series and are asked to identify the missing item from a multiple-choice of images (Figure 2.4). A score of 1 is awarded for a correct answer and 0 for an incorrect answer.

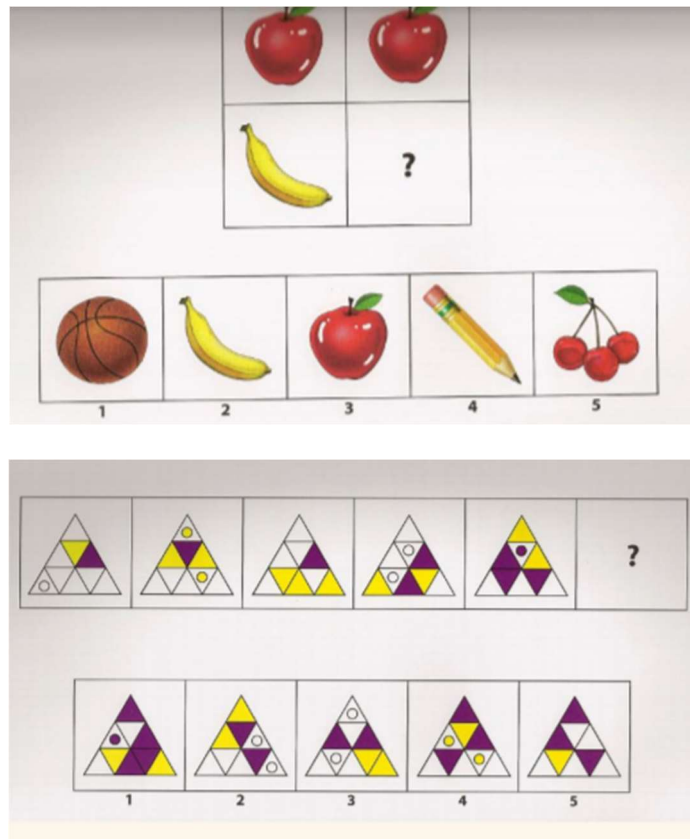


Figure 2.4: Screenshot of the WAIS-II Matrix Reasoning Task

2.2.5.6 Similarities

Designed to measure reasoning and verbal concept formation, the similarities subtest involves the participant being asked to identify the similarities between two words with common objects or concepts, of increasing difficulty. A score of 2 is awarded for a correct response, 1 for a partially correct response, and 0 for an incorrect response.

2.2.6 The Cambridge Automated Neuropsychological Cognitive Test Battery (CANTAB)

The CANTAB (CANTAB®, 2017) is considered a highly sensitive computerised assessment tool, which has become the gold standard for measurement of cognition in clinical trials. The tests are non-linguistic and culturally-blind. A major benefits of this computerised testing method includes the standardisation of instructions. Using CANTAB Connect for i-pad (CANTAB®, 2017), we assessed participants on the following domains/tasks:

Attention and Psychomotor Speed

2.2.6.1 Motor Screening Task (MOT)

The MOT was the first test in the battery. It is a short test of sensorimotor speed and comprehension and serves as an introduction to the touch screen format. Coloured crosses flash up on the screen one at a time (Figure 2.5). The participant is instructed to respond to seeing each cross by touching it with their forefinger as quickly and accurately as possible. Both speed of response and accuracy of the press are recorded. If unable to complete the MOT task, participants are unlikely to be able to complete other tests successfully. This task is also therefore used as a screening tool. **Approximate administration time: 2 minutes**

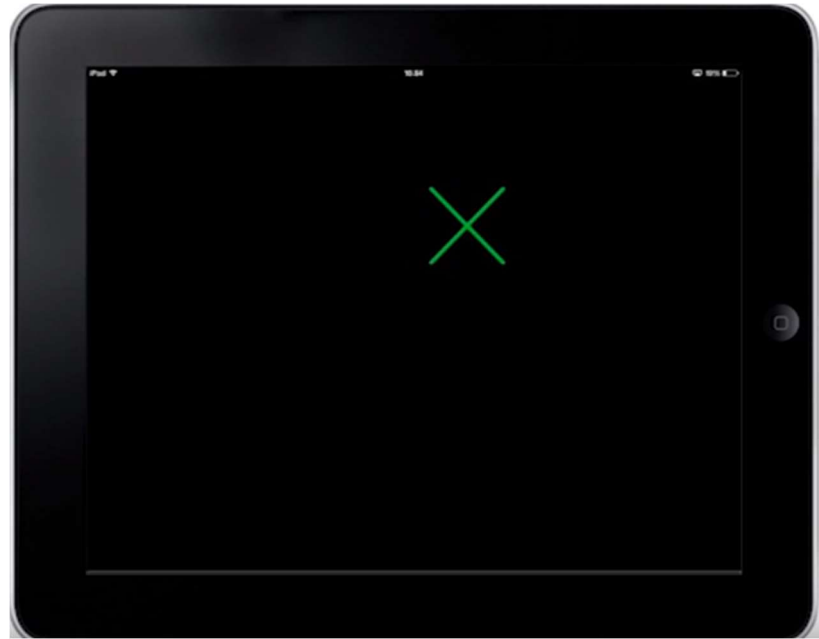


Figure 2.5: Screenshot of the CANTAB Motor Screening Task

2.2.6.2 Rapid Visual Information Processing (RVP)

The RVP task is a test of sustained attention. Participants are first presented with a box in the centre of the screen. Digits between 2 and 9 are presented at a rate of 100 digits per minute in apparent random order and the participant is instructed to respond as quickly as possible when seeing the consecutive sequence “3-5-7” by touching a button at the bottom of the screen (Figure 2.6). Response latency and probability of responding to false alarms are measured. **Administration time:** 7 minutes.



Figure 2.6: Screenshot of the CANTAB Rapid Visual Information Processing Task

2.2.6.3 Reaction Time (RTI)

The RTI task measures multiple functions including motor and mental response speed, reaction time and accuracy and impulsivity. Participants are presented with a touch-screen button at the bottom of the screen and asked to press and hold this at the beginning of each trial. When a yellow dot appears in a circle at the top of the screen, the participant is asked to press this as quickly as possible using the same finger with which they are holding down the button. Responses were measured for both the “simple mode” in which there is only one circle at the top of the screen and the “five-choice mode” in which there are five buttons (Figure 2.7). Only one button will light up on each trial. Outcome measures included are for movement time and reaction time.

Approximate administration time: 3 minutes.



Figure 2.7: Screenshot of the CANTAB Emotion Recognition Task

Executive Functions

2.2.6.4 One Touch Stockings of Cambridge (OTS)

The Stockings of Cambridge tasks are computerised variants of the Towers of Hanoi task (CANTAB®, 2017). The OTS version requires participants to find a solution using working memory and spatial planning and to select the minimum number of moves required for the solution. Participants are presented with a split screen of two pictorial representations of a series of coloured balls suspended in “stockings” (Figure 2.8). Participants are asked to calculate the minimum number of moves necessary to make the lower image match the upper image, when considering a number of rules similar to those in the Towers of Hanoi task: it is not possible for a ball to be held in mid “air” and no ball can be moved from underneath another without first moving the ball on top. Once the participant has calculated the minimum number of moves necessary for the solution, they select this number from buttons labelled 1, 2, 3, 4, 5 6 and 7 at the bottom

of the screen. The main outcome measure is the number of trials solved correctly on the first trial. Speed of response is also calculated. **Approximate administration time:** 10 minutes.

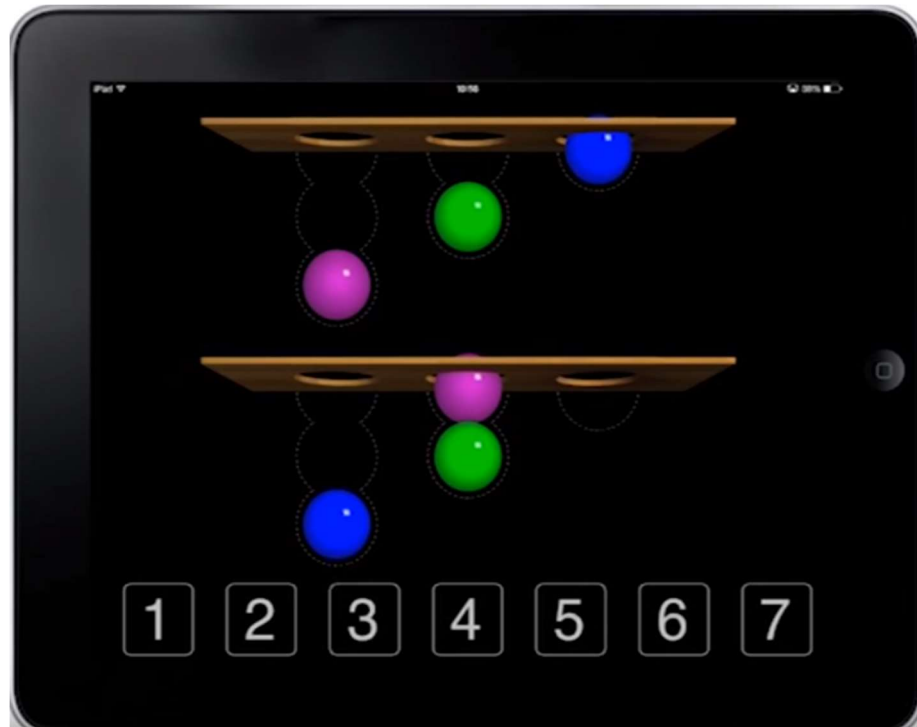


Figure 2.8: Screenshot of the CANTAB One Touch Stockings of Cambridge Task

2.2.6.5 Multitasking Test (MTT)

The MTT assesses participant ability to manage incongruent information. Participants are shown two buttons at the bottom of the screen and then presented with an arrow directly above one of the two boxes (Figure 2.9). Participants are first asked to press the box on same side of the screen as the arrow is presented. Following this, participants are asked to ignore the side of the screen the arrow is presented on, and to press the box on the side of the screen the arrow is pointing (left or right). In some tasks the rule remains the same, but later the rule changes with either the word “side” or “direction”

presented in the middle of the screen to give the participant instruction on which rule to follow. Some of the trials are congruent, where the arrow points to the same side as to that on which it is presented, and others are incongruent (e.g. presented on the left but pointing to the right). Outcome measures are response time and errors made. **Administration time:** 8 minutes.



Figure 2.9: Screenshot of the CANTAB Multitasking Test

Memory

2.2.6.6 Paired Associates Learning (PAL)

The PAL task is a measure of visual memory and learning. Participants are presented with boxes around the outside of the screen which open in an apparently random order. One of the boxes will contain a patterned image (Figure 2.10). Once all boxes have

finished opening, a pattern will be displayed in the centre of the screen and participants are asked to touch the box in which this pattern had appeared in. On each trial, if the participant gets this wrong, the boxes will open again in the same sequence for another attempt. Once correct, the participant moves on to the next trial which will have an increasing number of patterns and boxes, with the most difficult being 8 boxes with 8 unique patterns. Outcome measures include the number of attempts necessary to get each pattern correct, memory scores and number of stages which the participant successfully completed. **Approximate administration time: 8 minutes.**



Figure 2.10 Screenshots of the CANTAB Paired Associations Learning Task

2.2.6.7 Spatial Working Memory (SWM)

A further test of memory, the SWM task relies on executive functions and strategy use. Participants are presented with an increasing number of coloured boxes displayed in various stilted formations across the screen (to discourage stereotyped search strategies) (Figure 2.11). The instructions ask the participant to locate the box containing a token and, once found, to select a box on the side of the screen in which to put this

token. Participants are instructed of the number of tokens to be found and that tokens will never appear in the same box more than once. The most difficult task included 8 boxes, each containing a token. Outcome measures include number of times boxes already identified as containing a token were selected (errors) and strategy use.

Approximate administration time: 4 minutes

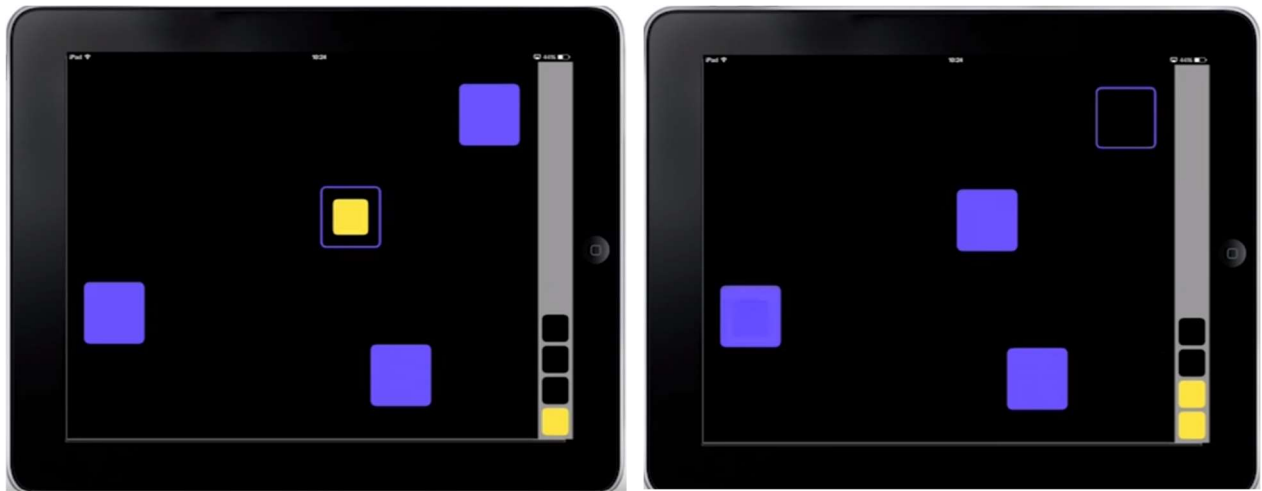


Figure 2.11: Screenshot of the CANTAB Spatial Working Memory Task

2.2.6.8 Order and Quality Check

Tasks were set up in an order which gave variation on type and length of test examined to maximise engagement (Table 2.4). The MOT task was placed first to identify if participants had any motor or comprehension problems which might impair their performance, from the outset. If any problems were encountered with any tests (e.g. participant distractibility or instruction misunderstanding) this was recorded at the end.

Table 2.4: Order of administration of CANTAB tests

Order	Test
1	Motor Screening Task (MOT)
2	Reaction Time (RTI)
3	One Touching Stockings of Cambridge (OTS)
4	Paired Associates Learning (PAL)
5	Multitasking Test (MTT)
6	Emotion Recognition Task (ERT)
7	Rapid Visual Information Processing (RVP)
8	Spatial Working Memory (SWM)

2.2.6.9 CANTAB Measures Used in the Analysis

To minimise the number of comparisons in the analysis, key measures were used for each CANTAB task, as detailed in the following table (Table 2.5)

Table 2.5: CANTAB measures used in analysis

Cognitive Task	Measures	Interpretation
AST	AST Total correct (AST): The number of trials for which the outcome was a correct response (subject pressed the correct button within the response window)	Higher number indicates better performance
OTS	OTS Problems Solved on First Choice (OTS): The total number of assessed trials where the subject chose the correct answer on their first attempt. Calculated across all assessed trials.	Higher number indicates better performance
PALS	PAL First Attempt Memory Score (PAL): The number of times a subject chose the correct box on their first attempt when recalling the pattern locations. Calculated across all assessed trials.	Higher number indicates better performance
RTI Simple	Simple Median Movement Time (RTI Simple Rel): The median time taken for a subject to release the response button and select the target stimulus after it flashed yellow on screen. Calculated across correct, assessed trials in which the stimulus could appear in one location only. Measured in milliseconds.	Lower number indicates better performance
	RTI Median Five-Choice Reaction Time (RTI Simple RT): The median duration it took for a subject to release the response button after the presentation of a target stimulus. Calculated across correct, assessed trials in which the stimulus could appear in any one of five locations. Measured in milliseconds.	Lower number indicates better performance
RTI 5-Choice	RTI Median Five-Choice Movement Time (RTI 5-Choice Rel): The median time taken for a subject to release the response button and select the target stimulus after it flashed yellow on screen. Calculated across correct, assessed trials in which the stimulus could appear in any one of five locations. Measured in milliseconds.	Lower number indicates better performance
	RTI Median Five-Choice Reaction Time (RTI 5-Choice RT): The median duration it took for a subject to release the response button after the presentation of a target stimulus. Calculated across correct, assessed trials in which the stimulus could appear in any one of five locations. Measured in milliseconds.	Lower number indicates better performance
RVP	RVP prime (RVP) is the signal detection measure of a subject's sensitivity to the target sequence (string of three numbers), regardless of response tendency (the expected range is 0.00 to 1.00; bad to good). In essence, this metric is a measure of how good the subject is at detecting target sequences.	Higher number indicates better performance
SWM Errors	SWM Between Errors (SWM): The number of times the subject incorrectly revisits a box in which a token has previously been found. Calculated across all assessed four, six and eight token trials.	Lower number indicates better performance

2.2.7 Clinical Measures

2.2.7.1 PANSS – See Section 2.1.7.1

2.2.7.2 Calgary Depression Scale for Schizophrenia (CDSS) - See Section 4.3.5.2

2.2.7.3 The Clinical Assessment Interview for Negative Symptoms (CAINS)

In addition to the PANSS sub-section, the CAINS (Kring et al., 2013) is used as a measure of negative symptoms. The CAINS is a newer measure of negative symptoms, which separates the different aspects of negative symptoms experienced by the individual. This semi-structured interview is conducted with the participant, who is rated on 13 different items, composing 2 sub-scales; a 9-item motivation scale and a 4-item pleasure scale. Each item is rated on a 5-point (0-4) scale with symptoms ranging from absent (0) to severe (4). This measure is shown to have good reliability and internal consistency.

2.2.8 Functional Outcome Measures

2.2.8.1 Social and Occupational Functioning Assessment Scale (SOFAS)

The SOFAS (Goldman et al., 1992) is similar to the GAF in that it gives a measure of functioning on a scale of 0 – 100 (grossly impaired – excellent) using 10 anchor points. However, in contrast to the GAF, the scale focusses on the participant's social and occupational functioning and is not directly influenced by the severity of the individual's clinical symptoms. The scale is completed by the rater using the anchor points and scoring guidance.

2.3 Data Analysis Methodology

2.3.1 General Assumptions

It is important that data meet the assumptions of the statistical test being employed. All data were therefore tested for outliers and normal distribution. Data were assessed for outliers using Statistical Package for the Social Sciences (SPSS) [IBM® SPSS® Statistics Version 25.0.] box-plots with univariate outliers considered to be those more than 3 interquartile ranges from the mean. Where multivariate outliers are assessed, values with a Cook's Distance of more than 3 times the mean were considered outliers and excluded in analyses. Data were examined for normal distribution using visual inspection of box plots, and tests of skewness and kurtosis. Non-normally distributed data were returned to normal distributions using logarithm transformations where possible. Where it was not possible to return data to a normal distribution, non-parametric equivalent statistics were used. Tables included in this thesis include means with standard deviations in parentheses unless otherwise stated. Minor differences in degrees of freedom are due to individual missing data points resulting from pairwise deletion

2.3.2 Study 1 – Cognitive Reserve: Relationship with neurocognitive, clinical and functional outcomes

The identification of cognitive clusters based on IQ trajectories were determined with the use of data-driven cluster analysis [IBM® SPSS® Statistics Version 25.0.] according to the method of Weickert et al., (2000). Pre-morbid and FSIQ were entered into a hierarchical cluster analysis using complete linkage and squared-Euclidean distances (to ensure maximum distance between clusters). The resulting dendrogram was used to

identify the number of clusters within the data and then entered into a *k*-means cluster analysis to create the cluster variables. This forces data into the most relevant cluster. Clusters were verified using discriminant function analysis (DFA). Resulting clusters were analysed using one-way analysis of variance (ANOVA) for continuous, current cognitive, clinical, functional and biological markers and Chi-square for demographic and other categorical data. Where there was need to control for potential confounders between groups, analysis of covariance (ANCOVA) was used. False-discovery rate (FDR) correction was applied to main effects to account for multiple testing. Post-hoc group comparisons were performed on significant ($p = <0.05$) results, with Bonferroni correction applied to correct for multiple comparisons. Effect sizes calculated using Cohen’s method (Cohen, 2013) were used to quantify the magnitude of the differences between groups. A list of covariates used for each analysis are shown in Table 2.6.

Table 2.6: List of covariates used in Study 1 analysis

Analysis	Covariates entered
Neurocognitive Measures	Sex
Clinical Symptom Measures	None
Functional/Social Outcome Measures	None
Neuroimaging	Age, sex, scan site, intracranial volume*
Inflammatory Markers	Age, sex, cannabis smoking status, body mass index (BMI)

*not included in analysis of: absolute intracranial volume, total brain volume, cortical thickness

2.3.3 Study 2 - Longitudinal Cognitive and Functional Trajectories of Neurocognitive Subtypes

Twelve-month follow-up data was used to examine the cognitive, clinical and functional outcomes of the different cognitive subtyped groups from study 1. Demographic data were analysed using chi-square tests for categorical variables and ANOVA for continuous variables. Differences between those who remained in the study and those who were not available at follow-up were analysed using t-tests. ANCOVAs were used to compare outcome differences between groups at follow-up, with experimental allocation of the randomised controlled trial (RCT) entered as a covariate in all analyses. Differences in change over time within and between the groups were investigated using repeated-measures ANCOVA. Additional covariates were entered to control for differences between groups, as at baseline (Table 2.7). Change in intracranial volume was also controlled for in the imaging analysis, to account for head position changes relative to baseline. FDR corrections were applied to all main effects, with Bonferroni corrections for multiple comparisons of significant main effects. A list of covariates included in study 2 analysis are shown in Table 2.7.

Table 2.7: List of covariates used in Study 2 analysis

Analysis	Covariates entered	
	Cross-Sectional	Change over time
Neurocognitive Measures	Sex and study allocation	Sex and study allocation
Clinical Symptom Measures	Study allocation	Study allocation
Functional/Social Outcome Measures	Study allocation	Study allocation
Neuroimaging	Age, sex, scan site, intracranial volume*, study allocation	Age, sex, scan site, change in intracranial volume*, study allocation
Inflammatory Markers	Age, sex, cannabis smoking status, BMI, study allocation	Age, sex, cannabis smoking status, BMI, study allocation

*not included in analysis of: intracranial volume, absolute total brain volume, cortical thickness

2.3.4 Study 3 - Neurocognitive Predictors of Global and Social Functional Outcomes in First-Episode Psychosis

The discriminant validity of IQ subtests and additional cognitive tasks at baseline was assessed using Pearson’s zero-order correlations. To assess relationships between all cognitive tasks and functioning, Pearson’s zero-order correlations between baseline cognitive variables and the GAF and SFS total and SFS subscales at 12-month follow-up were performed. To establish the amount of variance in specific outcomes predicted, hierarchical linear regressions using forward-step entry were performed, with baseline cognitive variables as independent variables and each social and global functioning

measure as the dependent variables. In addition to the cognitive subtests, correlational and regression analyses were performed with baseline and premorbid IQ entered as the independent variables. All correlations and the best fitting regression models were reported.

2.3.5 Study 4 - Social Cognitive Deficits in a First-episode Cohort

Healthy controls (n=50) and patients (n=84) were first compared on demographic characteristics using chi-square tests for categorical data and t-tests for continuous data. To examine differences on measures of social cognition, a series of ANCOVAs were performed covarying for age and sex. To adjust for neurocognition, full-scale IQ was then controlled for in an additional analysis. To determine discriminant and predictive validity of the social cognitive tests, Pearson 's zero-order correlations were performed between social cognition variables. FDR correction was used to correct for multiple comparisons.

2.3.6 Study 5 - Does Social Cognition Mediate the Relationship Between Neurocognition and Social Functioning?

Structural equation modelling (SEM) was used to explore the relationship between neurocognition, social cognition and functional outcomes. First, relationships between, neurocognition, social cognition and functional outcome variables were examined using two-tailed Pearson correlations, which were also examined using curve estimations. Those significantly linear, were included in SEM models, first using a basic model to examine the direct relationship between neurocognition and functional outcome using regression analysis and secondly examining the mediating effect of social cognition using a combination of regression and confirmatory factor analysis. The mediation model

consisted of first assessing the relationship between neurocognition and social cognition and between social cognition and social and occupational functioning (indirect effect) using regression. Social cognition was comprised of a latent variable of social cognitive domains significantly relating to social and occupational functioning. Both relationships were significant, meaning it was appropriate to examine the relationship between neurocognition and social and functional outcome once the mediator was controlled for (direct effect).

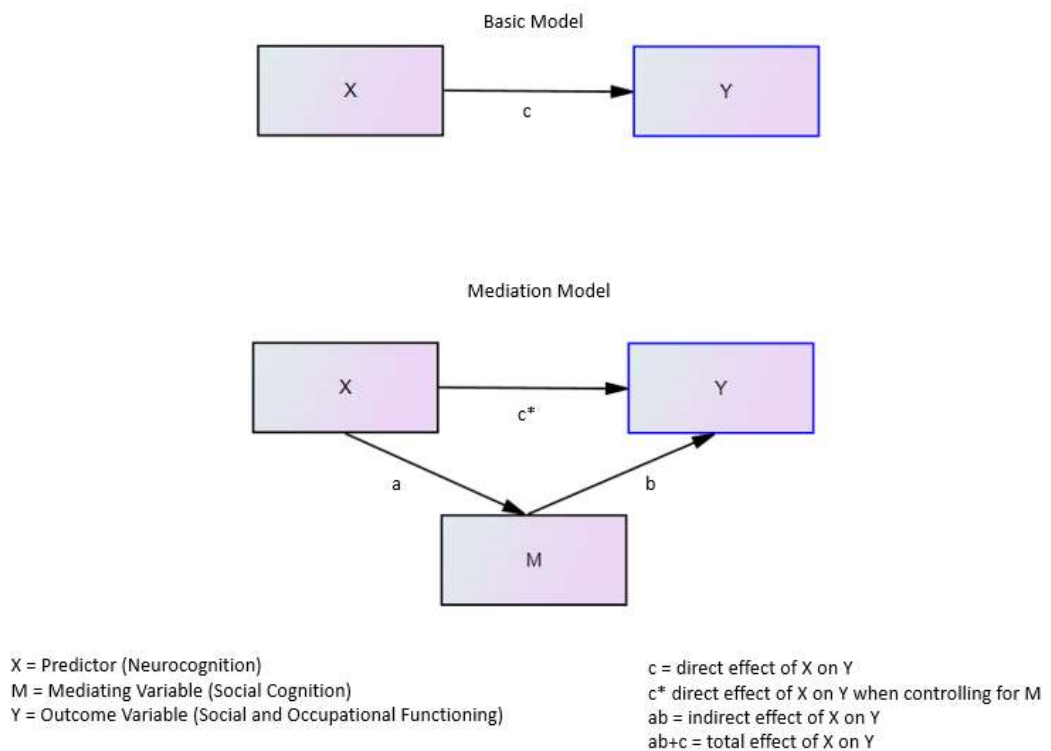


Figure 2.12: Schematic of Basic and Mediation Model Paths

3 Study 1 – Neurocognitive Subtypes: Relationship with cognitive, clinical and functional outcomes

3.1 Introduction

Cognitive dysfunction is considered a common feature of schizophrenia at all stages of illness (Reichenberg and Harvey, 2007, Meier et al., 2014), with variable social, functional and occupational outcomes following a first-episode of psychosis (FEP) attributed in part to heterogeneity in cognitive deficits in this population (Green et al., 2000, Green, 2006). Cognitive subtypes of schizophrenia have been identified based on differences between pre and post illness onset estimates of cognitive performance. In most studies patients have broadly been categorised into three trajectory classifications; preserved, deteriorated or compromised (see section 1.5.3) with studies categorising patients in long-standing schizophrenia populations identifying between 24.8% - 44.4% of their patient groups with putatively preserved cognition (Ohi et al., 2017).

Weickert et al., (2000) hypothesised that cognitive subgroups may reflect differential neurodevelopmental processes. If this is the case, one would expect to observe heterogeneous indices of neuropathology between groups. Given the relationship between brain volume and global intelligence (McDaniel, 2005) recent studies have attempted to establish whether cognitive subtypes are characterised by brain volumetric differences in schizophrenia samples (see section 1.5.5). There is also growing evidence that immune and inflammatory mechanisms may also play an important role in cognitive functioning (Roberts et al., 2009) and in schizophrenia (Fond et al., 2018, Ribeiro-Santos et al., 2014), with evidence that low grade systemic

inflammation increases risk for schizophrenia even when controlling for potential confounders (see section 1.5.6).

Recently, data-driven approaches have been used to identify IQ trajectory-based subtypes using cluster analyses (Weickert et al., 2000, Reser et al., 2015). Only one study has assessed IQ trajectory early in the course of illness (Leeson et al., 2011) and used predetermined clustering criteria and did not explore the biological characterisation of cognitive subtypes.

In this study an unbiased data driven approach was used to establish subtype relationships with cognition, clinical symptoms and functioning in a cross-section of patients following a FEP. Patients were clustered on the basis of decline on a general cognitive measure: IQ. This study aims to advance previous research by comparing cognitive subtypes based on total brain volume (TBV) and cortical thickness as well as inflammatory markers, in order to establish whether cognitive subtypes are characterised by differential neurobiological markers present early in the course of illness. It was predicted that cluster analysis would reveal three group trajectories, consistent with previous work (Leeson et al., 2011, Weickert et al., 2000, Wells et al., 2015). A compromised group was expected to have more negative symptoms, and smaller aTBV and ICV than preserved and deteriorated groups. Preserved groups were predicted to have better global cognitive function than the deteriorated and compromised groups, and superior social and global functioning. Whether the groups would be separable on measures of aTBV and TBV after adjusting ICV was uncertain and examining differential inflammatory marker profiles between groups remained exploratory.

3.2 Methods

3.2.1 Participants

The patient data were collected as part of the BeneMin study (see section 2.1). Healthy control data were collected as part of the West London First-Episode Study (Leeson et al., 2011) (see section 2.1.3). Once outliers were removed (using the same method as for the patient groups - described in section 2.3.1), 82 controls were included for comparison. Controls participants were not assessed on the COWAT and therefore this was not available for comparison.

3.2.2 Premorbid IQ

Premorbid IQ was measured using the Wechsler Test of Adult Reading (WTAR) (see section 2.1.6.2).

3.2.3 Current IQ

Current IQ was assessed with the WAIS-III Blyler Short-Form (Blyler et al., 2000), developed for use in schizophrenia (see sections 2.1.6.2 and 2.1.6.8).

3.2.4 Cluster Analysis

Patients with incomplete IQ data ($n = 41$) were not included in the analysis. Those with a premorbid IQ of more than 10 IQ points below current IQ ($n=5$) were considered outliers and also excluded as the WTAR was unrepresentative of their premorbid function. Patient data (premorbid IQ and current IQ) were entered into a hierarchical cluster analysis using complete linkage and squared-Euclidean distances (to ensure

maximum distance between clusters). The resulting dendrogram was used to identify the number of clusters. The data were then entered into a non-hierarchical iterative *k*-means cluster analysis to create clusters with the greatest separation after allowing for iterations. Discriminant function analysis (DFA) showed good separation of clusters with 96.3% of cases correctly classified.

3.2.5 Other Cognitive Measures

Additional cognitive measures were used to capture domains not measured as part of the Blyler WAIS-III short-form. The Rey Auditory Verbal Learning Test (AVLT) (Schmidt, 1996) was used to evaluate verbal learning and memory (see section 2.1.6.9).

3.2.6 Clinical and Functioning Measures

Psychotic symptoms were measured using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). For an additional measure of affective symptoms, the Calgary Depression Scale (CDSS) (Addington et al., 1990b) was used. Social functioning was measured using the self-report Social Function Scale (SFS) (Birchwood et al., 1990). To assess global functioning, the researcher completed the Global Assessment of Functioning (GAF). Cannabis use was assessed using a self-report measure as well as a dipstick urine drug-screen. See section 2.1 for details of the measures.

3.2.7 Neuroimaging

Collection and processing of neuroimaging data is described in chapter 2, section 2.1.10.

3.2.8 Measurement of Inflammatory Markers

Cytokine assays for IL1RA, IL6, TNF α and CRP were carried out at Kings College London using Meso Scale Discovery (MSD) V-PLEX sandwich immunoassays (Deakin et al., 2018)

3.2.9 Analysis

Resulting clusters were analysed using one-way analysis of variance (ANOVA) and analysis of covariance (ANCOVA) for normally distributed continuous cognitive, clinical and functional measures and Chi-square for demographic and other categorical data. Logarithm transformations were applied to non-normally distributed continuous data. Due to differences between the healthy controls and patient groups, sex was entered as a covariate in all cognitive analyses comparing patients with healthy controls. For the imaging analysis, sex, age and centre were controlled for when comparing groups. Additionally, BMI and cannabis use were controlled for as potential confounders in the inflammatory analysis. To control for multiple testing, false discovery rate (FDR) correction was applied to p -values using the Benjamini-Hochberg method set at 5% (Benjamini and Hochberg, 1995). For ease of interpretation, P -values are reported before correction. Post-hoc tests were performed only for those results significant after accounting for multiple comparisons (using FDR). Cognitive, clinical, functioning, imaging and inflammation variables were tested separately with alpha level set to 0.05. Where there was a significant effect of group, post-hoc group comparisons with Bonferroni correction were performed to compare subgroups. Effect sizes (ES) were calculated using the method of Cohen (Cohen, 2013). Z-score transformations of patient scaled scores were calculated using the mean and standard deviations of controls.

3.3 Results

3.3.1 Patients Vs Controls

3.3.1.1 Demographics

Demographic data of the patient and healthy control groups are shown in Table 3.1. The control group included significantly more females and had a mean of more years of education than the patient group. Sex was therefore controlled for when comparing patients with healthy controls in subsequent analyses. Years of education were not controlled for due to the association between education and IQ.

Table 3.1: Demographics of patients and control group

	Patients (n=161)	Controls (n=82)	t/χ^2	Significance
Age	25.36 (5.02)	26.83 (6.61)	t (242) = 3.72	<i>p</i> = 0.06
Sex (% Male)	77.01%	50.00%	χ^2 (1) = 18.19	<i>p</i> < .001
Years of Education	12.80 (1.89)	14.20 (2.03)	t (242) = -3.989	<i>p</i> < .001

Bold font denotes significance

3.3.1.2 Cognition

Table 3.2 shows the cognitive performance of healthy controls and patients. The groups did not differ on premorbid IQ measure. The healthy controls outperformed the patient group on all post-illness measures of cognition.

Table 3.2: Patient vs healthy control comparison of performance on IQ and cognitive subtasks at baseline (mean and standard deviations)

	Patients (n=161)	Controls (n=82)	t/χ^2	Significance
Premorbid IQ	98.98 (11.38)	100.75 (8.92)	t (242) = -1.240	<i>p</i> = 0.135
Full-Scale IQ	88.55 (13.86)	100.31 (11.63)	t (242) = -6.616	<i>p</i> < 0.001
Digit Symbol	6.23 (2.42)	9.24 (2.27)	t (242) = -9.401	<i>p</i> < 0.001
Arithmetic	8.11 (3.04)	9.40 (2.79)	t (242) = -3.230	<i>p</i> = 0.001
Information	9.75 (3.22)	11.37 (2.44)	t (242) = -4.007	<i>p</i> < 0.001
Block Design	9.04 (2.92)	10.30 (2.51)	t (242) = -3.315	<i>p</i> = 0.001
AVLT Immediate	5.03 (1.82)	6.04 (1.75)	t (239) = -4.145	<i>p</i> < 0.001
AVLT Total	37.72 (10.88)	49.84 (8.94)	t (240) = -8.597	<i>p</i> < 0.001

AVLT = Auditory Verbal Learning Test. Bold font denotes significance following FDR correction

3.3.2 Cluster Analysis

Hierarchical cluster analysis on the patient group produced a dendrogram indicating a three/four group solution as determined by consensus from AJW and EMJ [Figure 3.1]. Subsequent k-means cluster analysis with groups set to ‘3’ showed superior cluster stability indicated by fewer iterations than when set to “4”. Setting the groups to 3 resulting in 35% of patients classified as putatively preserved (PIQ), 38% as deteriorated (DIQ) and 27% as compromised (CIQ).

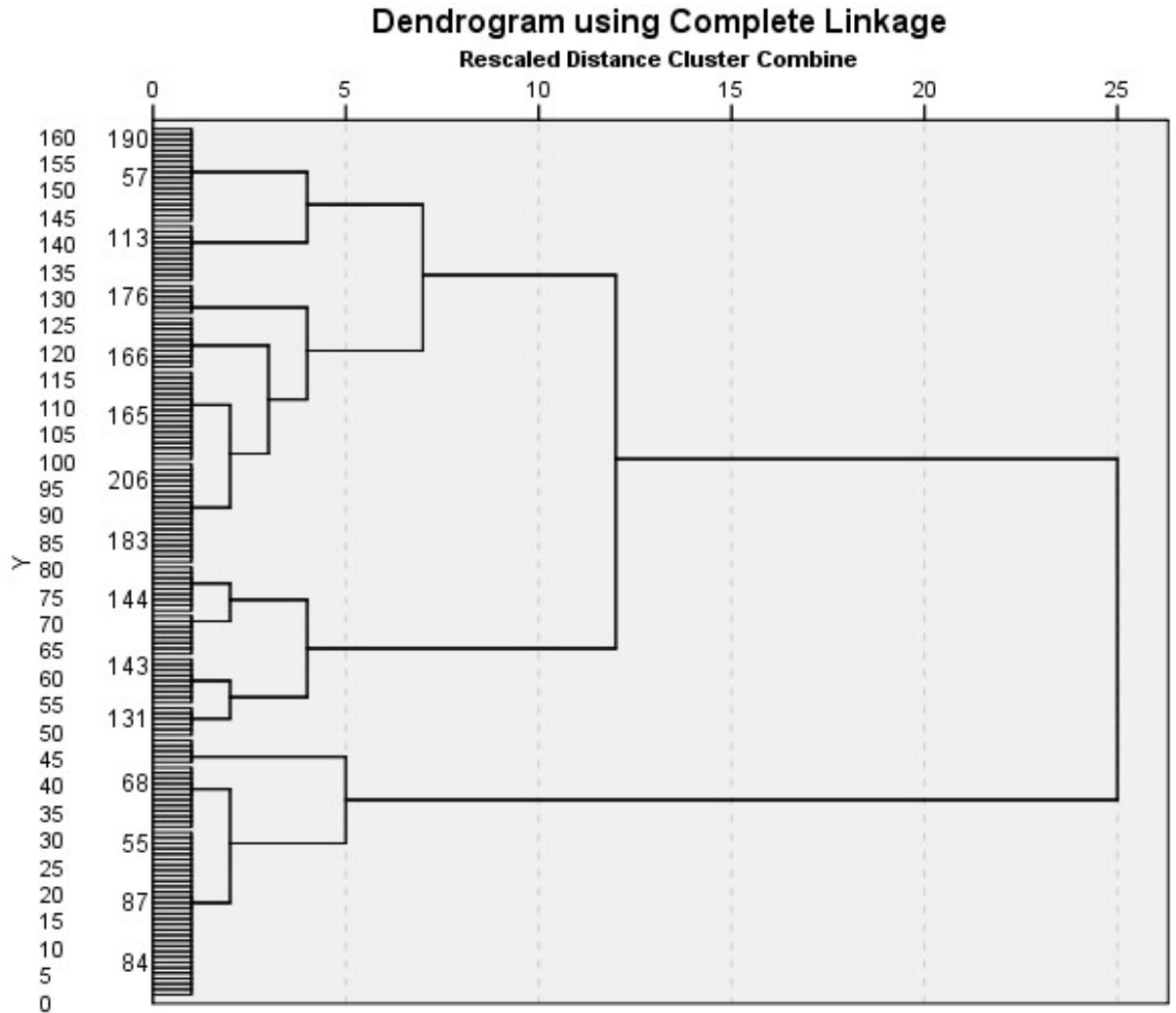


Figure 3.1: Dendrogram resulting from exploratory hierarchical cluster analysis with premorbid and current IQ entered as the only variables.

3.3.3 Demographics

Table 3.3 shows comparisons for the empirically derived cognitive subgroups and healthy controls. The PIQ and HC group had more years of education than the CIQ group. The HC group also had more years of education than the DIQ group. There were fewest “never” cannabis users in the PIQ group, but this comparison across groups was not statistically significant.

Table 3.3: Demographics of healthy controls and cognitive clusters

	HC (n=82)	PIQ (n=57)	DIQ (n=61)	CIQ (n=43)	Comparison	
					Main Effect (χ^2/F)	<i>post-hoc</i>
Age	26.83 (6.61)	25.63 (5.64)	24.30 (4.48)	26.28 (4.51)	F (3,242) = 2.497, <i>p</i> = 0.06	
Sex (% Male)	50.00%	84.20%	70.50%	76.74%	χ^2 (3) = 19.180, <i>p</i> = <0.001	HC < PIQ, DIQ, CIQ
Years of Education	14.20 (2.03)	13.20 (1.93)	12.92 (2.06)	11.72 (1.12)	F (3,242) = 8.581, <i>p</i> = <0.001	PIQ > CIQ; HC > DIQ + CIQ
Lifetime Cannabis Use (% Yes)	*	72.2%	47.5%	65.1%	χ^2 (2) = 0.589, <i>p</i> = 0.745	

HC, Healthy Controls; PIQ, Preserved IQ; DIQ, Deteriorated IQ; CIQ, Compromised IQ. Bold font denotes significance following FDR correction. *Data not available

3.3.4 Cognition

Figure 3.2 shows a scatterplot of the patients' premorbid and current IQ according to allocation to cognitive subgroups. Figure 3.3 shows this with the healthy control group scores superimposed. These illustrate variation in the degree of decline from premorbid IQ estimates in all groups, including healthy controls.

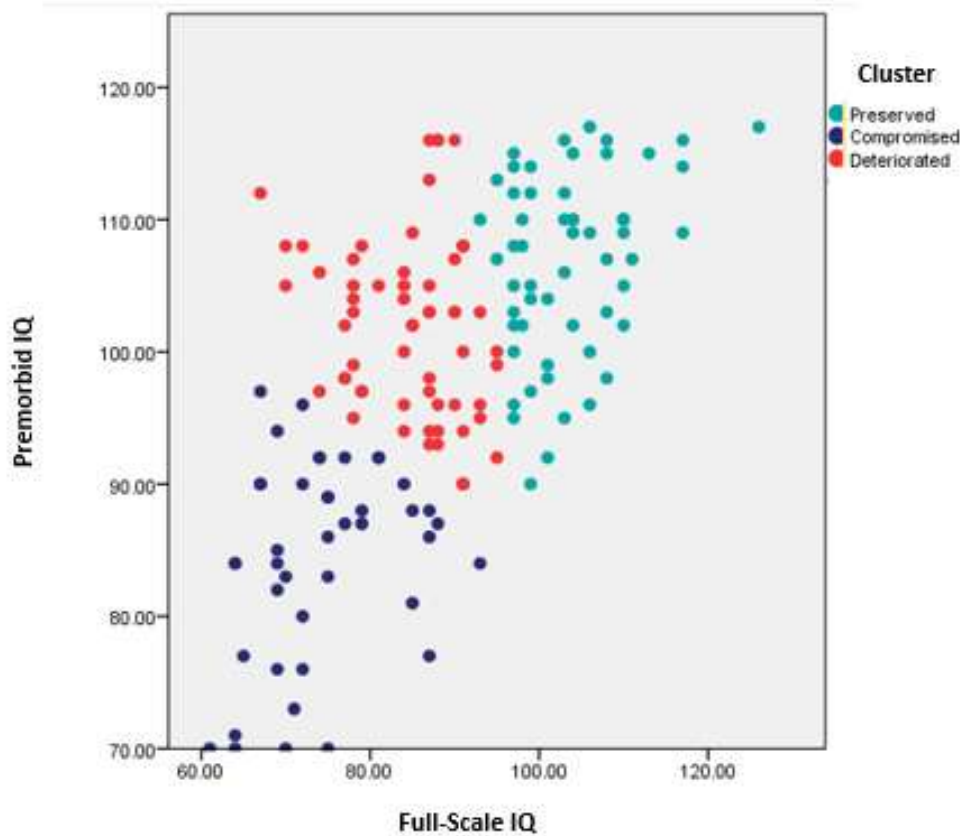


Figure 3.2 – Scatterplot showing premorbid and full-scale IQs of clustered patients

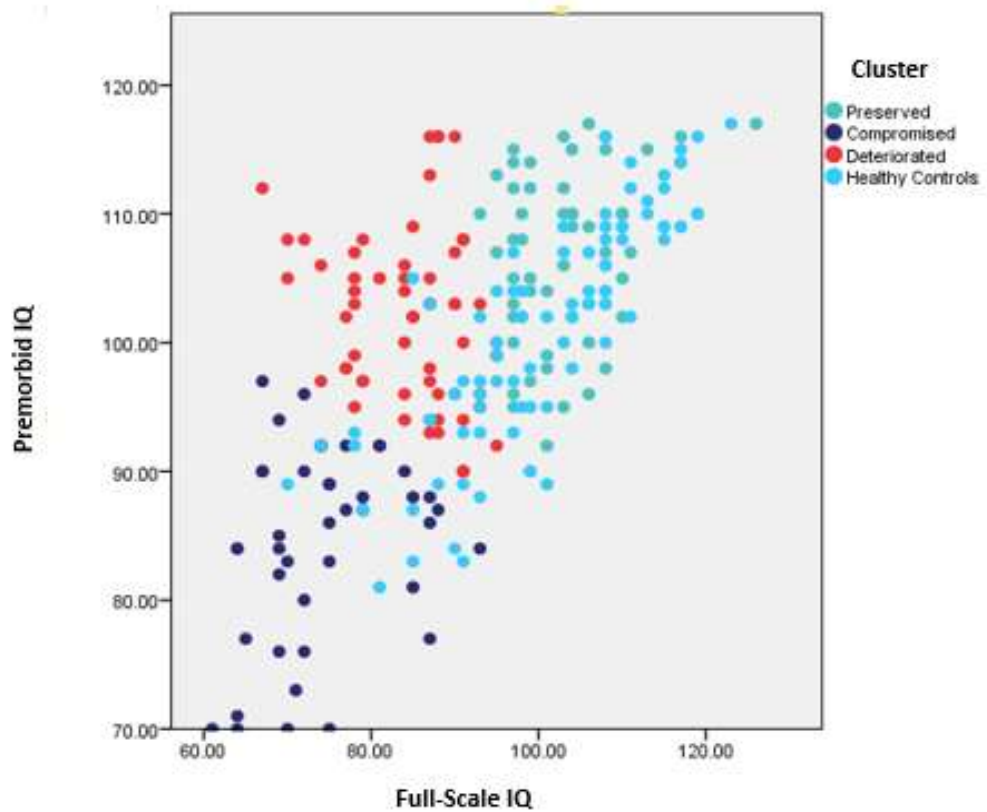


Figure 3.3 – Scatterplot of premorbid and full-scale IQs of clustered patients and healthy controls

One-way ANCOVAs controlling for sex, on each of the cognitive variables showed significant differences between groups on all cognitive tests and significant post-hoc tests for all variables following Bonferroni corrections. Table 3.4 shows the cognitive performance means for all groups. The PIQ group had significantly higher estimated

premorbid IQ than the HC group. The current IQ of the PIQ and HC groups was not significantly different.

For IQ subtests, the preserved group showed scores significantly superior to HCs on tests of information (crystallised knowledge), block design and arithmetic, but significantly inferior performance on the digit symbol (processing speed) task [ES = 0.67].

Figure 3.4 shows that the HC, PIQ and DIQ groups had a premorbid IQ in the average range and the CIQ group in the low average range. The current IQ of the PIQ and HC groups remained in the average range although there was small but significant fall in IQ in the PIQ group ($t [56] = 2.993, p = .004$). To enable comparison with other studies, this group are referred to throughout this thesis as “preserved IQ”, but would be better thought of as “relatively preserved” or “high-functioning”. The DIQ group had a significant fall in mean IQ into the low average range ($t [60] = 12.485, p < .001$) and the CIQ group showed further significant deterioration into the ‘borderline’ range ($t [42] = 6.952, p < .001$)

Table 3.4: Comparison of group cognitive function at baseline

	HC (n=82)	PIQ (n=57)	DIQ (n=61)	CIQ (n=43)	Comparison							
					Main Effect (F)	<i>post-hoc</i> ^a	Effect Size (d)					
							HC vs PIQ	HC vs DIQ	HC vs CIQ	PIQ vs DIQ	PIQ vs CIQ	DIQ vs CIQ
Premorbid IQ ^a	100.96 (8.78)	106.75 (6.91)	101.75 (6.80)	84.74 (7.93)	F (3, 239) = 71.31, <i>p</i> < 0.001	PIQ > HC, DIQ > CIQ	0.7*	0.1	1.9**	0.7*	3.0**	2.3**
FSIQ ^a	100.34 (11.70)	103.59 (6.67)	84.72 (6.80)	74.04 (7.95)	F (3, 239) = 127.22, <i>p</i> < 0.001	HC, PIQ > DIQ > CIQ	0.3	1.8**	2.6**	2.8**	4.0**	1.4**
Digit Symbol ^a	9.24 (2.27)	7.53 (2.79)	5.93 (1.94)	4.93 (1.56)	F (3, 239) = 44.83, <i>p</i> < 0.001	HC > PIQ > DIQ, CIQ	0.7*	1.6*	2.2**	0.7*	1.2**	0.6*
Block Design ^a	10.29 (2.52)	11.45 (2.39)	8.22 (2.29)	7.02 (2.09)	F (3, 239) = 37.52, <i>p</i> < 0.001	PIQ > HC > DIQ, CIQ	0.5*	0.8**	1.4**	1.3**	1.9**	0.5*
Information ^a	11.39 (2.45)	12.49 (2.29)	9.22 (2.57)	6.88 (2.03)	F (3, 239) = 55.43, <i>p</i> < 0.001	PIQ > HC > DIQ > CIQ	0.5*	0.9**	2.0**	1.4**	2.6**	1.1*
Arithmetic ^a	9.41 (2.81)	10.73 (2.05)	7.44 (2.33)	5.60 (2.31)	F (3, 239) = 43.60, <i>p</i> < 0.001	PIQ > HC > DIQ > CIQ	0.5*	0.8**	1.5**	1.5**	2.3**	0.8**
AVLT Immediate ^a	6.08 (1.73)	5.48 (2.08)	5.16 (1.60)	4.23 (1.52)	F (3, 236) = 10.64, <i>p</i> < 0.001	HC > DIQ > CIQ; PIQ > CIQ	0.35	0.6*	1.1**	0.1	0.7*	0.6*
AVLT Total ^a	49.86 (8.82)	42.76 (11.19)	37.25 (8.71)	32.04 (10.28)	F (3, 236) = 37.95, <i>p</i> < 0.001	HC > PIQ > DIQ > CIQ	0.7**	1.4**	1.9*	0.5*	1.0**	0.5*
Verbal Fluency	*	94.84 (24.13)	80.03 (18.73)	67.95 (18.17)	F (2, 158) = 20.89, <i>p</i> < 0.001	PIQ > DIQ > CIQ	*	*	*	0.7*	1.2**	0.6*

^a Sex was entered as a covariate for comparisons with healthy controls. *indicates medium effect size, ** indicates large effect size. HC = healthy controls, PIQ = preserved IQ group, DIQ = deteriorated IQ group, CIQ = compromised IQ group. FSIQ = full-scale IQ. AVLT = Auditory Verbal Learning Test. Bold font denotes significance following FDR correction.

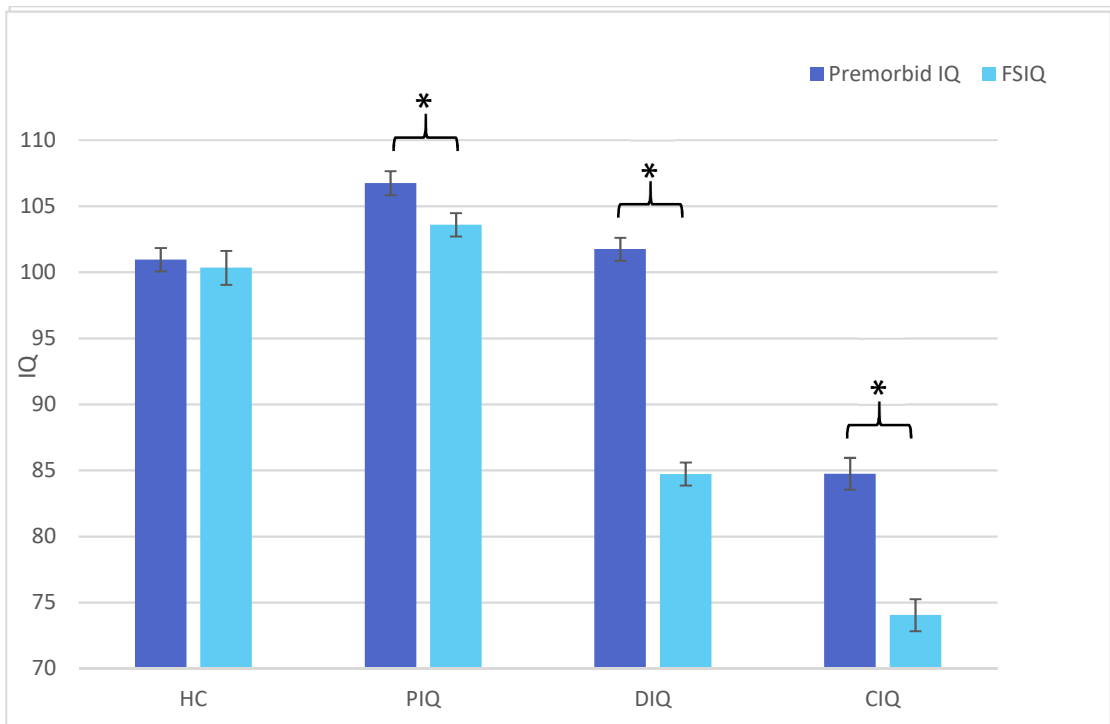


Figure 3.4: Bar chart comparing estimated premorbid IQ and full-scale current IQ scores for cognitive subtypes and healthy controls

HC = healthy controls, PIQ = preserved IQ group, DIQ = deteriorated IQ group, CIQ = compromised IQ group. FSIQ = Full-scale IQ. * denotes statistical significance. Error bars represent standard error of mean (SE).

To illustrate the discrepancies from healthy controls, Figure 3.5 shows subdomain scaled scores and standardised z-scores from healthy control performance. The PIQ group performed 0.74 standard deviations below HCs on the digit symbol task. The PIQ performed better than the DIQ on all IQ subtests, who in turn performed better or equivalent to the CIQ group except for block design where there was no difference between the DIQ and CIQ groups. HCs also performed significantly better than the PIQ group on the AVLT test who performed significantly better than DIQ and CIQ groups (Figure 3.6).

A mixed within and between subjects ANCOVA to test for differences in performance across subtests revealed a significant main effect of WAIS III subtest ($F(3) = 32.252, P < 0.001$) indicating that the performance profile was not flat for any of the groups. There was also a significant subtest x group interaction ($F(9) = 3.993, P < 0.001$). To further explore differences in subtest performance profile, deviation contrasts were performed comparing mean scores on each subtest with the grand means across the remaining 3 subtests (Table 3.5). Within groups, there was a significant deviation from average on the digit symbol subtest for all groups, and on the information-subtests (for all but the CIQ); reflecting above average performance on the information task and below average performance on the digit symbol task. The PIQ and CIQ groups had relatively greater scores on the block design test whereas this was average in the HC and DIQ groups. The HC group had within-group below average performance on the arithmetic task, whilst this was average in the other groups.

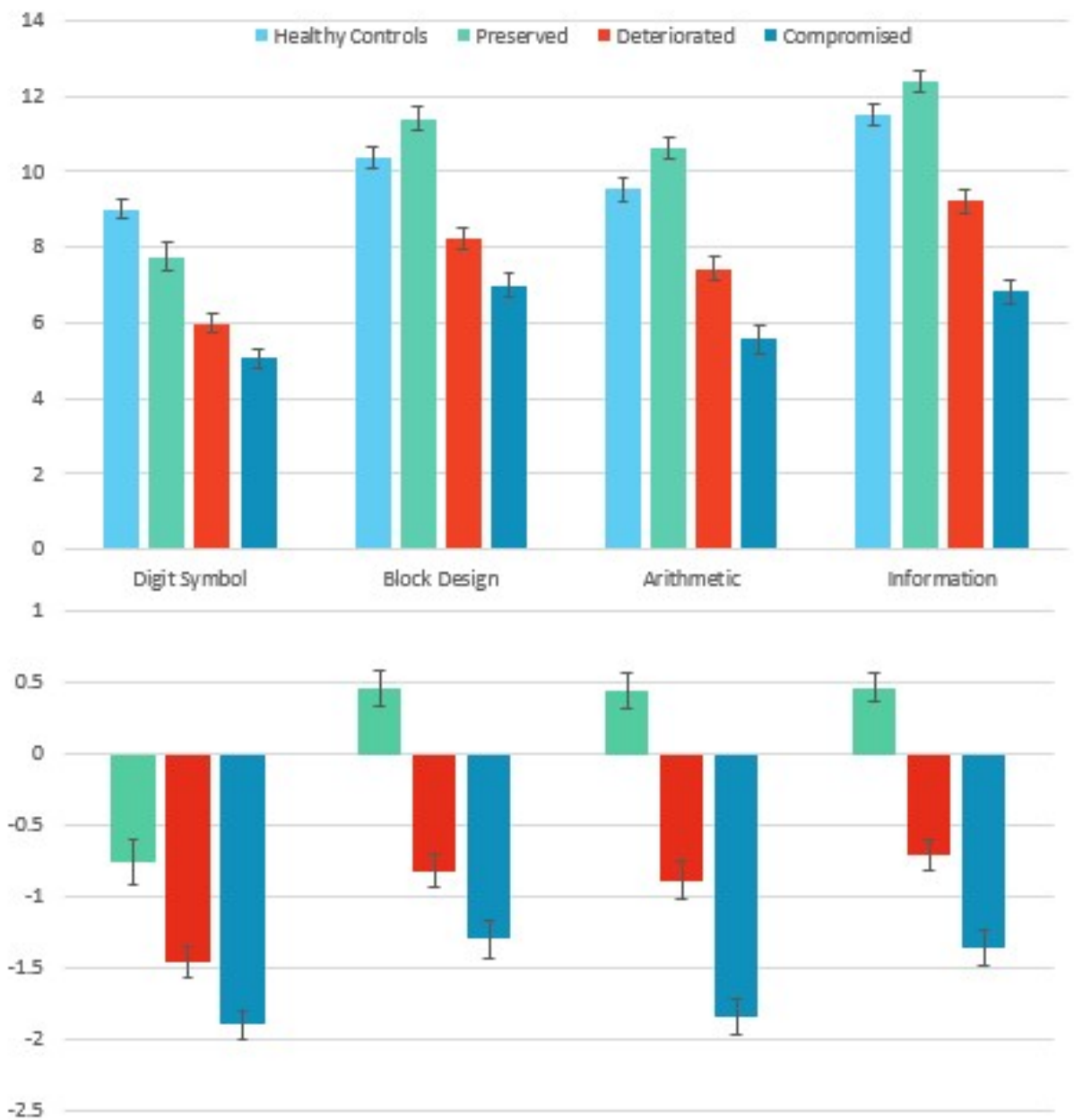


Figure 3.5: IQ cognitive sub-domain profiles shown as scaled scores (top figure) and z-scores relative to healthy control performance (bottom figure).

Error bars represent standard error of the mean (SE).

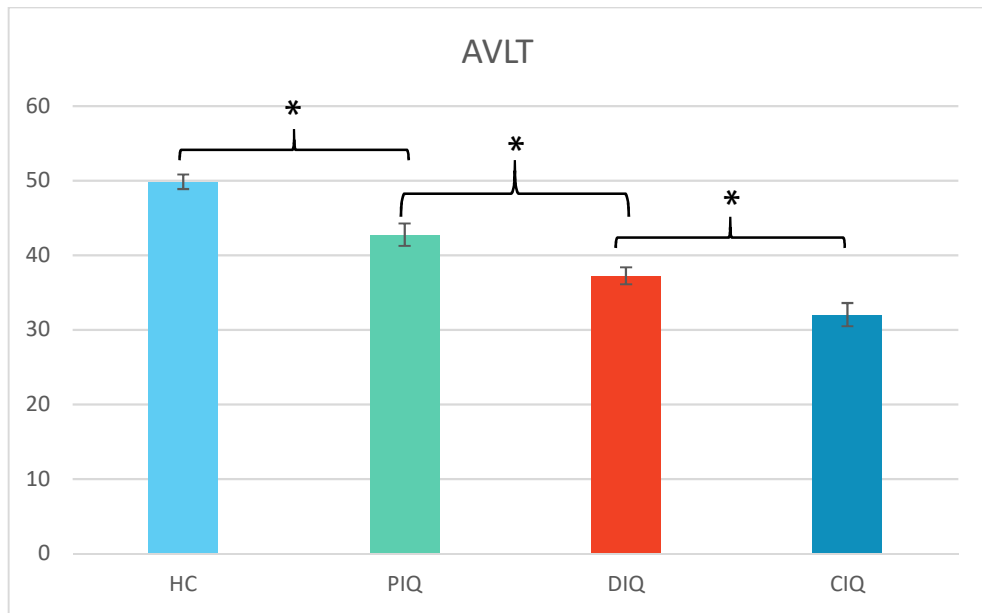


Figure 3.6: Raw total AVLT score of the healthy control and clustered patient sub-groups

HC = healthy controls, PIQ = preserved IQ group, DIQ = deteriorated IQ group, CIQ = compromised IQ group. FSIQ = Full-scale IQ. * denotes statistical significance. Error bars represent SE.

Table 3.5: Comparison of subtype task performance relative to other tasks

	Digit Symbol	Information	Arithmetic	Block Design
HCS	-	+	=	=
PIQ	-	+	+	=
DIQ	-	+	=	=
CIQ	-	=	=	+

+ Denotes superior performance, = Denotes equal performance, - denotes comparatively worse performance within each group

3.3.5 Baseline Clinical, Social and Global Functioning

The clustered groups did not differ on any measure of symptom severity or global functioning. On the Social Function Scale (SFS), the PIQ had highest rates of employment, ($F [2, 156] = 3.86, p = 0.023$) but this did not survive FDR correction for multiple comparisons (Table 3.6).

Table 3.6: Between-group comparison of symptom and social functioning at baseline

	PIQ (n = 55)	DIQ (n = 61)	CIQ (n = 43)	
	Mean (SD)	Mean (SD)	Mean (SD)	Main Effect (F)
Positive Symptoms	16.42 (4.87)	16.74 (4.70)	16.44 (5.18)	$F (2, 156) = 0.07, p = 0.928$
Negative Symptoms	17.11 (5.90)	16.95 (6.08)	18.07 (6.25)	$F (2, 156) = 0.52, p = 0.592$
General Symptoms	33.16 (6.96)	33.75 (8.51)	24.58 (7.19)	$F (2, 156) = 0.66, p = 0.662$
Total Symptoms	66.69 (13.19)	67.44 (15.89)	69.09 (14.17)	$F (2, 156) = 0.41, p = 0.714$
Calgary Depression	5.65 (4.69)	5.04 (4.14)	4.27 (4.52)	$F (2, 156) = 2.85, p = 0.240$
Social Withdrawal	105.09 (12.57)	104.18 (14.66)	100.83 (14.53)	$F (2, 156) = 1.06, p = 0.348$
Relationships	117.05 (17.19)	114.16 (18.91)	110.02 (14.61)	$F (2, 156) = 1.38, p = 0.254$
Independence	105.16 (13.01)	103.12 (12.96)	105.17 (12.91)	$F (2, 156) = 0.47, p = 0.621$
Performance				
Recreation	108.27 (18.72)	105.88 (16.06)	104.84 (16.02)	$F (2, 156) = 0.63, p = 0.533$
Prosocial	110.08 (14.03)	104.55 (16.87)	109.64 (16.50)	$F (2, 156) = 2.79, p = 0.064$
Independence	111.21 (12.40)	109.10 (11.30)	107.05 (13.35)	$F (2, 155) = 1.17, p = 0.312$
Competence				
Employment	107.56 (11.22)	102.79 (11.01)	102.92 (9.71)	$F (2, 156) = 3.86, p = 0.023$
SFS Total	109.20 (9.88)	105.95 (9.74)	105.92 (9.31)	$F (2, 155) = 2.05, p = 0.132$
GAF	56.98 (10.52)	55.46 (12.61)	54.77 (7.32)	$F (2, 157) = 0.57, p = 0.564$

PIQ = Preserved IQ; DIQ = Deteriorated IQ; CIQ = Compromised IQ; SFS = Social Function Scale; GAF = global assessment of functioning

3.3.6 Neuroimaging

Global brain estimates showed that intracranial volume (ICV) was significantly larger in the PIQ than CIQ group and that absolute total brain volume (aTBV) was significantly smaller in the CIQ group than both the DIQ and PIQ groups. When controlling for ICV,

differences were not found between groups on measures of total brain volume (TBV), cortical volume, or grey matter volume. There was no difference between groups in mean cortical thickness (Table 3.7). Figures 3.7 – 3.11 show between-group comparisons of brain volumetric measures.

Table 3.7: Between-group comparison of total brain volumes and average cortical thickness at baseline.

	PIQ (n = 48)	DIQ (n = 47)	CIQ (n = 35)	Comparison				
	Mean (SE)	Mean (SE)	Mean (SE)	Main Effect (F)	<i>post-hoc</i> ^c	PIQ vs DIQ	PIQ vs CIQ	DIQ vs CIQ
Total Intracranial Volume ^a	1508768.99 (17456.66)	1473647.62 (17795.98)	1411307.42 (20331.44)	F (2, 124) = 6.407, <i>p</i> = 0.002	PIQ > CIQ	0.2	0.8**	0.4
Absolute Total Brain Volume ^a	1137800.66 (14809.29)	1115372.08 (15062.00)	1052023.93 (17217.09)	F (2, 124) = 7.453, <i>p</i> = 0.001	PIQ + DIQ > CIQ	0.2	0.8**	0.5*
Total Brain Volume ^b	1109822.82 (7347.788)	1112185.09 (7338.09)	1094672.33 (8653.16)	F (2, 123) = 1.302, <i>p</i> = 0.276				
Cortex ^b	460958.03 (4917.61)	455523.14 (4911.12)	446688.00 (5791.25)	F (2, 123) = 1.697, <i>p</i> = 0.188				
Total Grey Volume ^b	622627.60 (5378.53)	617262.10 (5371.44)	606327.09 (6334.06)	F (2, 123) = 1.871, <i>p</i> = 0.158				
Average Cortical Thickness ^a	2.41 (0.18)	2.39 (.018)	2.36 (.020)	F (2, 124) = 2.123, <i>p</i> = 0.124				

PIQ, Preserved IQ; DIQ, Deteriorated IQ; CIQ, Compromised IQ; ^aControlling for age, sex and site; ^bControlling for ICV, age, sex and site; ^cAfter Bonferonni correction. Bold font denotes significance following FDR correction. **indicates large effect size. *indicates medium effect size. Volumes in mm³

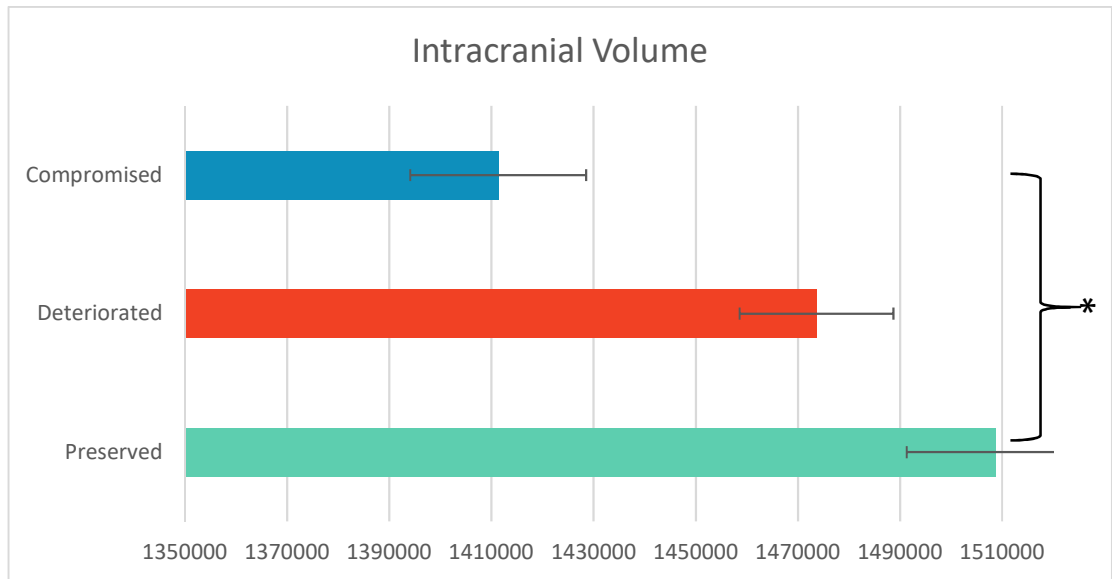


Figure 3.7: Between-group comparison of intracranial volume after controlling for age, sex, and scan site.

* Denotes statistical significance. Error bars represent SE. Volumes in mm³

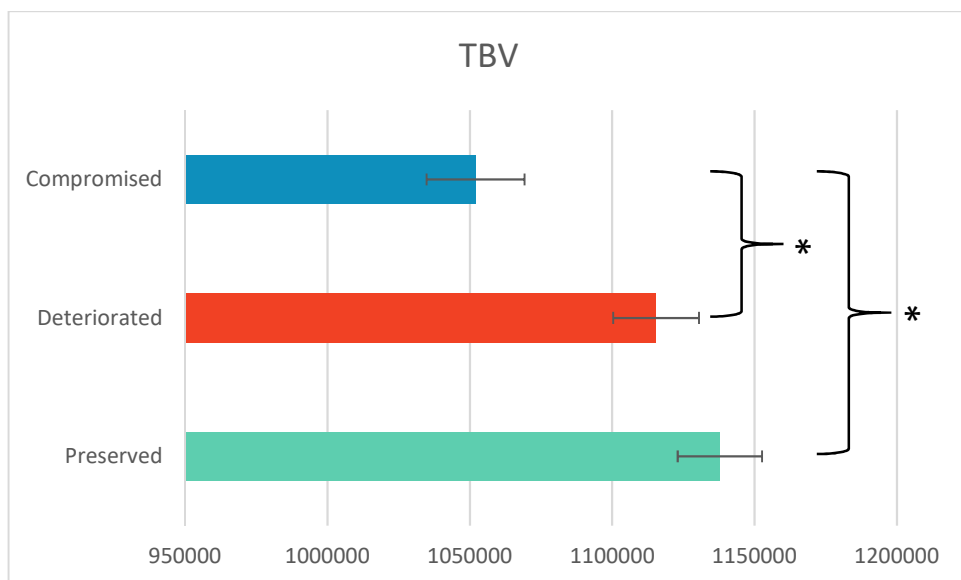


Figure 3.8: Between-group comparison of total brain volume after controlling for age, sex, and scan site

TBV = total brain volume. * denotes statistical significance. Error bars represent SE. Volumes in mm³

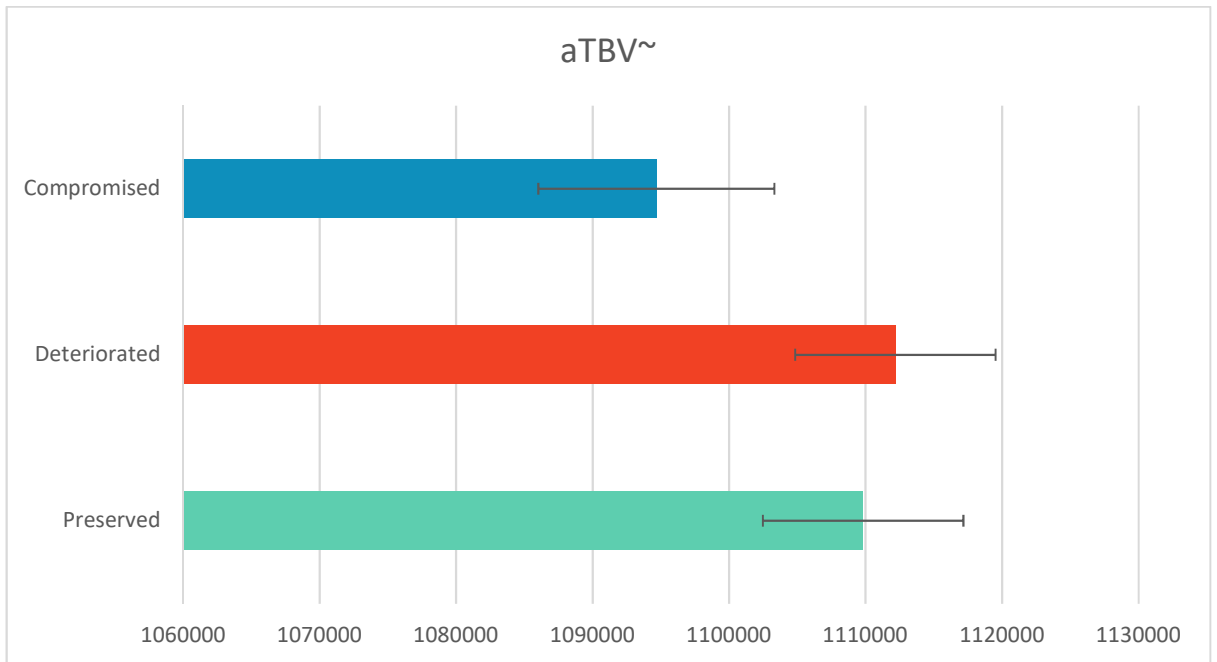


Figure 3.9: Between-group comparison total brain volume after controlling for intracranial volume, age, sex, and scan site

aTBV~ = TBV controlling for ICV. Error bars represent SE. Volumes in mm³

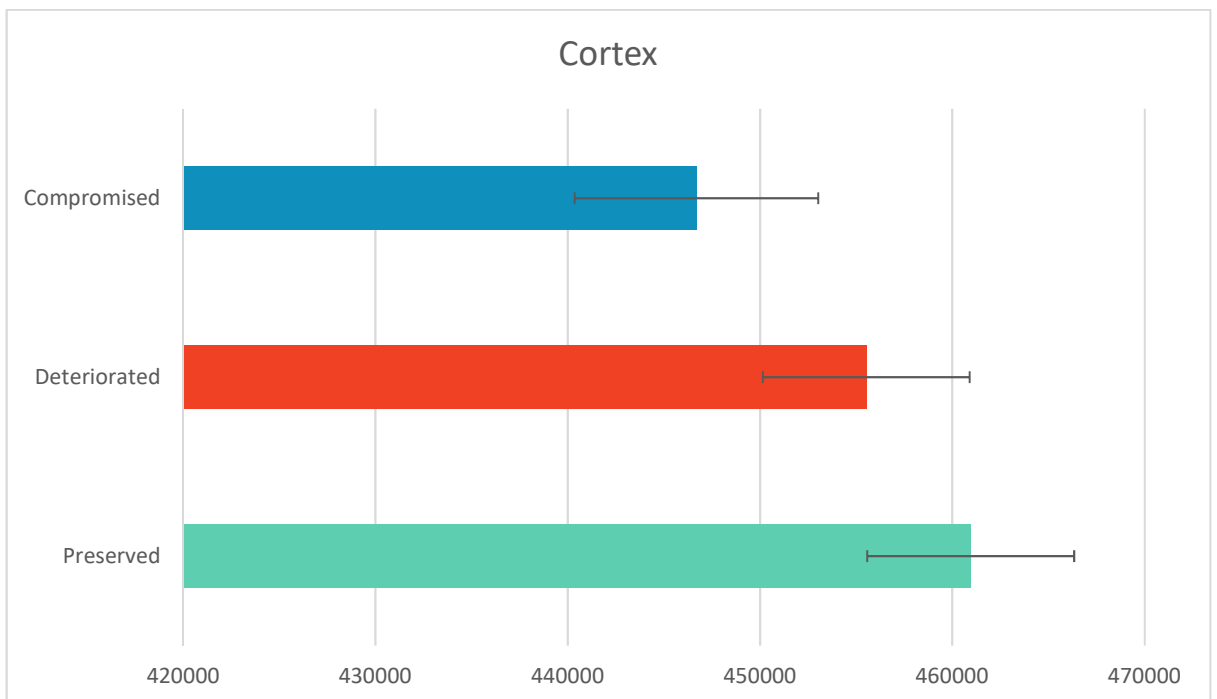


Figure 3.10: Between-group comparison of cortical volume after controlling for intracranial volume, age, sex, and scan site

Error bars represent SE. Volumes in mm³

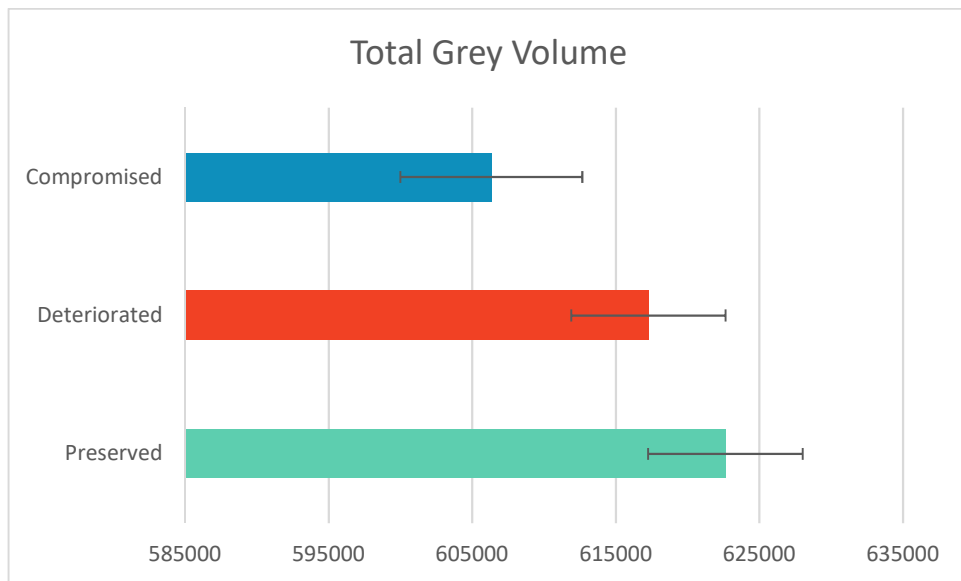


Figure 3.11: Between-group comparison of total grey volume after controlling for intracranial volume, age, sex, and scan site

Error bars represent SE. Volumes in mm³

3.3.7 Inflammatory Markers

Between-group comparisons were performed on log₁₀ transformed measures, adjusting for age, gender, BMI and cannabis use. There was a significant difference in hsCRP levels. Post-hoc tests showed that the PIQ group had significantly lower hsCRP levels than CIQ patients, even after correcting for multiple comparisons (Table 3.8). The raw means [SD] were: PIQ = 1.94 [2.18], DIQ = 2.84 [2.70] and CIQ = 3.18 [2.36]. There were no between group differences in any other measures of inflammation.

Table 3.8: Between-group comparison of hsCRP and cytokines

	PIQ (n= 49) Mean (SD)	DIQ (n = 54) Mean (SD)	CIQ (n =35) Mean (SD)	Comparison		Effect Size (d)		
				Main Effect (F)	<i>post-hoc</i>	PIQ vs DIQ	PIQ vs CIQ	DIQ vs CIQ
hs-CRP	.00 (.55)	.16 (.62)	.33 (.47)	F (2, 131) = 5.01, <i>p</i> = .008	PIQ < CIQ	0.3	0.6*	0.4
IL-1RA ^a	2.49 (.29)	2.48 (.30)	2.52 (.25)	F (2, 131) = 0.18, <i>p</i> = .829	-			
IL-6 ^a	-.21 (.29)	-.26 (.25)	-.16 (.19)	F (2, 132) = 0.71, <i>p</i> = .493				
TNF-a ^a	.36 (.09)	.39 (.10)	.38 (.11)	F (2, 131) = 2.29, <i>p</i> = .172				

^a Controlling for age, sex, BMI and cannabis smoking status. PIQ = preserved IQ, DIQ = deteriorated IQ, CIQ = compromised IQ. hs-CRP =high sensitivity c-reactive protein. IL-1RA = interleukin 1 receptor antagonist. IL-6 = interleukin 6, TNF = tumor necrosis factor alpha. Bold font denotes significance following FDR correction. *indicates medium effect size.

3.3.8 Summary of Results

Data-driven cluster analysis revealed 3 cognitive subgroups: preserved, deteriorated and compromised.

3.3.8.1 Premorbid IQ

The preserved group had significantly higher premorbid IQ than the healthy control comparison group. There was no difference between premorbid IQ in the deteriorated and healthy control groups. The compromised group had significantly lower premorbid IQ than all other groups. The premorbid IQ of the compromised group was in the below average range whereas that of the rest was in the average range.

3.3.8.2 IQ decline

The healthy control showed no decline. The preserved IQ group showed a small but significant mean decline, but IQ remained in the average range. The deteriorated group showed a significant mean decline in IQ from average to below average levels. The compromised group showed a significant mean decline in IQ from below average to ‘borderline’.

3.3.8.3 IQ subtests

There was no difference in current IQ between healthy control and preserved IQ groups. The preserved IQ group were significantly better than healthy controls on the block design, arithmetic and information subtests but significantly worse on the digit symbol test of processing speed.

3.3.8.4 Verbal memory

The preserved group were significantly worse than healthy controls on the measure of auditory verbal learning.

3.3.8.5 Symptoms and social function:

No significant effects were found.

3.3.8.6 Brain MRI

The compromised group had a significantly smaller mean absolute total brain volume than the preserved and deteriorated groups. The compromised group had smaller intracranial volumes than the preserved group.

3.3.8.7 Inflammation

The compromised group had higher levels of inflammatory marker hsCRP than the preserved group.

3.4 Discussion

This study examined whether unbiased cluster analysis can determine the existence and clinical validation of IQ-trajectory cognitive subtypes following a first episode of psychosis (FEP). It also sought to identify, early in the course of illness, the presence of

brain markers of differential neurodevelopmental and neurodeteriorating subgroups hypothesised by Woodward and Heckers., (2015). Finally, an exploratory analysis examined potential neurobiological and immunological characteristics of these cognitive subgroups.

The total patient and healthy control groups were matched for age. There was no difference between the total patient and healthy control groups on a measure of premorbid IQ. The average performance of the total patient group was worse on all cognitive measures, consistent with cognitive deficits observed in populations following onset of illness.

Hierarchical cluster analysis identified 3 cognitive subgroups, replicating previous studies in long-standing schizophrenia, schizoaffective and FEP populations (Uren et al., 2017, Weickert et al., 2000, Van Rheenen et al., 2017, Wells et al., 2015, Czepielewski et al., 2017). The assigned clusters revealed proportions generally consistent with a previous FEP study, which used a clinical classification approach (Leeson et al., 2011). There were no differences between preserved, deteriorated and compromised IQ groups on clinical symptoms or global and specific social functioning. Unlike studies in long-standing schizophrenia and other FEP populations, there was no evidence of more severe negative symptoms in the compromised group. Taken together, these findings do not support the previous findings that cognition is strongly related to functional outcome following onset of psychosis (Green et al., 2004).

The existence of a putatively preserved IQ group questions whether cognitive impairment is a core feature of psychosis. One possible explanation for the lack of difference in functioning between groups is that the PIQ group, in fact, have some neuropsychological compromise in comparison with healthy controls. Despite no

difference in IQ score between the PIQ group and HCs, the PIQ group showed comparatively aberrant cognitive profiles, with worse performance on the processing speed subtest and better performance on information, block design and arithmetic subtests. The PIQ group also showed worse performance than HCs on the auditory verbal learning task. Thus, the PIQ group had higher premorbid IQ scores than HCs and were able to maintain apparently preserved general intelligence scores by compensating for processing speed and verbal memory deficits with better performance in other cognitive domains. Processing speed and learning and memory deficits have previously been shown to impact on social and global functioning and deterioration in these domains and may drive functional impairments in this group (Wilk et al., 2005, Gray, 2013, Green, 1996). These findings in an FEP cohort, support findings by Wilk et al., (2005) who showed, in an established schizophrenia group, that even when IQ is closely matched with healthy controls, patients with schizophrenia showed performance deficits on tests of processing speed and verbal memory. Others have also found that those with seemingly intact cognition can be separated from healthy controls by poorer performance on tests of processing speed (Heinrichs et al., 2015, Gonzalez-Blanch et al., 2011) and verbal memory (Hill et al., 2004) and that these are the most impaired cognitive functions in schizophrenia (Sheffield et al., 2018) and have the worst trajectory over time (Kenney et al., 2015). The finding that all patient subgroups showed poorest performance on the processing speed IQ subtest is consistent with other studies finding this to be the most impaired cognitive domain in both FEP and schizophrenia (Mesholam-Gately et al., 2009, Dickinson et al., 2007a). The finding that the preserved group perform better than controls on the timed block design subtest suggests that their processing speed deficit is not purely a result of motoric impairment. Similarly, superior

performance on the time-limited arithmetic subtest, thought to reflect working memory, points to the impairment in the cognitive subgroups being specific to processing speed and verbal learning, without this impairment detrimentally effecting performance on the other IQ subtests. The finding that all patient groups performed poorer than HCs on the test of verbal memory supports Hill et al (2004) who found verbal memory deficits in those with FEP who were matched with healthy controls on IQ (Hill et al., 2004). There is evidence that processing speed deficits occur later than verbal IQ deficits, increase beyond the early teen years, and may reflect a core impairment in schizophrenia (Meier et al., 2014) necessary for other cognitive operations including types of memory and executive functions (Dickinson et al., 2007a, Leeson et al., 2010). The finding that even those with putatively preserved IQ perform worse than HCs on both verbal and non-verbal tasks yet maintain superior performance on the verbal WTAR test suggest that PIQ and DIQ groups may have later deterioration, or developmental lag, rather than early developmental deficits.

Processing speed and verbal memory deficits appear to be intrinsic to the disorder and are present even in FEP populations, with evidence in a small sample study of these domains showing poorest trajectory over time (Kenney et al., 2015) . It may be these domains of impairment have a severe negative impact on function and underpin functional impairments (Nuechterlein et al., 2011, Sanchez et al., 2009, Green et al., 2004). The extent of global cognitive impairment between cognitive subgroups alone does not appear to separate them on any of the measures of functional outcome. There is evidence that premorbid IQ scores in the high range may be underestimated by the WTAR (Wechsler, 2001) and thus deterioration in putatively preserved groups is underestimated. Kendler et al., (2016) found that deviation from the IQ level of

biological relatives, rather than IQ score itself, confers greatest risk for schizophrenia and it may be this change differential that impacts functional and symptomatic presentation and predicts outcomes.

As in previous studies, the CIQ group had significantly smaller absolute total brain volume (aTBV) than both the PIQ and DIQ groups but accounting for intracranial volume (ICV) abolished this difference. Controlling for ICV allows us to examine deviation in structural volumes from what is expected and can therefore be used as a proxy for deterioration. The CIQ group had smaller ICVs compared to the PIQ group, in keeping with the idea that there may be a more severe early developmental (or hypoplastic) impairment in this group and providing validation for the WTAR as a measure of premorbid intelligence in this group. Interestingly, the PIQ group did not have greater aTBV than the DIQ group, despite significantly greater current IQ scores. Finding that there are no between-group differences in total brain volume (TBV), i.e. when controlling for ICV, does not support the presence of separate neurodeteriorating and neurodevelopmental groups. Unlike previous studies, this study is limited by a lack of a neuroimaging HC group which might elucidate differences between patient and HC groups. The lack of difference in ICV controlled TBVs does not necessarily reflect absence of neurodeterioration in the groups but may instead reflect similar rates of deterioration across all of the patient clusters. Indeed, despite low premorbid IQ, the CIQ group had lower IQ scores at the time of testing than their premorbid estimates, with an average decrease of 10 IQ points. This finding supports that even those with early neurodevelopmental impairment may have a progressive disorder with decline in cognitive function at illness onset. In contrast, PIQ groups may have later illness onset and thus build up higher cognitive or “brain” reserve (Barnett et al., 2006, Watson and

Joyce, 2015) meaning they are better able to compensate following neurodeterioration. Unlike other studies, patients were assessed early in the course of illness, without the long-term effects of antipsychotic medication and exposure of associated environmental factors such as hospitalisation. Studies in FEP cohorts which include neuroimaging data from HC subjects are necessary for comparison with those unaffected by the illness. Given the lack of difference in aTBV between the PIQ and DIQ groups, measures of resting-state and functional connectivity, rather than brain volumetric measures may prove to be more fruitful when examining heterogeneity between cognitive subtypes (Lewandowski et al., 2018).

This is the first study to examine differences between cognitive subtypes on measures of inflammation. PIQ patients have lower levels of hsCRP than the CIQ groups, even when controlling for confounders. Several studies have shown a relationship between cognitive functioning (including IQ) and CRP, but the mechanisms of action and molecular pathways have not yet been elucidated and cohort studies are needed to assess the temporal relationship between hsCRP and cognition in psychosis. CRP is a commonly used biomarker of inflammation and may be a marker of mediators, such as acute stress (Aas et al., 2014), contributing to the pathophysiology of cognitive dysfunction in psychosis. Unlike other studies and despite the close relationship with hsCRP, there were no differences between groups on measures of Il-6, or any other cytokine. These findings add to a growing body of evidence that hsCRP is related to cognitive functioning in schizophrenia, though there remains heterogeneity, with group differences in CRP likely to reflect a linear relationship with cognitive functioning, rather than a biomarker of differential deteriorating or developmental processes.

3.4.1 Methodological Considerations

There are several limitations to the study approach. Whilst the WTAR has been shown to be a reliable hold measure and is cross-validated with the WAIS, we were unable to control for whether English was the individual's first language or not. It would undeniably be preferable to have the same measure of IQ both pre and post illness onset in a prospective cohort study. This would also allow us to see whether processing speed deficits are the result of developmental deficits or "lag" (Reichenberg et al., 2010), relative to HCs, or whether deterioration is a result of illness onset. Furthermore, the use of a pro-rated IQ short-form consisting of only 4 subtests may mask subtle domain-specific differences in individual global functioning.

All participants were receiving antipsychotic medication which some have shown to have a negative effect on processing speed (Veselinovic et al., 2013). Having a group naïve to antipsychotic medication would rule out a neuroleptic effect on cognitive profiles, though the majority of evidence suggests antipsychotic medication has a small positive effect on cognition including processing speed (Keefe et al., 2006b, Woodward et al., 2005, Keefe et al., 2007b, Hill et al., 2010). It must also be noted that the healthy control participants are all recruited from the West London area and may not be representative of those in the patient sample. This study also does not include healthy control measures for comparison of MRI or inflammatory measures. Though this limits the ability to infer whether brain volumes or inflammation differ relative to healthy controls, we are able to assess the usefulness of identifying cognitive subtypes and whether they are neuropsychologically and biologically distinct from one another. Furthermore, whilst we endeavoured to control for potential confounds of inflammatory status, we did not have data to adjust for smoking quantity. Due to missing

data, it was also not possible to co-vary for antipsychotic treatment, though research suggests that CRP is not altered by either first or second generation antipsychotics (Fernandes et al., 2016) and correlational analysis on the data available did not reveal a significant relationship between olanzapine dose and hsCRP levels [Appendix Table A.1].

3.4.2 Clinical Implications

Cluster analysis provides useful clinical insights into linear relationships with clinical markers of associated cognitive impairments but has limitations in establishing distinct illness subtypes. When assessing neurocognition in patient groups, it is necessary to examine individual strengths and weaknesses in cognitive subdomains, rather than global measures of intelligence. Those with putatively high cognitive functioning may still need cognitive remediation to compensate for verbal learning and processing speed deficits if they are to return to premorbid levels of functioning. Processing speed and auditory verbal learning must be key targets for psychological and pharmacological remediation in early psychosis and considered at the point of contact with services. Those presenting with early psychosis should routinely be assessed for cognitive impairments, with the aim of remediating deficits with cognitive training. In particular impaired patients, remediation of basic cognitive skills may need to be supplemented with more intensive cognitive training for higher order functioning, requiring consolidation over time. Whilst antipsychotic effects on cognition should be considered when prescribing, cognitive enhancement through pharmacological interventions requires further research before being utilised in this population.

3.4.3 Conclusions

Caution should be taken when using general intelligence measures, particularly short-forms, as indices of cognitive preservation. Compensatory superior performance on some subtests may conceal cognitive deficits in other domains in pre-morbidly high-functioning patient groups. Longitudinal cohort and twin studies should be used in order to determine whether processing speed and auditory verbal learning deficits in those with putatively preserved IQs represent a deteriorating or developmental deficit and a core feature of psychosis. Early in the course of illness there are minimal differences between cognitive subtypes in clinical and social functioning, highlighting need to examine potential mediating or moderating variables, such as social cognition, between neurocognition and functional outcomes.

Parcellation of cognitive heterogeneity in FEP and schizophrenia populations has been a challenge, with varying findings. The findings of the current study support the notion that cognitive impairments are a core feature of FEP. IQ-based cognitive trajectories in this population share a relationship with ICV, aTBV and hsCRP and are likely to occur along a continuum, potentially relating to stage of developmental onset rather than indicative of separable pathological processes. In the absence of longitudinal studies with premorbid IQ measures, future studies may also benefit from clustering on the basis of deviation from an individual's expected performance rather than premorbid estimates. Examining subtype differences in brain functional connectivity may be preferable to more crude measures of volume and thickness.

4 Study 2 – Longitudinal Cognitive and Functional Trajectories of Neurocognitive Subtypes

4.1 Introduction

The early phase of psychosis has been thought to be a critical period with deterioration predictive of poor long-term outcome (Birchwood et al., 1998, Allott et al., 2011). The introduction of EISs aimed at secondary prevention has been shown to be of overall benefit, but available evidence shows that early intervention does not necessarily change the clinical course of the illness in many patients (Marshall and Rathbone, 2011). Following a first-episode of psychosis, a proportion of patients will enter symptomatic remission, with some experiencing further episodes, and others remaining treatment refractory.

There remains debate as to the course of cognitive functioning following illness-onset, with most evidence showing stability (Leeson et al., 2009, Heaton et al., 2001, Lewandowski et al., 2011, Kurtz, 2005), but some opposing evidence of either further decline (Stirling et al., 2003) or improvement (Keefe et al., 2007b, Rund et al., 2007, Ayesa-Arriola et al., 2013) in general cognition. In keeping with these inconsistencies, there is evidence for continuing brain grey matter loss over the course of the illness in some studies (van Haren et al., 2007, van Haren et al., 2008), whilst other studies find no change (Lieberman, 2005). Longitudinal studies are few, and many have used only short follow-up periods (Green et al., 2004). There remains a gap in our knowledge about the determinants of long-term outcome and whether they can be identified at an early stage. The majority of longitudinal studies which have examined change in

cognitive functioning and symptoms after onset of illness have supported that whilst cognitive function remains stable, symptoms can fluctuate.

To date there has been some research into different cognitive subtypes and their differing illness presentations, but few studies have followed patients over time to assess the different cognitive, symptom and functional trajectories (Leeson et al., 2011, Reser et al., 2015). It is only by understanding differing courses of illness that individually targeted interventions can be advanced. Following patients up for 3-years, Leeson et al., (2011) found that a premorbidly compromised IQ subtype showed no significant IQ score improvement and that improvement in those with preserved and deteriorated IQ was no greater than that of healthy controls and therefore likely the result of practice effects. These findings are in keeping with those of other controlled studies (Frangou, 2010, Hoff et al., 2005). Furthermore, Leeson et al., (2011) found all 3 cognitive subtypes improved on symptom measures except for the preserved group who had significantly fewer symptoms than the other groups at baseline, and that when analysis was limited to core negative symptoms, the deteriorated group had more symptoms than the preserved group. On a measure of social function, only differences in occupational functioning were found, with the deteriorated and compromised IQ groups having lower levels of employment than the preserved group. Despite a long follow-up period and relatively large sample size, this study was limited in that cognitive subtypes were devised based on predetermined criteria and may not reflect the data. Furthermore, at follow-up, there was only a small group of participants remaining in the compromised (or "low") IQ group and no biological measures were recorded.

It is important to understand the biological correlates of different cognitive trajectories and what may explain heterogeneity in the trajectory in long-term outcomes. It is

possible that heterogeneity of trajectories may reflect different pathological processes of illness and may be marked by biological changes such as structural brain loss or changes in inflammation (Weickert, 2000). No studies to date have examined differential long-term inflammatory or volumetric trajectories of hypothesised cognitive subtypes. The main hypothesis for this study was that there is long-term stability of cognitive functioning and brain volume/thickness in compromised groups and that this has a persistent influence on social and functional outcome. We predicted that preserved groups will show continued cognitive stability and improving functional outcomes. Whether deteriorated groups continue to deteriorate or make cognitive gains back to levels of premorbid function and the effect this has on outcomes was explored. Focussing on cognitive remediation in those identified as being at risk of poor outcomes, as soon as possible after psychosis onset is a clinical imperative (Marder and Fenton, 2004). Findings from this study will be particularly relevant to early intervention services and will inform clinical practice as to the patients in the most need of early remediation strategies.

4.2 Methods

Participants were assessed 12-months after first assessment. All those who agreed to continue in the trial were contacted and asked to re-consent verbally. Those who agreed underwent the same cognitive, clinical, functional outcome, MRI and inflammatory marker assessments as described in Chapter 2, section, 2.1. Healthy control participants were followed up as part of the West-London first-episode study (Leeson et al., 2011)

and underwent the same cognitive tasks as at baseline, at 12-month follow-up (see section 2.1.3)

4.2.1 Analysis

Baseline demographic and IQ characteristics of those who completed the study were compared with the characteristics of those who did not to assess if the follow-up groups were representative of the total baseline group. Baseline demographics of controls were compared with those of the total patient groups using chi-square test for categorical and ANOVA for continuous variables. Differences between cognitive subtypes and HC groups in outcome scores for cognitive, clinical and biological markers were compared using ANOVA for normally distributed variables. Kruskal-Wallis tests were used for clinical variables which were non-normally distributed variables and could not be returned to normal distributions using logarithm transformations. Change over time was analysed using repeated-measures ANCOVAs, controlling for the same variables as in Study 1. For non-normally distributed clinical variables, Wilcoxon signed-ranks was used to assess differences between groups in change over time. Due to this data coming from a cohort who took part in a clinical trial, study treatment allocation was additionally controlled for in all analyses. For neuroimaging variables, the additional control of change in intracranial volume (ICV) was used to account for differences in head positioning between baseline and follow-up. Given that groups were clustered based on cognitive functioning, equal values between groups were not expected at baseline and so we did not control for baseline values in the analysis of change, given that this can lead to spurious statistical associations (Glymour et al., 2005, Lord, 1965). Main effects were assessed for FDR with Bonferonni correction applied to all post-hoc comparisons.

4.3 Results

4.3.1 Attrition

Attrition was significantly greater in the CIQ group than the other groups, with only 37% of participants completing follow-up assessments compared to 63% in both the HC and PIQ groups and 61% in the DIQ group (Table 4.1). Groups did not differ between baseline and follow-up on any other demographic or on premorbid or full-scale IQ.

Table 4.1: Demographic and IQ differences of completers vs non-completers

Group		HC	PIQ	DIQ	CIQ
N (completers/non-completers)		52/30	35/22	37/24	16/27
Percent completers vs non-completers	Completers	63%	63%	61%	37%
	Non-Completers	37%	39%	39%	63%
	<i>Cluster x follow-up comparison</i>	$\chi^2=9.351, p = \mathbf{0.025}$, Post-Hoc CIQ < HC, PIQ and DIQ^a			
Age	Completers	27.00 (7.24)	25.67 (5.92)	25.00 (4.92)	27.82 (4.69)
	Non-completers	26.53 (4.81)	25.55 (5.23)	23.21 (3.53)	25.27 (4.18)
	<i>Comparison</i>	$t = 0.42, p = 0.671$	$t = 0.077, p = 0.938$	$t = 1.541, p = 0.128$	$t = 1.848, p = 0.071$
Sex (M/F)	Completers	53%/47%	86%/34%	71%/29%	75%/25%
	Non-completers	43%/57%	74%/36%	70%/30%	78%/22%
	<i>Comparison</i>	$\chi^2 = 0.841, p = 0.492$	$\chi^2 = 1.297, p = 0.296$	$\chi^2 = .015, p = 0.999$	$\chi^2 = 0.043, 0.999$
Estimated Premorbid IQ	Completers	101.92 (8.32)	106.85 (6.85)	102.13 (7.15)	83.43 (8.91)
	Non-completers	99.30 (9.44)	106.59 (7.15)	101.12 (6.29)	85.51 (7.35)
	<i>Comparison</i>	$t = 1.307, p = 0.194$	$t = 0.137, p = 0.891$	$t = 0.564, p = 0.574$	$t = 0.828, p = 0.412$
Baseline full-Scale current IQ	Completers	101.05 (11.83)	103.68 (7.21)	85.91 (9.55)	83.43 (8.91)
	Non-completers	99.10 (11.57)	103.45 (5.86)	84.18 (7.10)	85.51 (7.35)
	<i>Comparison</i>	$t = 0.724, p = 0.470$	$t = 0.125, p = 0.900$	$t = 0.760, p = 0.449$	$t = 0.828, p = 0.412$

^aComparison of attrition rate between groups.

4.3.2 Demographics

The patient group had a mean age of 25.75 [5.35] and 82% were male. Controls had a mean age of 27.00 [7.24] and 55% were male: significantly fewer than the patient group (Table 4.2).

Table 4.2: Demographics of healthy control and patient groups.

	Patients (n=88)	Healthy Controls (n=52)	F/χ^2	Significance
Age	25.75 (5.35)	27.00 (7.24)	F (138) = 2.757	$p = 0.245$
Sex (% Male)	82%	55%	$\chi^2 (1) = 9.066$	$p = \mathbf{0.003}$

Bold font denotes significance following FDR correction.

4.3.3 Cognition

Mean IQ and domain specific scores for the entire sample and patient and cognitive subgroups at follow-up are shown in Appendix tables A.2 and A.3 (Chapter 10). There was no main effect of Time on FSIQ or any of the IQ subtests within groups (Table 4.3). Significant interaction effects indicated that the HC and DIQ groups improved over time for the information subtest whereas the PIQ and CIQ groups did not (Figure 4.1) and PIQ and DIQ improved on AVLT total score, whilst the HC group were worse (Figure 4.1).

Table 4.3– Repeated measures ANOVA effects for cognitive subgroups and healthy controls. Current IQ and specific cognitive performance scores at baseline and 12-month follow-up were compared.

	Group		Time	Group x Time	
		Post-Hoc			Post-Hoc
FSIQ ^a	F (3, 135) = 35.845, <i>p</i> < 0.001	PIQ, HC > DIQ > CIQ	F (1, 135) = 2.255, <i>p</i> = 0.136	F (3, 135) = 0.2.688, <i>p</i> = 0.049	
Digit Symbol ^a	F 3, 135 = 21.082, <i>p</i> < 0.001	HC > PIQ, DIQ, CIQ PIQ > CIQ	F (1, 135) = 1.583, <i>p</i> = 0.211	F (3, 135) = 0.417, <i>p</i> = 0.741	
Block Design ^a	F (3, 135) = .11.572, <i>p</i> < 0.001	PIQ, HC > DIQ, CIQ	F (1, 135) = 1.555, <i>p</i> = 0.618	F (3, 135) = 0.596, <i>p</i> = 0.618	
Information ^a	F (3, 135) = 14.169, <i>p</i> < 0.001	PIQ, HC > DIQ > CIQ	F (1, 135) = 0.145, <i>p</i> = 0.704	F (3, 135) = 4.538, <i>p</i> = 0.005	DIQ +
Arithmetic ^a	F (3, 135) = 12.996, <i>p</i> < 0.001	PIQ, HC > DIQ + CIQ	F (1, 135) = 0.039, <i>p</i> = 0.843	F (3, 135) = 2.012, <i>p</i> = 0.115	
AVLT Immediate ^a	F (3, 133) = 3.58, <i>p</i> = 0.015	PIQ, HC > CIQ	F (1, 134) = 7.239, <i>p</i> = 0.008	F (3, 134) = 2.415, <i>p</i> = 0.069	
AVLT Total ^a	F (3, 134) = 6.321, <i>p</i> < 0.001	PIQ, HC > DIQ	F (1, 134) = 3.338, <i>p</i> = 0.060	F (3, 134) = 6.128, <i>p</i> = 0.001	DIQ +, PIQ +, HC -
Verbal Fluency ^a	F (2, 83) = 8.382, <i>p</i> < 0.001	PIQ, DIQ > CIQ	F (1, 83) = 0.390, <i>p</i> = 0.534	F (2, 82) = 3.586, <i>p</i> = 0.032	

Factors are Group: healthy controls (HC = 52): preserved IQ (n = 35): deteriorated IQ (n = 37): compromised IQ (n = 16) and Time: baseline and 12 months. Bold font indicates significant effects after FDR correction. + indicates significant improvement. - indicates significant worsening.

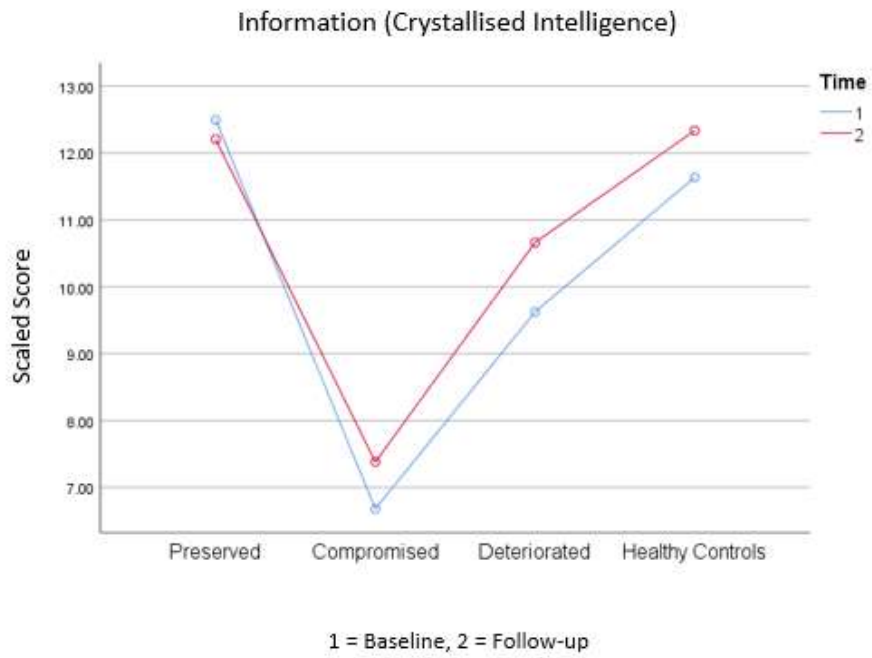


Figure 4.1: Line graph illustrating crossover effect in Time x Cognitive group interaction from baseline to 12-month follow-up on Information subtest scaled score

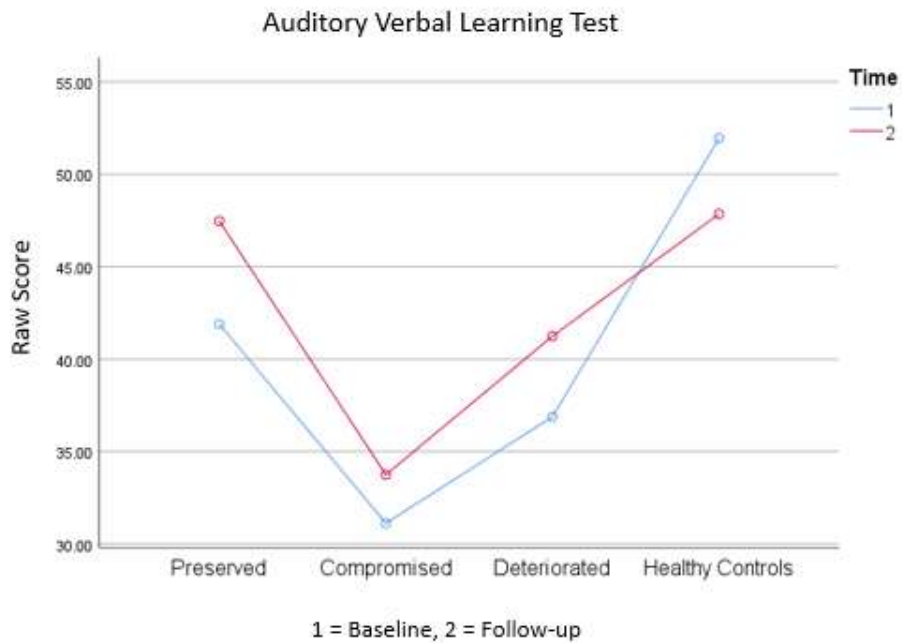


Figure 4.2– Line graph illustrating crossover effect in Time x Cognitive group interaction from baseline to 12-month follow-up on Auditory Verbal Learning Test Total Score

4.3.4 Clinical Symptoms

Mean IQ and domain specific scores for the patient and cognitive subgroups at follow-up are shown in Appendix table A.4 (Pages). Table 4.4 shows Wilcoxon signed rank tests comparing patient groups on measures of clinical symptoms. Both the PIQ and DIQ patients improved on PANSS positive, negative, and total scores at 12-month follow-up. The PIQ group also showed improvement on the global symptom subscale, whereas the CIQ group improved only on the positive symptoms scale. The PIQ and DIQ also showed significant improvements in depression scores, whereas the CIQ group did not. Figure 4.3 shows that at 12-month follow-up, the groups differed on negative symptom scores ($\chi^2 [2] = 9.014, p = 0.11$) representing fewer negative symptoms in the PIQ group than in the CIQ group (ES = 0.8). There were no outcome differences between groups on the positive ($\chi^2 [2] = 1.511, p = .470$), general ($\chi^2 [2] = 1.401, p = .496$) or total ($\chi^2 [2] = .3396, p = .183$) scales.

Table 4.4: Non-parametric analysis of change in symptom scores between baseline and 12-month follow-up.

	PIQ (n = 35)	DIQ (n = 37)	CIQ (n = 15)
Positive Symptoms	Z (2) = -3.575, <i>p</i> < 0.001	Z (2) = -3.098, <i>p</i> = 0.002	Z (2) = -2.205, <i>p</i> = 0.027
Negative Symptoms	Z (2) = -2.748, <i>p</i> = 0.006	Z (2) = -2.472, <i>p</i> = 0.013	Z (2) = -0.888, <i>p</i> = 0.374
General Symptoms	Z (2) = -3.185, <i>p</i> = 0.001	Z (2) = -2.334, <i>p</i> = 0.020	Z (2) = -1.549, <i>p</i> = 0.121
Total Symptoms	Z (2) = -3.743, <i>p</i> < 0.001	Z (2) = -2.985, <i>p</i> = 0.003	Z (2) = -1.793, <i>p</i> = 0.073
Calgary Depression	Z (2) = -3.199, <i>p</i> = 0.001	Z (2) = -2.349, <i>p</i> = 0.019	Z (2) = -.035, <i>p</i> = 0.972

Wilcoxon – change over time for non-normally distributed variables. PIQ = preserved IQ; DIQ = deteriorated IQ; CIQ = compromised IQ. Bold font indicates significance following FDR correction.

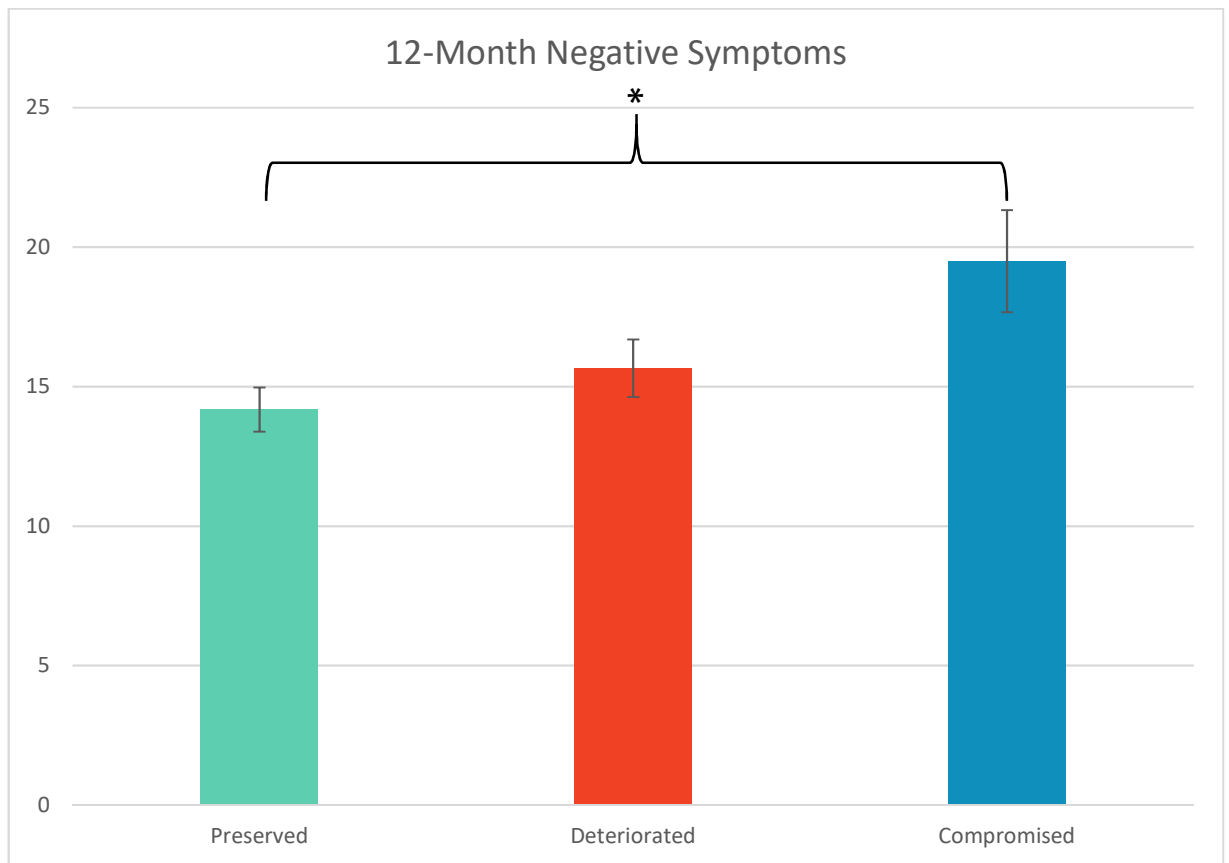


Figure 4.3: Bar-graph showing negative symptom scores of patient clusters at 12-month follow-up.

*denotes statistical significance. Error bars represent SE.

4.3.5 Social and Global Functioning

There were no within group 12-month outcome differences on any measure of social or global functioning (Table 4.5). There was a group x time interaction effect on the prosocial subscale of the SFS. This reflected improvement of the DIQ group and worsening of the CIQ group (Figure 4.4).

Table 4.5: Repeated measures ANOVA effects for cognitive subgroups. Global and social functioning scores at baseline and 12-month follow-up were compared

	Group	Time	Group x Time	Post-Hoc
Social Withdrawal	F (2, 83) = 2.016, $p = 0.140$	F (1, 83) = 2.079, $p = 0.153$	F (2, 83) = 2.032, $p = 0.138$	
Relationships	F (2, 83) = 2.624, $p = .078$	F (1, 83) = 0.053, $p = 0.819$	F (2, 83) = 0.834, $p = 0.438$	
Independence Performance	F (2, 83) = 1.013, $p = 0.368$	F (1, 95) = .2.699, $p = 0.104$	F (2, 83) = 4.873, $p = \mathbf{0.010}$	DIQ +
Recreation	F (2, 83) = 1.795, $p = 0.173$	F (1,82) = 1.026, $p = 0.314$	F (2, 82) = 0.840, $p = 0.436$	
Prosocial	F (2, 83) = 1.004, $p = 0.371$	F (1, 82) = 0.033, $p = 0.857$	F (2, 82) = 5.663, $p = \mathbf{0.005}$	DIQ + CIQ -
Independence Competence	F (2, 83) = 1.406, $p = 0.251$	F (1, 83) = 0.160, $p = 0.691$	F (2, 83) = 4.199, $p = 0.018$	
Employment	F (2, 83) = 0.517, $p = 0.598$	F (1, 83) = 0.281, $p = 0.597$	F (2, 83) = 0.477, $p = 0.623$	
SFS Total	F (2, 82) = 1.797, $p = 0.172$	F (1, 82) = 2.079, $p = 0.153$	F (2, 82) = 2.032, $p = 0.138$	
GAF	F (2, 83) = 1.565, $p = 0.215$	F (1, 83) = 2.146, $p = 0.147$	F (2, 82) = 2.010, $p = 0.140$	

Factors are Group: preserved IQ (n = 35): deteriorated IQ (n = 37): compromised IQ (n = 16) and Time: baseline and 12 months. Bold font indicates significant effects after FDR correction. + indicates significant improvement. - indicates significant worsening.

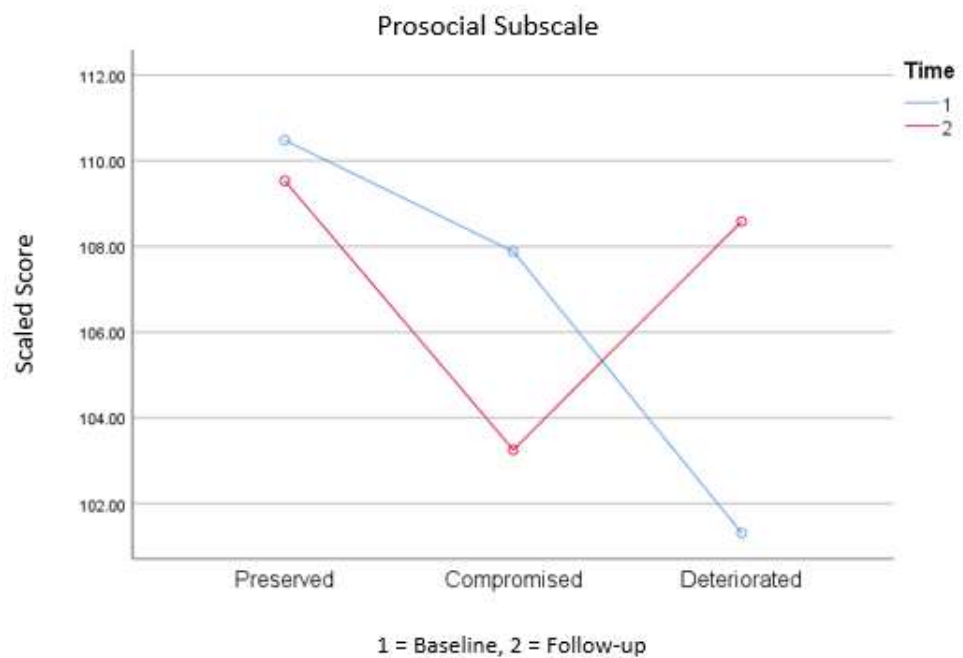


Figure 4.4: Line graph illustrating crossover effect in time x cognitive group interaction from baseline to 12-month follow-up on prosocial scaled score

4.3.6 Neuroimaging and Inflammatory Markers

On those who underwent MRI scanning at follow-up, neuroimaging analysis showed no difference between groups on any of the global measures at follow-up and no effect of Time or Time x Group interaction indicating absence of continued loss of cortical volume (Table 4.6). There was no significant change in inflammatory profile at 12-month follow-up and no time x group interaction after controlling for potential confounders. There was an absolute difference between groups in levels of TNF-a, but this did not survive testing for multiple comparisons (Table 4.7).

Table 4.6: Repeated measures ANOVA effects for cognitive subgroups. Global brain volumes and thickness at baseline and 12-month follow-up were compared.

	Group	Time	Group x Time
Total Intracranial Volume	F (2, 59) = 1.127, $p = 0.331$	F (1, 65) = 1.151, $p = 0.287$	F (2, 59) = 3.071, $p = 0.054$
Absolute TBV ^a	F (2, 59) = 1.329, $p = 0.272$	F (1, 65) = 0.122, $p = 0.728$	F (2, 59) = 1.493, $p = 0.233$
TBV ^{~a}	F (2, 58) = 0.333, $p = 0.718$	F (1, 64) = 0.139, $p = 0.503$	F (2, 58) = 0.245, $p = 0.783$
Cortex ^a	F (2, 58) = 0.010, $p = 0.990$	F (1, 64) = 2.987, $p = 0.089$	F (2, 58) = 1.505, $p = 0.230$
Grey Volume ^a	F (2, 58) = 0.349, $p = 0.707$	F (1, 64) = 3.723, $p = 0.058$	F (2, 58) = 0.129, $p = 0.879$
Mean Cortical Thickness	F (2, 59) = 0.521, $p = 0.597$	F (1, 65) = 1.470, $p = 0.238$	F (2, 59) = 0.325, $p = 0.723$

Factors are Group: preserved IQ (n = 32): deteriorated IQ (n = 23): compromised IQ (n = 13) and Time: baseline and 12 months. ^aControlling for change in ICV, age, sex, site, allocation. TBV = total brain volume. TBV[~] = total brain volume after adjusting for ICV.

4.3.7 Inflammatory Markers

Table 4.7: Repeated measures ANOVA effects for cognitive subgroups. Inflammatory markers at baseline and 12-month follow-up were compared

	Group	Time ^b	Group x Time ^b
hs-CRP	F (2, 64) = 0.559, $p = 0.552$	F (1, 61) = 2.808, $p = 0.099$	F (2, 61) = 0.108, $p = 0.898$
IL-1RA	F (2, 67) = 1.713, $p = 0.188$	F (1, 63) = 1.029, $p = 0.314$	F (2, 63) = 0.032, $p = 0.968$
IL-6	F (2, 67) = 0.623, $p = 0.539$	F (1, 63) = 0.175, $p = 0.677$	F (2, 63) = 0.904, $p = 0.410$
TNF- α	F (2, 67) = 3.564, $p = 0.034$	F (1, 64) = 0.019, $p = .892$	F (2, 64) = 0.981, $p = 0.381$

Factors are Group: preserved IQ (n = 30): deteriorated IQ (n = 31): compromised IQ (n = 14) and Time: baseline and 12 months. Performed on log-transformed scores. ^aControlling for age, sex, BMI, trial allocation and cannabis smoking status. ^bControlling for age, sex, BMI change, trial allocation and cannabis smoking status.

4.3.8 Summary of Results

At 12-month follow-up there was disproportionate attrition of compromised patients. IQ remained static in the whole population and across all subtypes. The deteriorated group showed improvements on the information subtest and the deteriorated and preserved groups showed improvement in AVLT performance, which worsened in healthy controls. The deteriorated and preserved groups improved on all clinical measures, whilst the compromised group only improved on positive symptom scores. The compromised group had higher negative symptoms scores at follow-up than the other patient groups. The deteriorated group improved on prosocial and independence outcome measures, whilst the compromised group worsened on the prosocial subscale. There was no significant change from baseline on brain volumetric or inflammatory measures.

4.4 Discussion

Participants of Study 1 were followed-up after 12-months. The main finding was that IQ remained static and there is no evidence of either further deterioration or improvement in IQ scores beyond that of practice effects (as determined by healthy control performance) in either the entire group nor in any of the cognitive subtypes. As seen in other studies and meta-analyses, the majority of patients experienced some decline from premorbid levels of intelligence, with apparent stability following the onset of symptoms (Rund, 1998, Heaton et al., 2001, Szoke et al., 2008, Hoff et al., 2005). Examining IQ subtests, the DIQ group showed improvement on a measure of crystallised intelligence (information) which was not shared by the CIQ, HC and PIQ groups. This

difference is likely to be a result of ceiling effects for the PIQ and HC groups, and of lesser practice effects in the CIQ group. This lesser practice effect in the CIQ group was also seen on the AVLT test, with PIQ and DIQ groups making significant improvements, whilst the CIQ group showed no improvement. These findings should be treated with caution, given that HCs performed significantly worse at follow-up, albeit from previously having the highest levels of performance. The finding that there is relative stability of cognitive functioning within all subtypes adds to the understanding of cognitive trajectories, showing that stability occurs soon after illness onset and extends to groups with different cognitive trajectories. Those with preserved IQ show no later deterioration and those thought to be on deteriorating trajectories neither continue to decline nor return to levels of premorbid cognitive functioning. Longitudinal studies over much longer periods have argued that cognitive impairment in schizophrenia develops over decades, and that further cognitive deterioration or lag may only be detectable over post-onset follow-up periods of decades (Zanelli et al., 2019). The present study followed patients over 12-months early in their course of illness, a period which is deemed critical to social function (Birchwood et al., 1998). This follow-up period is longer than many comparable studies and importantly finds that there is no detectable continued deterioration in cognition. Unfortunately, there is also no indication of improvement beyond practice effects among the whole group or individual subgroups other than on the auditory verbal learning task in preserved and deteriorated groups, and crystallised intelligence in the deteriorated group. A lack of learning effect has been seen in other studies assessing those with low premorbid intelligence (Leeson et al., 2011) and may be representative of pathological process beginning early in development.

Importantly, this study shows that symptoms may be more tractable in the groups with higher premorbid intelligence (PIQ and DIQ groups) than in the CIQ group. Early intervention services have been shown to successfully treat positive symptoms of psychosis (Tsiachristas et al., 2016), reflected in improvement in positive symptoms for all patient groups in this study. The CIQ group showed significant improvement on the PANSS positive symptom scale but no improvement on any other symptom measure. The PIQ and DIQ groups both showed significant improvement in positive, negative, general and total symptoms as well as on the Calgary Depression Scale. Only the CIQ group did not show improvement in depression scores, but this is likely to be due to the low levels of depression in this group at baseline. Despite some important symptom trajectory improvements, groups were only separable with respect to negative symptom scores at 12-months, which were lower in the PIQ compared to the CIQ group, in consonance with findings in long-standing schizophrenia samples of cognitive subtypes (Wells et al., 2015, Czepielewski et al., 2017). Other studies were also able to separate DIQ and CIQ groups in negative symptoms (Carruthers et al., 2019, Leeson et al., 2011). This finding is important, given that persistent negative symptoms are thought to be a key determinant of poor long-term outcome (Rabinowitz et al., 2012, Milev et al., 2005). There is some evidence of overlap between negative symptoms and cognition (Leanza et al., 2018), though lack of discriminant validity of measures seems unlikely to account for this finding, given that groups were not separable on the same measure in the baseline analysis. The finding that those with putatively preserved IQ have fewest negative symptoms at follow-up is in keeping with other studies which have proposed a possible relationship with insight (Cernis et al., 2015).

There were no differences between groups in social and global functional outcome measures. The DIQ group show significant improvements on the prosocial and independence - performance subscales, which give cause for optimism and may reflect the lessening of clinical symptoms in this group. In contrast, the CIQ group showed worsening on the prosocial subscale for those remaining in the study and may be the result of persisting negative symptoms. The CIQ are a hypothesised neurodevelopmentally vulnerable group who may be at greatest need of additional care and support at presentation. Overall outcome differences are likely to be clouded by the high attrition rate in this group seen in this and other studies (Leeson et al., 2011). Reasons for much greater study attrition in the CIQ group may reveal whether this group are in fact more prone to relapse and poorer outcomes which may have led to significantly fewer participants being able to complete assessments at follow-up. Further longitudinal studies are needed to elucidate other mediators which may drive functional impairments in schizophrenia populations and may moderate functional outcomes in different cognitive subgroups.

There were no significant differences between groups at outcome on any of the biological measures, and no effect of time or time x group interactions. Outcome measures may be confounded by the disproportionate loss to follow-up of compromised participants, or by the loss of statistical power to detect differences. This being said, heterogeneity at presentation is also likely to be reflected by heterogeneity of trajectories (Pantelis et al., 2009) and with a lack of a healthy comparison group it may be difficult to detect subtle brain changes present in clinical populations. Measures of brain volume and thickness may be too crude measures of difference, with investigating disruption to cortical circuits likely to be a better measure to detect individual and group

differences in cognition, which may in turn reflect differential outcomes. The finding that there is no effect of time on any measure of inflammation is interesting, particularly given that this was a patient group in which 50% of clinical participants were prescribed the antibiotic minocycline. Even though trial allocation was controlled for, the findings may be confounded by adherence to the trial investigational medicinal product (IMP). Interestingly, analysis by the lead trial site found that minocycline appeared to have no effect on inflammatory markers even in a high adherence sub-group (Deakin et al., 2018). Given that the compromised subgroup was small at follow-up, absolute differences in outcome at follow-up need to be interpreted with caution and may be underestimated as a result. Aside from issues of sample size at follow-up, Johnsen et al (2016) argue that fluctuation in the inverse relationship between cognition and inflammation may in part be state-dependent, resulting from a relationship with symptoms (Johnsen et al., 2016). However, in the current study there is no evidence of between-group differences in symptoms at baseline suggesting that the absence of association at follow-up may result from individual variability or disproportionate loss of individuals from the group with highest baseline levels of hsCRP.

4.4.1 Methodological Considerations

This study has the advantage over Study 1 that the data are longitudinal, and therefore able to investigate whether the cognitive subtype at baseline influences outcomes at 12-month follow-up and change over time. Few studies to date have examined this, and this is the largest in a FEP group as well as being the first to examine neurobiological and inflammatory markers over time. Despite this, the limitations from Study 1 remain, including lack of control for antipsychotic medication and lack of healthy controls for

neuropathological and inflammatory markers. This study has the additional limitation of a smaller sample size due to attrition, particularly in the compromised group, although still large comparative with previous follow-up studies (Leeson et al., 2011). There is the additional limitation of results being potentially confounded by the trial medication – minocycline. Minocycline was found to have no effect on any cognitive, symptom or biological outcome measure in the RCT (Deakin et al., 2018). However, even in a negative trial, it is still important to interpret findings with caution given that placebo or nocebo effects may have led to outcomes being different to those which may have been observed in naturalistic clinical populations. For better interpretation of cluster outcomes, it would be desirable to know individual reasons for withdrawal from the study, given that much greater attrition in the CIQ group may conceal much worse outcomes beyond that of negative symptoms, such as higher relapse rates and poorer social and occupational outcomes.

4.4.2 Clinical Implications

Given previous literature in this area and lack of routine cognitive remediation interventions delivered in this population, it is of little surprise that cognition does not improve over a one-year period. All those taking part in the study were prescribed antipsychotic medication and any benefit this has on cognition would have likely already been achieved at initial assessment. There is cause for optimism given that the deteriorated group show some prosocial improvements and improvement in verbal learning, but in order to improve outcomes in this population, psychological and pharmacological cognitive remediation should be a clinical imperative. Though there seems to be little difference in global and social functioning between cognitive subtypes,

this may be the result of all groups being impaired by cognitive deficits which may be more specific in “preserved” groups and global in those thought to be premorbidly compromised. Remediation of core cognitive deficits should be targeted across all cognitive subtypes. The compromised and deteriorated subtypes may need additional support early after presentation to EIS teams, with the CIQ group at particular risk of more negative symptoms which may lead to a more persistent functional impairments over longer follow-up periods.

4.4.3 Conclusions

Over a 12-month period following a first-episode of psychosis, IQ appears to remain static in the entire patient group as well as in identified cognitive subtypes. There was no evidence of progressive loss of global brain volume or thickness in the entire patient group or subtypes. Follow-up performance on learning and crystallised intelligence tasks hint at poorer learning in those with below average intelligence both premorbidly and post-illness onset. There is also evidence that those with compromised intelligence may have less tractable clinical symptoms, and greater negative symptoms than those with putatively preserved cognition. Those with low premorbid intelligence may therefore have the greatest need for early identification and intervention. The deteriorated group showed signs of improvements in prosocial function, which worsened in the compromised group. Findings are limited by higher attrition rate in this group which may reflect poorer clinical and social functional outcomes in those who withdrew.

Identifying cognitive trajectories may help to identify those most at risk of persistent clinical symptoms. Lack of global and social functional outcome differences between those with intact cognitive function and those with deteriorated and compromised

function indicate there are other important predictors of functional outcomes beyond neurocognition alone. To better understand the complex relationship between neurocognition and social and functional outcome, it is important to identify and targeting other potential mediators and moderators of this relationship if we are to successfully alter outcomes of those who have experienced a first-episode of psychosis.

5 Study 3 – Neurocognitive Predictors of Global and Social Functional Outcomes in First-Episode Psychosis

5.1 Introduction

Cognitive subtypes have been shown to be useful in identifying those at greatest risk of poor outcomes (Keefe and Kahn, 2017). Despite some differences between groups with varying IQ trajectories, the relationship between premorbid or current neurocognition and functional outcomes may operate at a linear level. Given the lack of consistent group biological phenotypes, differences between cognitive subtypes may be the result of discrepancies resulting from linear relationships, which are maximal between the highest and lowest performing individuals and weakest at those performing either side of group boundaries. A meta-analysis of methodologically rigorous cohort studies found an inverse relationship between premorbid IQ and risk for schizophrenia, with each IQ point fewer conferring a 3.8% increased risk for the development of schizophrenia (Khandaker et al., 2011), a finding which has since been replicated in a large Swedish cohort study (Kendler et al., 2015). Neurocognition may share a similar linear relationship with functional outcomes, acting as a proxy for cognitive reserve or severity of illness. Indeed, studies have found a linear relationship between neurocognitive functioning and functional outcomes in both established schizophrenia and FEP populations (Green et al., 2000, Leeson et al., 2009). There is evidence that measures of global intelligence have the strongest relationship with functional outcomes, though there is also some evidence that individual neurocognitive domains are related to specific domains of functioning (see section 1.4.6). Many studies examining whether

premorbid IQ or IQ at illness onset is predictive of later social functioning have been limited by their cross-sectional nature and small sample sizes. Furthermore, longitudinal studies have often had only short follow-up periods and relatively few studies have followed FEP groups over time.

The concept of cognitive reserve poses that those with higher intelligence are better able to maintain higher levels of functioning when faced with illness pathology, and often have better outcomes than those with lower intelligence as a result (Stern, 2002). Given that IQ declines in the vast majority of people with schizophrenia, there is still some debate as to whether premorbid intelligence acts as cognitive reserve, or whether this reserve is reduced in a substantial proportion of individuals and this has the greatest effect on social and functional outcomes (Leeson et al., 2011, van Winkel et al., 2007).

In a FEP cohort, using regression analysis, Leeson et al., (2009) found that premorbid and current IQ at first-episode and 1-year follow-up predicted outcome after 4-years. Examining the predictive validity of specific cognitive domains on specific domains of social functioning revealed some significant associations, but these were weaker and less consistent than the predictive ability of IQ.

The aim of the current study is to establish; the discriminant validity of the cognitive tasks used; the amount of variance in outcomes explained by domain specific and global measures of intelligence; whether cognitive measures relate to global or specific outcome; and whether the predictive ability of baseline neurocognition is stronger over time.

5.2 Methods

The measures used in the BeneMin cohort are detailed in the 'Methods' (section 2.1) and as in Study 1 (section 3.2) and Study 2 (section 4.2). This study assessed the ability of baseline cognitive measures across the whole cohort to predict social and global functioning both cross-sectionally and at 12-month follow-up.

5.2.1.1 Participants

The complete group of patients included in the cluster analysis in Study 1 (section 3.2) and Study 2 (section 4.2) was collapsed (n =161).

5.2.1.2 Neurocognitive Measures

All neurocognitive measures were included for examination of their relationship with baseline and 12-month functioning. Both premorbid and current IQ were considered as measured by the WTAR and WAIS-III respectively. The four IQ subtest scaled scores (digit symbol, arithmetic, information and block design) along with the additional AVLT and verbal fluency task were also considered independently.

5.2.1.3 Outcome Measures

The two outcome measures from the main study, the GAF and the SFS were used as measures of global functioning and social functioning respectively. Standardised scores of the SFS total and subscales (social withdrawal; interpersonal behaviour; pro-social activities; recreation; independence-competence; independence-performance; and

employment) were also used to assess the relationship between cognitive variables and different components of social functioning.

5.2.1.4 Analysis

Relationships between the IQ subtests and additional cognitive tasks measuring verbal learning and fluency (AVLT and verbal fluency) were assessed using Pearson's zero-order correlations to test for discriminant validity. Pearson's zero-order correlations between the cognitive variables and functional outcome measures were then performed. To determine the amount of variance in outcomes predicted by cognition both cross-sectionally and at follow-up, separate hierarchical linear regressions using forward-step entry were performed with outcome measures as the dependent variables. All IQ subtests, AVLT and verbal fluency were entered as the independent variables using stepwise entry. Separate regressions were then performed with premorbid IQ and FSIQ as the independent variables. For the longitudinal analysis, study allocation was additionally entered into the first block. Significant models are reported.

5.3 Results

5.3.1 Group Characteristics

Patients had a premorbid IQ within the average range (98.98) but a current IQ below average (88.5). As per inclusion criteria, all participants were taking antipsychotic medication at baseline. Mean score on the GAF (55.81) indicates moderate symptoms or moderate difficulty in social, occupational or school functioning and a SFS total score

of 107.09 [9.74]. Mean PANSS score was 16.55 [4.86] for positive symptoms, 17.31 [5.73] for negative symptoms and 33.77 [7.62] for general symptoms (Table 5.1).

Table 5.1: Neurocognitive and social functioning scores for the complete group (n=161)

Variable	Mean (SD)
Premorbid IQ	98.98 (11.38)
FSIQ	88.50 (13.86)
Digit Symbol	6.23 (2.42)
Arithmetic	8.11 (3.04)
Information	9.75 (3.22)
Block Design	9.04 (2.92)
AVLT Immediate	5.03 (1.82)
AVLT Total	37.72 (10.88)
Verbal Fluency	82.15 (23.16)
GAF	55.81 (10.64)
SFS Total	107.09 (9.74)

FSIQ = full-scale IQ. AVLT = Auditory Verbal Learning Test. GAF = Global Assessment of Functioning. IQ subtests represent scaled scores.

5.3.2 Discriminant Validity of Neurocognitive Tests

As shown in Table 5.2, all separate cognitive tests except digit symbol and AVLT immediate, significantly correlated with one another, with significant Pearson’s r values ranging from .198 (arithmetic and AVLT immediate) to .489 (information and arithmetic) indicating moderate discriminant validity of these tests (Weber and Lamb, 1970).

Table 5.2: Correlation matrix showing associations between cognitive variables at baseline

N = 161	Digit Symbol	Arithmetic	Information	Block Design	AVLT Immediate	AVLT Total	Verbal Fluency
Digit Symbol	1						
Arithmetic	.272**	1					
Information	.230**	.489**	1				
Block Design	.257**	.462**	.344**	1			
AVLT Immediate	.116	.198*	.255**	.183*	1		
AVLT Total	.342**	.365**	.344**	.341**	.563**	1	
Verbal Fluency	.367**	.344**	.402**	.314**	.269**	.416**	1

Pearson’s r correlations. AVLT = Auditory Verbal Learning Test. Bold font denotes significance. * = p < 0.05, ** = p < 0.01

5.3.3 Cognition and Outcomes: Cross-Sectional

Tables 5.3 and 5.4 show that that there were no consistent cognitive correlates with global or total social functioning. Most cognitive measures significantly correlated with employment, with verbal fluency (VF) the having the strongest relationship ($r = .341$). Only AVLT total and VF significantly correlated with total social functioning score and global functioning scores, with VF being the best predictor of total SFS score ($r = .173$) and AVLT having the most predictive validity of global functioning ($r = .192$). Premorbid IQ and FSIQ significantly correlated only with employment scores, but to a lesser extent than AVLT and VF.

Table 5.3: Correlation analysis showing associations between specific cognition domains and global and social functioning at baseline

N = 161	Digit Symbol	Arithmetic	Information	Block Design	AVLT Immediate	AVLT Total	Verbal Fluency
GAF	.118	.057	.065	.030	.183*	.192*	.182*
Social Withdrawal	.105	.172*	-.025	-.023	.143	.122	.064
Relationships	.067	.130	.162*	.013	.079	.125	.194*
Independence	.121	-.020	-.014	-.028	.038	.087	.074
Performance							
Recreation	.099	-.001	-.018	.078	.110	.157	.084
Prosocial	.049	.083	.009	-.069	.065	.056	.043
Independence	.056	.008	.110	.062	-.018	.007	.066
Competence							
Employment	.240**	.148	.162*	.174*	.194*	.240**	.341**
Social Function	.149	.109	.080	.028	.129	.161*	.173*
Total							

Values = Pearson's r : GAF = Global Assessment of Functioning. AVLT = Auditory Verbal Learning Test. Bold font denotes significance. * = $p < 0.05$, ** = $p < 0.01$

Table 5.4: Correlation analysis showing associations between premorbid and current IQ and global and social functioning at baseline

<u>N = 161</u>	Premorbid IQ	FSIQ
GAF	.133	.096
Social Withdrawal	.130	.064
Relationships	.151	.132
Independence Performance	.063	.027
Recreation	.046	.051
Prosocial	-.031	.032
Independence Competence	.155	.082
Employment	.168*	.226**
Social Function Total	.137	.126

Values = Pearson's r: GAF = Global Assessment of Functioning. FSIQ = full-scale IQ. Bold font denotes significance. * = $p < 0.05$, ** = $p < 0.01$

Tables 5.5 and 5.6 show significant neurocognitive variables in linear regression analyses of predictors of social and global functioning after accounting for age, sex and trial allocation. None of the models had more than one significant predictor. The strongest predictors of global and total social functioning were AVLT and VF respectively, accounting for 6.5% of variance in global functioning and 10.2% of variance in employment respectively.

Table 5.5: Baseline cross-sectional stepwise linear regressions analysis with IQ subtests and additional cognitive variables entered as independent variables. Significant regressions reported. N = 161

Dependent Variable	Baseline Independent Variable	Standardised β	R2 Adj	Model Fit
GAF	AVLT Total	.255	.065	F = 5.82 <i>p</i> = 0.017
SFS Withdrawal	Arithmetic	.178	.032	F = 5.05 <i>p</i> = 0.026
SFS Relationships	Verbal Fluency	.202	.035	F = 6.55 <i>p</i> = 0.011
SFS Employment	Verbal Fluency	.328	.102	F = 18.60 <i>P</i> < 0.001
SFS Total	Verbal Fluency	.181	.026	F = 5.40 <i>p</i> = 0.021

SFS = Social Functioning Scale. GAF = Global Assessment of Functioning, AVLT = Auditory Verbal Learning Test

Table 5.6: Baseline cross-sectional stepwise linear regressions analysis with premorbid and current IQ entered as independent variables. Significant regressions reported. N = 161

Dependent Variable	Baseline Independent Variable	Standardised β	R2 Adj	Model Fit
SFS Employment	FSIQ	.250	.056	F = 10.45 <i>p</i> = 0.001

SFS = Social Functioning Scale. FSIQ = full-scale IQ

5.3.4 Cognition and Outcomes: Longitudinal

Zero-order correlations between baseline neurocognitive measures and 12-month global and social outcomes (Table 5.7) showed verbal fluency has the most consistent relationship across the cognitive tasks, significantly correlating with 5 of the 9 outcome measures. Auditory verbal learning total also had several significant relationships, though these were weaker than verbal fluency. Digit symbol was the only significant correlate with employment at follow-up (.287). When global measures of premorbid and current intelligence were analysed (Table 5.8), premorbid IQ had more and stronger relationships with global and social outcomes than baseline IQ, though baseline IQ had a significant relationship with recreation where premorbid IQ did not. The measure of crystallised intelligence (information) was also correlated with global functioning and the best predictor of relationships at 12-month follow-up.

Table 5.7: Correlation analysis showing associations between specific cognition domains at baseline and global and social functioning at 12-month follow-up

N = 88	Digit Symbol	Arithmetic	Information	Block Design	AVLT Immediate	AVLT Total	Verbal Fluency
12m GAF	.091	.010	.212*	.006	.184	.231*	.255*
12m Social Withdrawal	.048	-.002	-.005	-.079	.117	.000	.199*
12m Relationships	.093	.184	.302**	.050	.198*	.234*	.263**
12m Independence Performance	.142	.007	.062	-.047	.076	.079	.148
12m Recreation	.217*	.155	.177	.159	.251*	.253*	.243*
12m Prosocial	.114	.139	.178	-.057	.127	.020	.121
12m Independence Competence	.135	-.062	.065	-.013	.063	-.010	.121
12m Employment	.287**	.066	.027	.052	.067	.039	.076
12m Social Function Total	.201	.105	.166	.023	.181	.134	.239*

Values = Pearson's r: 12m = 12- Month, GAF = Global Assessment of Functioning. AVLT = Auditory Verbal Learning Test. Bold font denotes significance. * = p < 0.05, ** = p < 0.01

Table 5.8: Correlation analysis showing associations between global measures of cognition at baseline and global and social functioning at 1-year follow-up

N = 88	Premorbid IQ	FSIQ
12m GAF	.241*	.111
12m Social Withdrawal	.179	-.042
12m Relationships	.258*	.236*
12m Independence Performance	.235*	.035
12m Recreation	.159	.252*
12m Prosocial	.207*	.135
12m Independence Competence	.157	.031
12m Employment	.078	.113
12m Social Function Total	.254*	.157

12m = 12-Month, GAF = Global Assessment of Functioning. FSIQ = full-scale IQ

Stepwise linear regressions (Tables 5.9 and 5.10) showed verbal fluency accounted for between 4.7% and 5% of the variance in overall social and global functioning, comparable with premorbid IQ (4.8% and 5.4%). The strongest predictor of any of the subscales was processing speed, which explains 7.3% of variance in follow-up employment scores. In contrast to baseline, premorbid IQ was a significant predictor of 5 of the functional outcome measures, explaining between 4.5% and 5.4% of variance.

Table 5.9: Longitudinal stepwise linear regressions analysis with baseline IQ subtest and additional cognitive variables entered as independent variables. Significant regressions reported. N = 88

Dependent Variable	Independent Variable	Standardised β	R² Adj	Model Fit
12-Month GAF	Verbal Fluency	.053	.055	F = 6.59 p = 0.012
12-Month Social Withdrawal	Verbal Fluency	.199	.030	F = 4.01 p = 0.048
12-Month Relationships	Information	.302	.082	F = 9.76 p = 0.002
12-Month Recreation	AVLT	.253	.054	F = 6.58 p = 0.012
12-Month Employment	Digit Symbol	.287	.073	F = 8.71 p = 0.004
12-Month SFS Total	Verbal Fluency	.239	.047	F = 5.75 p = 0.018

GAF = Global Assessment of Functioning. SFS = Social Functioning Scale. AVLT = Auditory Verbal Learning Test

Table 5.10: Longitudinal stepwise linear regressions analysis with premorbid and baseline IQ entered as independent variables. Significant regressions reported. N = 88

Dependent Variable	Baseline Independent Variable	Standardised β	R2 Adj	Model Fit
12m GAF	Premorbid IQ	.241	.048	F = 5.85 <i>p</i> = 0.017
12m Prosocial	Premorbid IQ	.207	.033	F = 4.30 <i>p</i> = 0.041
12m Recreation	FSIQ	.252	.054	F = 6.51 <i>p</i> = 0.012
12m Independence Performance	Premorbid IQ	.235	.045	F = 5.64 <i>p</i> = 0.019
12m Relationships	Premorbid IQ	.248	.052	F = 6.354 <i>p</i> = 0.013
12m SFS Total	Premorbid IQ	.254	.054	F = 6.53 <i>p</i> = 0.012

GAF = Global Assessment of Functioning. SFS = Social Functioning Scale. FSIQ = full-scale IQ

5.3.5 Summary of Results

The neurocognitive measures showed moderate-good discriminant validity. Cross-sectional analysis found cognitive tasks differentially predict specific elements of social functioning. Verbal fluency was the most consistent predictor of functioning, including employment, relationships and total social function score. Full-scale IQ only significantly predicted baseline employment. At 12-months, social withdrawal, SFS total and global functioning were significantly predicted by verbal fluency at baseline, and employment was predicted by processing speed. Measures of crystallised intelligence including premorbid IQ and the WAIS III information subtest were stronger predictors of outcomes than FSIQ at illness onset. Measures of neurocognition explained only a small proportion of the variance in social functioning both cross-sectionally and at 12-month follow-up (2.6% – 10.2%).

5.4 Discussion

The primary aim of this study was to establish whether specific or global cognitive deficits present early after the onset of illness are predictive of global or social functioning cross-sectionally and at 1-year follow-up. Results showed that the cognitive tasks showed moderate-good discriminant validity and measured neurocognitive domains with some distinction. Cross-sectional correlation analysis found that both global measures of cognition and measures of specific domains (except for arithmetic) were significantly correlated with employment. Verbal fluency showed the strongest relationship, with regression analysis showing verbal fluency accounted for 10.2% of variance in employment scores. Auditory verbal learning and verbal fluency also had significant relationships with total social functioning scores and global functioning. Arithmetic, which broadly measures working memory was significantly related to social withdrawal, whilst information and verbal fluency were significantly related to the relationship subscale of the SFS. Despite these findings, correlations were generally weak and constituted between 2% - 10% of explanation of variance in outcomes. Premorbid and full-scale IQ were only significantly correlated with employment and showed weaker relationships with this domain than verbal fluency. At 12-month follow-up, correlations were inconsistent, with processing speed, as measured by the digit symbol task, being the strongest predictor of employment, explaining just over 7% of the variance in this domain. Verbal fluency continued to correlate with most outcome domains, but these correlations were comparable in size to those explained by premorbid IQ. The information subtest, which also measures crystallised intelligence, was the best predictor of the SFS relationship subscale and accounted for 8% of the variance at 12-months. Premorbid IQ, was a better predictor of most social and global

functioning than current IQ, with the exception of recreation, where current IQ was a better predictor.

These findings show that both domain-specific and global measures of cognitive functioning are significant predictors of functioning at 12-month follow-up, albeit leaving a large proportion of variance in outcomes unexplained. Relationships between cognitive variables and outcome appear to be inconsistent, with premorbid and crystallised intelligence becoming more important in predicting function after 1-year than at baseline. This may be due to instability in cognitive function at baseline, perhaps due to fluctuation in mental-states and social functioning. Interestingly, premorbid IQ was a better predictor of functioning at 12-month follow-up than baseline IQ. The need to draw on cognitive reserve may become more important and more apparent once symptoms have stabilised. This may explain early findings of limited differences in global and social functioning between those who apparently have a reduction in IQ and those whose IQ appears preserved. Addington et al., (2005) found that once symptoms were included in regression analyses, the relationship between neurocognition and functional outcomes significantly lessened, and suggest that cognitive ability after 12-months may be a more appropriate baseline for prediction of later social and global functioning due to the stabilisation of symptoms by this time. However, given that symptoms are unstable early in the course of illness, it may not be reliable to include them when examining predictive validity over long follow-up periods.

The findings that premorbid IQ is a more reliable predictor of functional outcome longitudinally than current IQ are in line with the longitudinal study by Van Winkel., (van Winkel et al., 2007). This may be due to non-uniformity in decline from premorbid

function at illness presentation, though in the previous study there was evidence that cognitive function remains stable over time.

Verbal fluency appears to be the most reliable predictor of global and social functioning at illness onset in cross-sectional analysis and may be due to an overlap with negative or depressive symptoms. Verbal fluency and premorbid IQ as measured soon after illness onset are the most reliable predictors of social and global functioning. Premorbid IQ is a better predictor of functional outcome than baseline IQ, indicating that cognitive reserve held before illness onset may act to maintain preferable outcomes in the years following illness onset. Similarly, Information, measuring crystallised intelligence was the best predictor of the social functioning relationships sub-scale and it cannot be discounted that higher premorbid IQ improves outcomes through the ability to attain and maintain relationships and support networks which are valuable for maintaining functioning and aiding recovery. Interestingly, the processing speed measure was the best predictor of employment at follow-up, and auditory verbal learning was a significant predictor of recreation. These domains were those shown to be affected even in those with apparently preserved IQ (see Study 1) and, along with verbal fluency, should be core targets for remediation soon after illness-onset in order to improve outcomes. It cannot be ignored that although cognition at illness onset is predictive of functioning both cross-sectionally and over 12-months, most measures account for only a small proportion of variance and the inclusion of additional variables to models added no additional explanatory power, suggesting overlap in the predictive validity of neurocognitive tests. This is likely due to interactions between cognitive processes (Dickinson et al., 2008b) or potential mediation by other factors such as social cognition, motivation, or negative symptoms.

5.4.1 Methodological Considerations

This study examines the relationship between neurocognition and functional outcomes early in the course of illness in a relatively large group, both cross-sectionally and over a 12-month period. Despite a range of neurocognitive measures, the Blyer-short form IQ measure is calculated from only 4 domains and the tests used could be argued not to cover all domains of neurocognition, with reliable and specific tests of some domains which may be predictive of functional outcome (e.g. executive functioning), not included in the battery. Including such measures may have shown an increase in the predictive validity of neurocognition measures. Furthermore, tests such as Block Design and Arithmetic have been argued to require the recruitment of several different neurocognitive functions for their completion. Results are further limited by the outcome measures used in the study, with updated and more sensitive measures of social functioning than the SFS now available, whilst the GAF is scored based on both social and occupational functioning and clinical symptoms. Functional outcome measures are relative, and those which are able to capture functioning of patients relative to pre-illness functioning should be considered in future research studies. Finally, it cannot be ignored that participants in this study were taking part in a clinical trial. Despite no significant effect of the IMP on any outcome measure and accounting for the effect of trial allocation in the analysis, it must be noted that individuals may have differential response to the medication, as well as the potential confounds of placebo and nocebo effects on individual outcomes.

5.4.2 Clinical Implications

Neurocognitive functioning is related to functioning both cross-sectionally and at 12-month follow-up. Cross-sectionally, verbal fluency is the strongest predictor of social functioning, but may result from a shared relationship with other factors such as negative symptoms. Treating the cause of verbal fluency deficits should be a treatment priority for clinical teams. At 12-month follow-up, crystallised intelligence appears more important as a predictor of outcome, indicating that those with poor premorbid cognitive function may be at the highest risk of poor outcomes. Intervening early with cognitive remediation strategies to boost cognitive reserve in those with poorest premorbid cognitive functioning may improve longitudinal outcomes in this population.

5.4.3 Conclusions

Neurocognitive functioning showed only modest ability to predict social and global functioning both cross-sectionally and at 12-month follow-up. At baseline, neurocognition was most consistently associated with employment level and most strongly predicted by verbal fluency. At 12-month follow-up, measures of crystallised intelligence were the best predictors of outcome, with premorbid IQ acting as a better predictor of outcome than current IQ on the majority of measures. In the longitudinal course of illness, cognitive reserve as measured by premorbid intelligence may be an important indicator of outcomes. Longitudinal studies with longer follow-up periods are needed to address this relationship further. The modest ability of neurocognition to predict global and social functioning indicates the need to examine other variables which may act as a mediator between neurocognition and functional outcomes.

6 Study 4 – Social Cognition in First-Episode Psychosis: Comparison with Healthy Controls

6.1 Introduction

Neurocognition is considered a core deficit in people with schizophrenia, impacting social and occupational functioning (Kahn and Keefe, 2013). Despite studies showing neurocognition to be one of the best predictors of functional status across a range of outcome domains (Green, 1996, Green et al., 2000), there is a large amount of unexplained variance in predicting functional outcomes. In an attempt to facilitate the development and measurement of new treatments, the MATRICS consensus (Marder, 2006) identified seven key cognitive domains to be prioritised for assessment and evaluation in patients with schizophrenia, six of which were neurocognitive and one of which was social cognition. Despite the MATRICS consensus and rising interest in social cognitive deficits and interventions in schizophrenia over the past decade, most studies have focussed on exploring neurocognitive impairments including processing speed, attention, memory and executive functions. Social cognition encompasses “the psychological processes that are involved in the perception, encoding, storage, retrieval and regulation of information about other people and ourselves” (Green et al., 2015). There is general consensus that social cognition consists of 4 distinct domains: emotion processing (EP), social perception (SP), attribution bias (AB) and theory of mind (ToM) (Pinkham et al., 2014). The vast majority of studies which have investigated social cognition in people with schizophrenia have focussed on those with long-standing illness (Savla et al., 2013), and the few studies involving those early in the course of illness have largely investigated only one or two social cognitive domains (Healey et al., 2016). In

established schizophrenia, patients consistently show large deficits in emotion recognition and theory of mind (Savla et al., 2013) although there has been little consistency in the measures used to assess these domains. Fewer studies in people with established schizophrenia have assessed social perception, but a meta-analysis consisting of 13 studies indicates a large deficit compared to healthy controls (Savla et al., 2013). Studies of attribution bias have prevalently focussed on patients with delusions, resulting in mixed findings, with some studies showing worse performance than healthy controls and others finding no differences (Randall et al., 2003, Lincoln et al., 2011, Langdon et al., 2010, Kinderman and Bentall, 1997).

Studies attempting to elucidate whether these deficits are a result of “state or trait”, have found evidence of social cognition deficits across several domains even in patients in symptomatic remission (Inoue et al., 2006) and in healthy siblings of those with schizophrenia (Cella et al., 2015). These studies conclude that at least some social cognition deficits are likely to be trait phenomena associated with the genetic risk for schizophrenia. To explore this further, research has begun in populations early in the course of illness and in those at high-risk for psychosis (Thompson et al., 2013, Healey et al., 2016). Similar to neurocognition, social cognitive deficits may have trait elements which exacerbate with illness onset and severity. If this is the case, it would be expected that those with high risk for psychosis would perform worse than healthy controls, and that those early in the course of illness would also show impairments relative to healthy controls, but of smaller magnitude than those with established schizophrenia. Currently the majority of evidence shows that individuals with FEP show social cognitive deficits of comparable magnitude to those with established schizophrenia and that these deficits remain stable over time (Addington et al., 2006b, Bertrand et al., 2007, McCleery

et al., 2016, Inoue et al., 2006, Green et al., 2012a). Some studies, however, report those with established schizophrenia to have larger deficits in social cognition than those early in the course of illness, particularly in emotion processing (Comparelli et al., 2011, Romero-Ferreiro et al., 2016) and most longitudinal studies do not include a healthy control group for comparison, making it difficult to interpret the stability of these deficits without accounting for the confounds of practice and learning effects. The majority of FEP studies, many with small sample sizes, have examined ToM or emotional processing, finding significant impairment in these domains compared to HCs. Furthermore, studies of emotion processing have found deficits to be specific to negative emotions, and recognition of sad and of fearful expressions in particular (Healey et al., 2016, Amminger et al., 2012, Comparelli et al., 2011, Kucharska-Pietura et al., 2005). Few studies, early in the course of illness, have assessed attributional bias and social perception in FEP, with less consistent findings and failure to consistently control for neurocognition (Randall et al., 2003, Lincoln et al., 2011, Kinderman and Bentall, 1996, Langdon et al., 2010)

Understanding social cognitive impairments present early after the onset of psychosis is important if we are to characterise mechanisms which may contribute to long term poor functional outcomes in this population. Research in social cognition has been hampered by a lack of consensus on validity of measures of social cognition and its sub-domains (Pinkham et al., 2014). Results from a recent psychometric evaluation of social cognition measures for four core social cognitive domains has since identified those suitable for clinical trials in schizophrenia (Pinkham et al., 2017) and FEP (Ludwig et al., 2017). It is particularly important that measures shown to be valid, reliable and acceptable to

patients are consistently used, and therefore those with the best psychometric properties were chosen in the current study.

There is still some debate as to whether social cognition and neurocognition should be considered as entirely separate constructs. In patients with long-standing schizophrenia there is evidence that social cognition is at least partly separable from neurocognition, with correlations between neurocognitive and social cognitive tests being in the small to moderate range (Ventura et al., 2013). These findings come largely from populations with established schizophrenia and compare only a small proportion of the recognised domains. Despite some overlap and although evidence suggests social cognition impairments may be smaller in magnitude than neurocognitive impairments, findings from studies suggest these emotionally relevant deficits have stronger associations with functional outcomes than neurocognitive deficits, with correlations approximately twice the size (Pinkham and Penn, 2006, Fett et al., 2011).

Few studies have compared how social cognitive domains relate to each other in patients and in healthy controls. Determining differences between healthy controls and patient groups is important to determine if impairments are unified or specific to individual domains. Studies which investigated this (Addington and Addington, 1998, Deckler et al., 2018) have found differential relationships, with weaker correlations between tasks in healthy control than patient groups. The authors concluded that some social cognitive tasks tap into complex constructs which may be negatively affected by a unified latent impairment not present in controls. Whether this unified impairment is restricted to the domain of social cognition or whether social cognitive impairments are a downstream result of more basic neurocognitive impairments remains unanswered.

Evidence shows that social cognitive ability varies by age and sex (Blakemore, 2012) and these variables must be taken into account when comparing individual and group performance. Furthermore, despite being considered by many to be distinct from neurocognitive ability, several studies have shown social cognition to be related to generalised neurocognitive impairment (Corcoran et al., 1995, Fett et al., 2011, Couture et al., 2006). If social cognition is distinct from neurocognitive ability, social cognitive impairments will be apparent even after adjusting for neurocognitive ability. Unlike many other studies, the current study has the additional advantage of controlling for potential confounding effects of general intelligence, using measures of current IQ. This study aims to characterise social cognitive impairments in a FEP group and to compare these to a healthy control group. In addition, the discriminant validity of tasks in the patient group will be compared. It is predicted that, compared to healthy controls, the patient group will show significantly worse performance on all social cognition domains and there will be stronger associations between all social cognition tasks in the patient group.

6.2 Method

6.2.1 ECLIPSE Cohort

The measures used in the ECLIPSE cohort are detailed in the 'Methods' (section 2.2.) These data were collected cross-sectionally from a subsection of those who took part in the ECLIPSE trial and consented to complete additional social cognition measures.

6.2.2 Participants

Patients who were recruited to the main ECLIPSE trial at the North London, South London and Coventry and Warwick sites were given the option to complete additional social cognition measures and compensated £5 for their time. The inclusion and exclusion criteria were therefore identical to that of the main trial (sections 2.2.2.1 and 2.2.2.2).

Healthy controls for comparison were recruited by researchers based in London as part of a separate project supervised by MC and AJW. Ethical permissions were granted by King's College London ethics, Psychiatry, Nursing and Midwifery Research Ethics Subcommittees (ethical approval reference: HR-17/18-5270). For validity of the comparison, the majority of the inclusion criteria were the same as the main ECLIPSE study. The exceptions to this were a broader age range (18 – 60) and diagnostic criteria, where healthy controls were not included if they had any history of mental illness.

6.2.3 Demographics and Covariate Measures

Age and sex were recorded for all participants and adjusted for in the analysis. To account for differences in neurocognitive ability between healthy controls and patients, IQ was included as a covariate. In healthy controls IQ was estimated using the WTAR. For the patient sample, the WASI-II FSIQ was used since the WTAR does not accurately measure current IQ in this group due to cognitive deterioration following psychosis onset. Current antipsychotic medication was recorded from patient clinical notes and dichotomised as “current - yes” or “current - no”.

6.2.4 Social Cognition Measures

The social cognition measures are detailed in the Chapter 2 (section 2.2.4). These were: The Ambiguous Intentions and Hostility Questionnaire (AIHQ); The Hinting Task (HT); The Social Attribution Task – Multiple Choice (SAT-MC); and the CANTAB Emotion Recognition Task (ERT). The AIHQ included sub-domains of intentionality, anger, hostility, blame and aggression. As recommended by Pinkham et al (2016) ,in addition to the AIHQ total score, the AIHQ blame score was considered a good indicator of attribution bias (Pinkham et al., 2016b). The SAT-MC and HT total scores were the sum of their respective sub-questions. For analysis of the CANTAB ERT, the total number of correct trials was used in the main analysis, with a sub-analysis of median response time across all trials. To assess recognition of different emotions unbiased hit rates for each of anger, disgust, fear, sadness, happiness and surprise were assessed (Table 6.1). These scores were adjusted to ensure they were not affected by response guessing or response bias effects.

Table 6.1: Tasks, scoring ranges and interpretation for social cognition assessments

Task (Minimum score – Maximum Score)	Measures	Interpretation
Ambiguous Intentions and Hostility Questionnaire (5 – 25)	AIHQ Total: The sum of scores on all AIHQ sub-scales across 5 different scenarios including those independently rated (intentionality and aggression) and self-report (hostility, anger and blame).	Lower score indicates lower attributional bias
	AIHQ Blame: The sum of all self-reported blame scores.	
Hinting Task (0 – 20)	The sum of scores (0, 1 or 2) on all Hinting Task questionnaire vignettes.	Higher score indicates better ToM
Social Attribution Task-Multiple Choice (0 – 19)	The sum of scores (0 or 1) on all 19 SAT-MC questions.	Higher score indicates better social perception
Emotion Recognition Task	ERT Median Reaction Time: The overall median latency for a subject to select an emotion word after being presented with a stimulus. Calculated across all assessed trials.	Lower score indicates better functioning
	ERT Total Hits (ERTTH): The total number of correct responses (emotion selection) the subject made across all assessed trials.	Higher score indicates better functioning
	ERT Anger: Unbiased Hit Rate Anger: The unbiased hit rate ensures that recognition accuracy of the Anger emotion is not influenced by response guessing or response bias effects. It takes into consideration the joint probability of an individual making a correct response, based on the presentation of the correct stimulus out of the available possibilities. Calculated for assessed Anger trials only.	
	ERT Disgust: Unbiased Hit Rate Disgust: The unbiased hit rate ensures that recognition accuracy of the Disgust emotion is not influenced by response guessing or response bias effects. It takes into consideration the joint probability of an individual making a correct response, based on the presentation of the correct stimulus out of the available possibilities. Calculated for assessed Disgust trials only.	
	ERT Fear: Unbiased Hit Rate Fear: The unbiased hit rate ensures that recognition accuracy of the Fear emotion is not influenced by response guessing or response bias effects. It takes into consideration the joint probability of an individual making a correct response, based on the presentation of the correct stimulus out of the available possibilities. Calculated for assessed Fear trials only.	
	ERT Happiness: Unbiased Hit Rate Happiness: The unbiased hit rate ensures that recognition accuracy of the Happiness emotion is not influenced by response guessing or response bias effects. It takes into consideration the joint probability of an individual making a correct response, based on the presentation of the correct stimulus out of the available possibilities. Calculated for assessed Happiness trials only.	
	ERT Sadness: Unbiased Hit Rate Sadness: The unbiased hit rate ensures that recognition accuracy of the Sadness emotion is not influenced by response guessing or response bias effects. It takes into consideration the joint probability of an individual making a correct response, based on the presentation of the correct stimulus out of the available possibilities. Calculated for assessed Sadness trials only.	
	ERT Surprise: Unbiased Hit Rate Surprise: The unbiased hit rate ensures that recognition accuracy of the Surprise emotion is not influenced by response guessing or response bias effects. It takes into consideration the joint probability of an individual making a correct response, based on the presentation of the correct stimulus out of the available possibilities. Calculated for assessed Surprise trials only.	

AIHQ = Ambiguous Intention and Hostility Questionnaire, SAT-MC = Social Attribution Test – Multiple Choice, ERT = Emotion Recognition Test

6.2.5 Clinical and Functional Measures

To characterise the patient group, the PANSS was used for measures of positive, negative and global symptoms (see section 2.1.7.1) and the CAINS was used as an additional measure of negative symptom dimensions including expressive and motivation/pleasure (see section 2.2.7.3). To assess social and occupational functioning, the Social and Occupational Functioning Assessment Scale (SOFAS) was used, with a range from 0 (poor functioning) to 100 (excellent functioning) as detailed in the methods (see section 2.2.8.1).

6.2.6 Analysis

All variables were inspected for outliers and non-normal distributions. Group means and standard deviations were calculated for patients and controls for descriptive purposes. To compare groups on these variables, independent t-tests were used where the variables were continuous, and chi-square tests where dichotomous.

For comparison on social cognition measures, univariate ANCOVAs were employed, controlling for potential confounding variables such as sex and age. Separate one-way ANCOVAs were performed with the covariate of estimated IQ, in addition to age and sex, to examine and account for group differences in global neurocognition. For comparisons, data were excluded pairwise, with minor variations in group size indicated by variation in degrees of freedom. To account for the effect of multiple testing, false discovery rate (FDR) correction was applied to main effects. Statistics surviving FDR correction are denoted with the p-value in bold font.

To examine the discriminant validity of the social cognition measures, Pearson's r zero-order correlations were calculated for both healthy controls and patients separately.

6.3 Results

6.3.1 Demographics

A total of 90 patients took part in this study. Five participants were excluded due to missing data on several social cognition tasks and 1 further participant was excluded because of outlying scores by more than 3 standard deviations from the mean on the SOFAS, IQ and ERT task. Three PANSS scores were outlying and not included in the descriptive summary.

Patient and healthy controls differed in number of males and current IQ. The healthy control group had significantly fewer males than the patient group (43% vs 79%) and significantly higher estimated current IQ (103.91 vs 85.89) (Table 6.2). The groups were well-matched for age. The healthy control group had an age range of 18 – 54, with 8% of those in the healthy control group over the age of 45. The patient group had an age range of 17 – 45.

Table 6.2: Patient and control demographic and covariate characteristics

Variable	Patients (n=84) Mean (SD)	Healthy Controls (n=50) Mean (SD)	t test/ χ^2
Sex (% male)	79%	43%	χ^2 (1) = 17.85, $p < 0.001$
Age	26.44 (6.47)	25.38 (8.92)	t = (1, 133) - 0.673, $p = 0.402$
Estimated Current IQ	85.89 (15.51)	103.92 (11.13)	t (1, 132) = 7.806, $p = 0.003$

SD = standard deviation. Bold font denotes significance following FDR adjustment

6.3.2 Clinical and Functioning

Clinical and functioning measures were only available for the patient group and are shown in Table 6.3. A score of 64.45 [12.60] on the SOFAS is indicative of some difficulty in social, occupational or school functioning. The vast majority of patients (94%) were being prescribed antipsychotic medication at the time of assessment.

Table 6.3: Patient group clinical and functional outcome characteristics (n = 84)

Variable	Patients Mean (SD)
PANSS Positive	13.81 (5.42)
PANNS Negative	14.07 (6.35)
PANSS General	31.01 (8.40)
PANSS Total	59.90 (16.91)
CAINS MAP	13.65 (7.10)
CAINS EXP	3.34 (3.89)
CAINS Total	16.99 (9.03)
SOFAS	64.45 (12.60)
Antipsychotic Medication (% Yes)	94

PANSS = Positive and Negative Syndrome Scale, CAINS = Clinical Assessment Interview for Negative Symptoms, MAP = mood and personality subscale, EXP = expressive deficit subscale, SOFAS = Social and Occupation Functional Assessment Scale.

6.3.3 Social Cognition

Descriptive statistics for the social cognition measures are shown in Table 6.4. When controlling for age and sex alone (Table 6.5), the patient group performed significantly worse than healthy controls on the SAT-MC, The Hinting Task and ERT total score (Figure 6.1). In addition, patients had significantly slower reaction times on the ERT and correctly recognised fewer fearful, sad and surprised expressions. There was no difference between healthy controls and patients in performance on the AIHQ.

Once controlling for estimated current IQ, there were no longer any significant differences between the groups (Table 6.6).

Table 6.4: Social cognition score descriptives (controlling for age and sex)

Variable	Patients	Controls
	Mean (SD)	Mean (SD)
	N = 84	N = 50
AIHQ Total	57.99 (15.78)	54.48 (10.68)
AIHQ Hostility	10.13 (3.09)	8.46 (2.63)
AIHQ Intentionality	15.01 (5.31)	13.00 (3.41)
AIHQ Anger	10.68 (4.30)	11.74 (3.06)
AIHQ Blame	12.81 (5.16)	11.82 (3.29)
AIHQ Aggression	9.36 (2.04)	9.46 (1.83)
Hinting Task Total	13.56 (3.98)	15.46 (2.59)
SAT-MC	13.05 (4.02)	15.80 (2.96)
ERT Median Reaction Time	1696.53 (685.86)	1286.08 (391.13)
Total		
ERT Total Correct	26.26 (5.75)	30.02 (4.64)
ERT Anger	.33 (.18)	.41 (.15)
ERT Disgust	.29 (.17)	.37 (.18)
ERT Fear	.16 (.13)	.26 (.17)
ERT Happiness	.53 (.19)	.59 (.16)
ERT Sadness	.39 (.20)	.50 (.18)
ERT Surprise	.36 (.13)	.44 (.16)

AIHQ = Ambiguous Intentions and Hostility Questionnaire, SAT-MC – Social Attribution Task - Multiple Choice, ERT = Emotion Recognition Task. SD = standard deviation

Table 6.5: Comparison of patient and healthy control performance, controlling for age and sex

Variable	F
	Sex/Age
	N = 84 vs 50
AIHQ Total	F [1, 130] = 1.569, $p = 0.213$
AIHQ Blame	F [1, 130] = 1.028, $p = 0.312$
Hinting Task Total	F [1, 130] = 4.981, $p = \mathbf{0.027}$
SAT-MC	F [1, 130] = 15.267, $p < \mathbf{0.001}$
ERT Total Correct	F [1, 130] = 10.837, $p = \mathbf{0.001}$
ERT Median Reaction Time Total	F [1, 130] = 9.306, $p = \mathbf{0.003}$
ERT Anger	F [1, 128] = 2.950, $p = 0.088$
ERT Disgust	F [1, 129] = 3.234, $p = 0.074$
ERT Fear	F [1, 130] = 8.910, $p = \mathbf{0.003}$
ERT Sadness	F [1, 130] = 9.590, $p = \mathbf{0.002}$
ERT Happiness	F [1, 130] = 1.825, $p = 0.179$
ERT Surprise	F [1, 130] = 6.761, $p = \mathbf{0.010}$

AIHQ = Ambiguous Intentions and Hostility Questionnaire, SAT-MC – Social Attribution Task - Multiple Choice, ERT = Emotion Recognition Task. Discrepancies in df due to individual missing data points on ERT Disgust (n =1) and ERT Anger (n = 2). Bold font denotes significance following FDR adjustment.

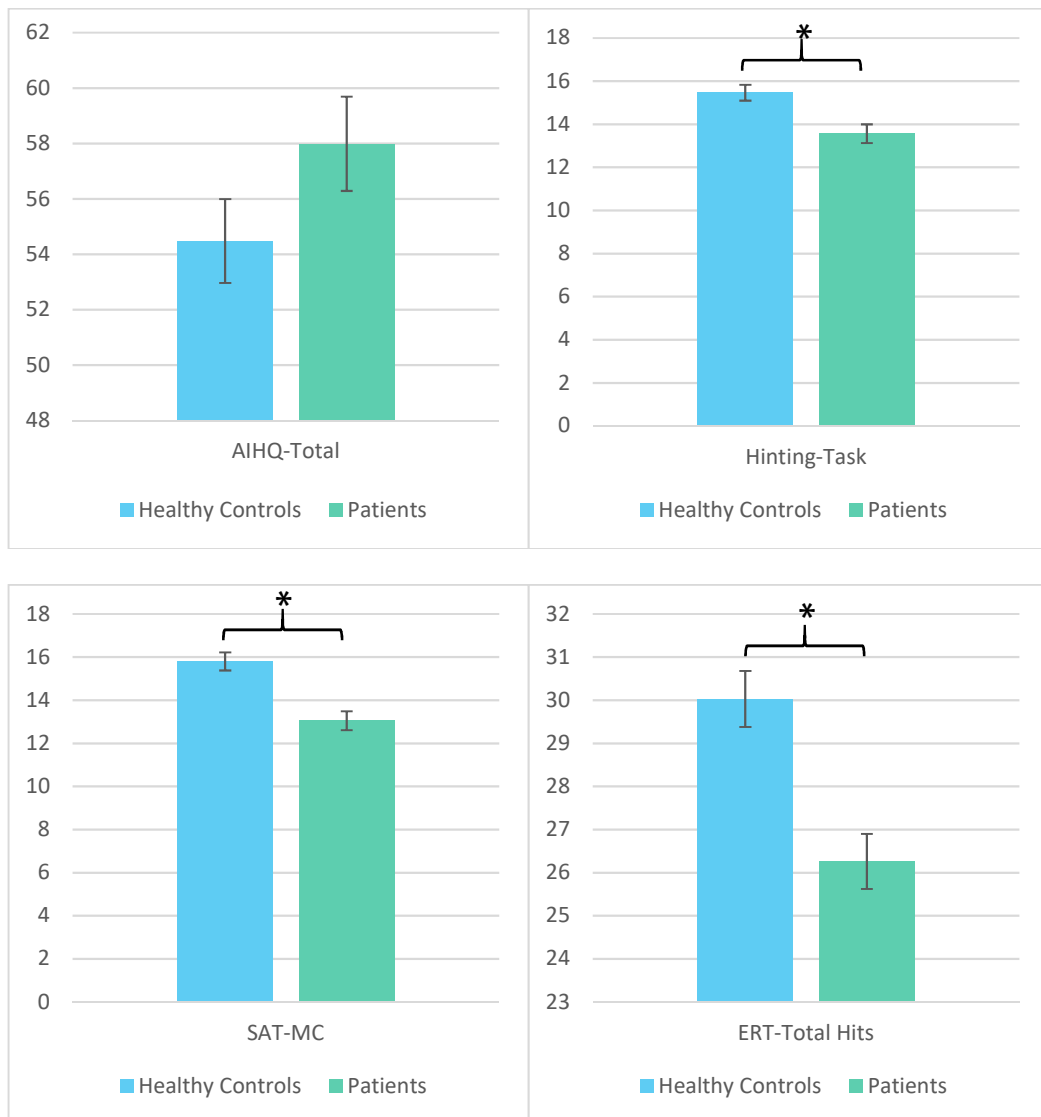


Figure 6.1: Graphical representation of healthy control and patient performance on each of the social cognition total score measures.

AIHQ = Ambiguous Intentions and Hostility Questionnaire, SAT-MC = Social Attribution Task – Multiple Choice, ERT = Emotion Recognition Task. * = statistically significant at $P < 0.05$ after FDR correction.

Table 6.6: Comparison of patient and healthy control performance, controlling for age, sex and estimated current IQ

Variable	F Sex/Age/Current IQ N = 84 vs N = 50
AIHQ Total	F [1, 129] = 0.161, $p = 0.689$
AIHQ Blame	F [1, 129] = 0.041, $p = 0.840$
Hinting Task Total	F [1, 129] = 0.644, $p = 0.424$
SAT-MC	F [1, 129] = 1.524, $p = 0.219$
ERT Total Correct	F [1, 129] = 0.007, $p = 0.935$
ERT Median Reaction Time Total	F [1, 129] = 1.900, $p = 0.171$
ERT Anger	F [1, 127] = 0.837, $p = 0.362$
ERT Disgust	F [1, 128] = 1.372, $p = 0.244$
ERT Fear	F [1, 129] = 0.739, $p = 0.375$
ERT Sadness	F [1, 129] = 0.317, $p = 0.575$
ERT Happiness	F [1, 129] = 0.009, $p = 0.924$
ERT Surprise	F [1, 129] = 0.707, $p = 0.402$

AIHQ = Ambiguous Intentions and Hostility Questionnaire, SAT-MC – Social Attribution Task - Multiple Choice, ERT = Emotion Recognition Task.

6.3.4 Discriminant Validity of Social Cognitive Tests

In the healthy control group ($n = 50$), Pearson’s correlations between social cognitive tasks revealed no significant correlations between either the AIHQ or The Hinting Task with any other measures. The SAT-MC had a small but significant relationship with ERT total score (Table 6.7). When performing the same correlations in the patient group ($n = 84$), there was no significant relationship between the AIHQ and any other measure but there were significant relationships between the Hinting Task total, SAT-MC and ERT totals and between the SAT-MC and ERT total (Table 6.8).

Table 6.7: Pearson’s r Correlations of relationship between performances on social cognitive tests for healthy controls

<u>N = 50</u>	AIHQ	Hinting	SAT-MC	ERTTH
AIHQ Total	1			
Hinting Total	-.055	1		
SAT-MC Total	.012	.002	1	
ERT Total	-.042	.244	.285*	1

*Significant at P < 0.05, **Significant at P < 0.01

Table 6.8: Pearson’s r correlations of relationships between social cognitive tests for patient groups

<u>N = 84</u>	AIHQ	Hinting	SAT-MC	ERTTH
AIHQ Total	1			
Hinting Total	.009	1		
SAT-MC Total	-.157	.373**	1	
ERT Total	-.059	.355*	.451**	1

*Significant at P < 0.05, **Significant at P < 0.01

6.3.5 Summary of Results

Compared to a healthy control group, patients were impaired on measures of theory of mind, social perception and emotion recognition. There was no significant difference between healthy controls and patients on a measure of attribution bias. Sub-analyses of the emotion recognition task found that patients were impaired on reaction times and correct recognition of sad, fearful and surprised faces. Once adjusting for differences in IQ, there were no differences between patients and healthy controls on any measure. Examining the discriminant validity of social cognition measures in both healthy controls and patient groups revealed no significant relationship between the AIHQ and any other measure in either group. The other measures were all significantly related in the patient group, whereas only the SAT-MC and ERT task showed significant association in the control group.

6.4 Discussion

This study compared healthy control and FEP performance across tests of 4 social cognition domains and examined the discriminant validity of tests in each group. There was no significant age difference between the HC and patient groups but there was a significantly higher percentage of females in the HC group. As to be expected due to cognitive impairment being a risk-factor and core feature of psychosis (Zammit et al., 2004, Reichenberg et al., 2010) the healthy control group had a higher current mean IQ than the patient group.

When controlling for age and sex alone, the patients performed significantly worse on measures of social perception (SAT-MC), theory of mind (The Hinting Task) and two key measures of emotion recognition (ERT number of correct responses and reaction time). There was no significant difference between groups on the key attributional bias measures. Further analysis of ERT performance found that the patient group performance was significantly impaired in the recognition of sad and fearful expressions, in keeping with findings from other studies in FEP populations (Amminger et al., 2012, Comparelli et al., 2013, Seiferth et al., 2009, Romero-Ferreiro et al., 2016, Yang et al., 2015, Allott et al., 2015). The emotion recognition impairment also extended to recognition of surprised emotions. When additionally controlling for current IQ, there were no differences between groups on all social cognition measures.

Results from previous studies of attribution bias and emotion recognition have been mixed (Healey et al., 2016) and studies assessing social perception have not controlled for neurocognitive ability (Addington et al., 2006b, Green et al., 2012a). In contrast to the current findings, other studies which used the Hinting Task and controlled for IQ found significant impairment in FEP patients compared to healthy controls (Bertrand et

al., 2007, Thompson et al., 2013, Montreuil et al., 2010, Lindgren et al., 2018). The reasons for contradictory findings are unclear, though Lindgren et al., (2018) found that when comparing FEP patients with healthy controls, 75% of the variance in the Hinting Task performance was explained by general neurocognitive performance.

These findings suggest that attribution bias may not be any worse in those with FEP than in the general population. This FEP group had relatively low levels of positive symptoms in comparison with other studies, and may explain the lack of difference, with attribution bias potentially relating closely to state positive symptoms such as suspiciousness and delusions (Pinkham et al., 2016a). The lack of differences between groups once IQ was accounted for raises the question of how strongly social cognitive impairment overlaps with neurocognition. These findings suggest that impairments in social cognition may occur secondary to, or 'downstream' of neurocognitive deficits. There is the view that processing emotionally laden information or "hot cognition" may be "cooled" in schizophrenia (Harvey and Penn, 2010). More research is required to establish whether this is a risk factor for illness onset or whether it occurs as a function of illness severity or the direct result of deficits in more neurocognitive processes such as attention and processing speed. An alternative view is that currently available measures of social cognition are not able to distinguish neuro- and social cognition and rely on global intelligence for successful completion. This may be due to measures of social cognition being performed in non-social environments and relying heavily on asking participants to imagine themselves in abstract situations. This method of testing social cognition may lack the ability to trigger the emotional or "hot" component necessary for real-world social cognitive function, with participants instead employing

“cold” neurocognitive functions such as problem solving and reasoning during these tasks.

Examining the discriminant validity of social cognitive tasks, the only significant correlation in the HC group was between the SAT-MC and the number of emotions correctly identified. This indicates good discriminant validity between social cognitive tasks in this group (Weber and Lamb, 1970). Surprisingly, given that the SAT-MC is thought to be a hybrid test incorporating ToM (Pinkham et al., 2017), there was no significant correlation between these tasks in the HC group. In addition to the correlation between social perception (SAT-MC) and emotion recognition (ERT) totals, also seen in healthy controls, the patient group showed additional correlations between theory of mind (The Hinting Task) and social perception (SAT-MC) and emotion recognition (ERT). Other studies which have examined discriminant validity in schizophrenia samples have also found differential patient and healthy control profiles (Deckler et al., 2018, Addington and Addington, 1998). The findings in the healthy control group comparing measures of 4 social cognition domains, supports the view that these social cognition measures show good discriminant validity and reflect different social cognitive constructs. However, differential relations seen in the FEP group suggest that these skills are complex and overarching impairments may negatively impact performance which could result in a more generalised deficit not seen in healthy controls. The attribution bias measure (AIHQ) appears to measure a separate construct, unrelated to other measures of social cognition in both the healthy control and patient groups, with no mean difference in performance. It could be argued that the associations between tasks are the result of a lack of ability to create completely orthogonal tests of social cognition, or that these domains share reliance on underlying

neurocognitive processes. The fact that these tests are more strongly associated in the patient group and that the associations are only moderate, points to the latter, with the relationship between social cognition and neurocognitive performance in the patient group requiring further research. This relationship will be examined in Study 5.

6.4.1 Methodological Considerations

Despite being the only known study to date examining all four social cognitive domains in an FEP group, the study has some limitations. One limitation is that there were more females in the healthy control group, but sex differences were adjusted for in the analyses to account for this. The age range criteria for the healthy control group was also wider, though analysis shows the vast majority of healthy control patients included in the analysis were within the same age range as the patients and there were no differences between groups in mean age. Age was also controlled for in all analyses. This study has the additional benefit over many other studies of being able to adjust for current IQ in the analysis. It must be noted, however, that two different measures for current IQ were used, which, although being highly correlated with one another, could potentially overestimate current IQ in the healthy control group.

The Hinting Task and AIHQ both rely on interpreting written or verbal material and are therefore language dependent, possibly relating to verbal ability and potentially sensitive to cultural differences. Regardless, we did not see a relationship between performance on the two measures. It is also possible that a relationship exists between social cognition and symptoms, particularly in attribution bias. Although beyond the scope of this project, this may be an important factor in social cognitive performance

and future studies should determine the relationship of clinical symptoms and social cognitive performance.

6.4.2 Clinical Implications

Findings from this study indicate that attribution bias is not impaired and therefore may not be a primary target for social cognitive training. Theory of mind, social perception and emotion recognition deficits may be a risk factor for development of schizophrenia and should be targeted soon after illness onset, or ideally, in those deemed at risk for development of psychosis. The relationship between neuro- and social cognition requires further investigation to determine if neurocognitive remediation programmes can simultaneously improve social cognition, or if these constructs are separate and require independent social cognitive training interventions. It is not clear that social cognitive interventions alone should be recommended.

6.4.3 Conclusions

The findings of this study show that following a FEP, patients have significant impairments in social perception, emotion recognition and theory of mind compared to a healthy control group. There was no greater attribution bias in this FEP group than evident in healthy controls. Adjusting for estimated current IQ eliminates differences in social cognition performance, indicating that social cognition deficits in people following a FEP may reflect trait deficits, which share a close relationship with global neurocognition and occur downstream of more basic neurocognitive deficits. Future studies should control for IQ when examining social cognition in schizophrenia, ideally

employing prospective cohort methods, with measures of premorbid and current IQ to establish the strength and temporality of the relationship between neuro- and social cognition. Furthermore, studies comparing social cognition across domains in FEP and established schizophrenia with healthy controls are needed to assess whether deficits remain stable over time and their relationship with stage of illness.

7 Study 5 – Does Social Cognition Mediate the Relationship Between Neurocognition and Social Functioning?

7.1 Introduction

Social cognition is shown to be impaired in individuals with established schizophrenia and is associated with neurocognition, accounting for some of the variance in social and functional outcomes (Deckler et al., 2018). Several studies, including two meta-analyses (Fett et al., 2011, Halverson et al., 2019) found social cognition domains to be more strongly correlated with community functioning than neurocognition. Neurocognition has been shown to predict functional outcomes, but due to large unexplained variance in outcomes, there has been a rising interest in examining potential mediators of this relationship. Given the existence of some overlap with neurocognition, social cognition is a potential candidate as a mediating variable and may explain additional variance in functioning.

In a review examining 15 studies in established schizophrenia using regression, path analysis or structural equation modelling (SEM), Schmidt et al., (2011) found that all but one showed that social cognition variables mediate the relationship between neurocognitive and functional outcome variables, in cross-sectional and longitudinal studies. These models are based on an a priori view of a sequential relationship: impaired neurocognition having a subsequent effect on social cognition, which impacts social and community function. In hypothesised full mediation models, once social cognition is taken into account, neurocognition has only an indirect relationship on functional outcomes and is fully explained by a direct effect on social cognition. As in

previous research in social cognition, a broad range of measures have been used, many of which have since been shown to have poor psychometric properties (Pinkham et al., 2017). In addition, neurocognitive and functional outcome measures used in mediation models vary widely, with some focussing on global cognition or functioning, and others on specific neurocognitive domains or aspects of social functioning. Social cognition is thought to be a multi-faceted construct comprised of 4 key domains (Green et al., 2015) but most models to date have assessed the mediating role of only one social cognitive construct. The majority of studies have been cross-sectional and address emotion perception or social perception as mediators, with a broad range of different neurocognitive domains across studies. Schmidt et al., (2011) found that, on average, mediation models explain 25% of variance in functional outcomes.

One study assessing whether social cognition acts as a mediator in individuals at ultra-high risk (UHR) for psychosis found the path between neurocognition and functional outcome was no longer significant once accounting for social cognition, but that social cognition no longer had a significant relationship with neurocognition (Barbato et al., 2013). The authors concluded that social cognition does not mediate the relationship between neurocognition and functional outcomes in UHR participants, potentially due to a weaker relationship between cognition and outcome prior to illness onset than in established schizophrenia. This is particularly important, given that studies have found that of those deemed at high-risk for schizophrenia, approximately between 10% to 30% will go on to experience a psychotic illness (Raballo et al., 2019). This leaves a large proportion of individuals who do not go on to develop schizophrenia and limits the usefulness of such studies. An alternative approach is to conduct studies early in the course of illness. To date, no studies have assessed whether social cognition acts as a

mediator of functional outcomes soon after the onset of the illness before potential confounds of the effects of prolonged illness.

Whether neurocognition and social cognition are separable constructs remains an issue of debate (van Hooren et al., 2008, Mehta et al., 2013, Hill et al., 2008, Allen et al., 2007) and the cross-sectional nature of many studies cannot fully address the temporality of the mediating effect. Studies have largely determined that neuro- and social cognition are distinct constructs (Allen et al., 2007, Pinkham et al., 2003) but do appear to have at least moderate overlap (Fett et al., 2011, Ventura et al., 2013). Some research has found performance on lower order tests of social cognition (e.g. emotion recognition) is associated with lower-order neurocognitive processes such as attention (Chung et al., 2011, Meyer and Kurtz, 2009) whereas higher order social cognitive skills (e.g. theory of mind) might require higher-order executive function (Abdel-Hamid et al., 2009, Bell et al., 2010). Further research is needed in this area, with studies early in the course of illness able to identify possible core neurocognitive abilities which relate more closely to social cognitive domains and may suggest specific targets for interventions.

The aim of this study is to examine the mediating effect of social cognition (comprised of 4 core social cognition domains) on neurocognition and social and occupational outcomes early in the course of a psychotic illness. To do this structural equation modelling (SEM) was used. This has a number of advantages over other types of analysis. The primary benefit is being able to employ a combination of confirmatory factor analysis and regression to allow for the inclusion of unobserved or "latent" variables which gives a more comprehensive measure of social cognition than inclusion of only single domains has been used in many studies (Schmidt et al., 2011). Additionally, correlational analysis allows characterisation of the relationship between

neurocognitive and social cognitive tasks and addresses the relationship between neuro- and social cognition domains. It is important to address the existing question of whether social cognitive tests are distinct from neurocognition and whether they overlap. The findings will have important implications for treatment targets.

Given previous evidence in patients with established schizophrenia and ultra high risk populations and the inclusion of measures of all social cognition domains, it is predicted that social cognition would fully or partially mediate the relationship between neurocognition and social and occupational outcomes and that social cognition domains would have weak to moderate relationships with neurocognitive domains.

7.2 Methods

7.2.1 Participants

Clinical participants were the same as those recruited to the previous study (section 6.2.2). SEM requires complete data, so all those with complete cognition and outcome measures were included in the model (n = 84).

7.2.2 Measures

The social cognition measures used are detailed in the methods section (2.2.4) and study 4 (see section 6.2.4). The SOFAS was used as the only measure of functional outcome. Due to the significant correlation between IQ and functional outcome, IQ as measured by the WASI-II was used as a measure of global neurocognition and included in the model as the independent variable. One measure of each of the social cognition assessments was included. For the AIHQ, a lower total score indicates better

performance, whereas for the SAT-MC, ERT and Hinting Task totals, a higher score is indicative of better performance. In addition to measures included in the model, all CANTAB measures as detailed in the methods section (see section 2.2.4.2) were included in correlational analysis to characterise the relationships between neuro- and social cognition measures.

7.2.3 Analysis

Analysis was conducted using SEM with maximum likelihood estimation of AMOS 25 (Arbuckle, J. L. (2014). After inspection and removal of outliers in the previous study (see section 6.2.6), only participants with complete data for the variables were included in the analysis. Due to a small amount of missing data, imputation of missing data was not appropriate. Variables were checked to assure they met assumptions for inclusion in the SEM model. To ensure causal and mediator variables were correlated with one another and with social outcomes, zero-order correlations including all neurocognitive measures were performed. Variables without a significant relationship with social functioning score were excluded from the models. According to conventions, two models were tested; a basic model examining the direct link between neurocognition and social and occupational outcomes; and a mediation model assessing this relationship once controlling for an intervening mediator variable (Figure 7.1). The SOFAS score was used as the endogenous outcome variable.

SEM combines confirmatory factor analysis with multiple regression analysis and has the benefit of allowing the use of several indicator variables per construct in complex models. Using multiple variables as measures of unobserved constructs increases the validity of the constructs measured and therefore conclusions of the analyses. IQ and social

functioning were estimated using direct indicator variables (WASI-II and SOFAS total scores). Social cognition was an unobserved construct (or latent variable) made up of hypothesised indicator variables, determined by significant standardised partial regression coefficients. To assess model fit, chi-square test was used (with non-significant test indicating acceptable fit of the data). The chi-square test can be sensitive to sample size (Ullman, 2006) so additional indices were used to estimate the model fitness: comparative fit index (CFI) root mean-squared error of approximation (RMSEA) and closeness of fit (PCLOSE) were used (Byrne, 2016). Baron and Kenny (1986) propose that for full mediation, once the mediator variable is taken into account, there should be a non-significant relationship between the predictor and outcome variable, and a significant relationship between the predictor and mediating variable, and between the mediator and outcome variable once controlling for the direct relationship. Standardised β 's and indices of model fit will be reported for each model.

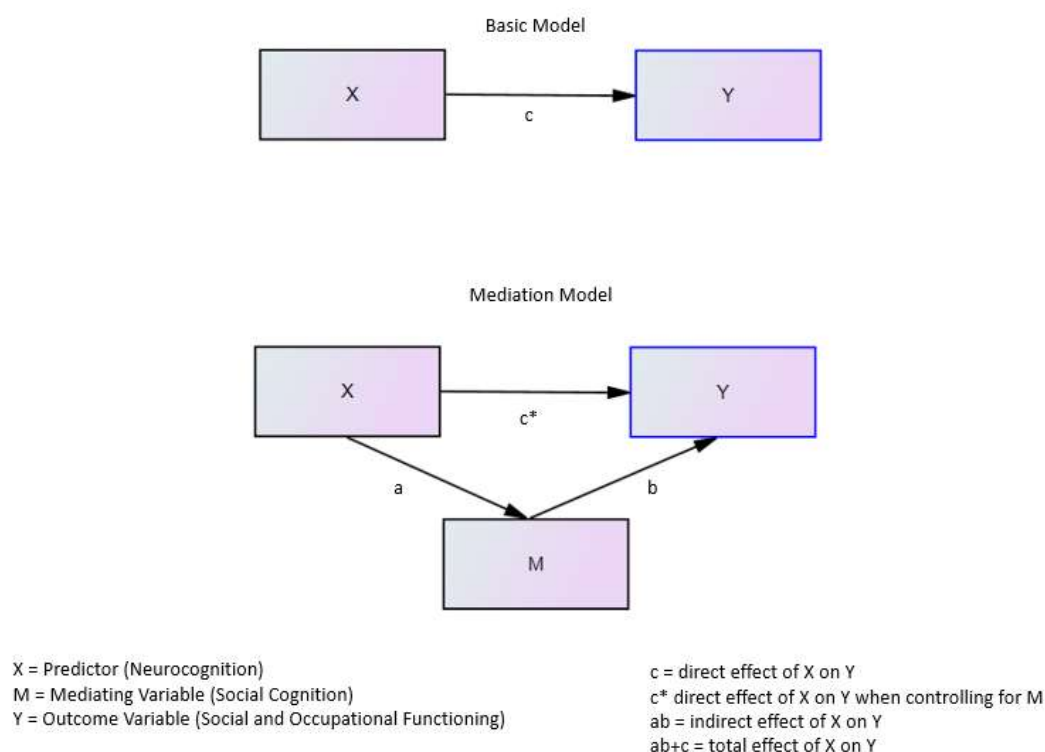


Figure 7.1: Schematic of the basic and mediation models tested

7.3 Results

Descriptive values of the variables included in both models are included in the previous study shown in Tables 6.2, 6.3 and 6.4 (see section 6.3). Two-tailed Pearson’s correlations revealed significant relationships between IQ, AIHQ total, SAT-MC total and ERT total scores (Table 7.1.) making them a good fit inclusion in a mediation model. The Hinting Task did not share a significant linear relationship with social functioning ($r = 0.177$) and therefore violated one of the steps required for testing mediation and was excluded from the model. Table 7.1 additionally, shows the relationship between the CANTAB neurocognitive tasks, social cognition and social and occupational function

measures. The AIHQ did not have a significant relationship with any of the neurocognitive tasks. The ERT task had a significant relationship with all CANTAB tasks other than the reaction time tests and large correlations with the AST ($r = .64$), OTS ($r = .52$), RVP ($r = .58$) and SWM errors ($r = -.55$). The SAT-MC had a significant relationship with all neurocognitive tasks, with large correlations with OTS ($r = .52$) and RVP ($r = .53$). The Hinting Task had smaller but significant small to moderate relationships with the OTS ($r = .43$), PALS ($r = .26$), RVP ($r = .33$) and SWM ($r = -.26$) tasks. The CANTAB tasks were all significantly correlated with the SOFAS, with the exception of the RTI simple and 5-choice reaction times and the 5-choice release time. The correlations were of similar strength to those of the social cognition measures (weak to moderate). Of both neurocognitive and social cognition measures, IQ had the strongest relationship with the SOFAS ($r = .39$). It is important to note that these correlations were not controlled for multiple comparisons, meaning there is increased risk of type 1 errors.

Table 7.1: Listwise zero-order Pearson's R correlations of neurocognitive, social cognitive and social functioning variables.

	<u>N = 84</u>	AST	OTS	PALS	RTI Simple RT	RTI Simple Rel	RTI 5- Choice RT	RTI 5- Choice Rel	RVP	SWM Errors	FSIQ	AIHQ	Hinting Task	SAT-MC	ERT	SOFAS
1	AST	1														
2	OTS	.421**	1													
3	PALS	.392**	.493**	1												
4	RTI Simple RT	-.137	-.172	-.242*	1											
5	RTI Simple Rel	-.377**	-.461**	-.352**	.469**	1										
6	RTI 5 Choice RT	-.052	-.207	-.219*	.880**	.477**	1									
7	RTI 5-Choice Rel	-.285**	-.374**	-.394**	.417**	.715**	.489**	1								
8	RVP	.569**	.526**	.518**	-.226*	-.534**	-.218*	-.481**	1							
9	SWM Errors	-.543**	-.566**	-.474**	.103	.419**	.123	.320**	-.512**	1						
10	FSIQ	.541**	.588**	.438**	-.139	-.320**	-.074	-.204	.444*	-.610**	1					
11	AIHQ	-.065	-.119	-.132	-.097	.037	-.050	-.057	-.016	.196	-.254*	1				
12	Hinting Task	.193	.434**	.263*	-.058	-.163	-.057	-.058	.338**	-.262*	.440**	.016	1			
13	SAT-MC	.392**	.526**	.413**	-.244*	-.496**	-.333**	.387**	.533**	-.434**	.444**	-.136	.369**	1		
14	ERT	.647**	.522**	.455**	-.148	-.317**	-.115	-.329**	.583**	-.555**	.628**	-.040	.349**	.419**	1	
15	SOFAS	.276*	.276*	.280*	-.147	-.266*	.146	-.180	.264*	-.218	.397**	-.232*	.177	.267*	.305**	1

AST = attention switching task, OTS = one-touch stockings task, PALS = paired associates learning task, RTI RT = reaction time task, RTI Rel = reaction time task release time, RVP = rapid visual processing task, SWM errors = spatial working memory errors, FSIQ = full-scale IQ, AIHQ = ambiguous intentions and hostility questionnaire, SAT-MC = social attribution task, ERT = emotion recognition task, SOFAS = social and occupational functioning assessment scale. Table not corrected for multiple comparisons.

7.3.1 Basic Model

The basic model (Figure 7.2) assessed the relationship between neurocognition and social functioning. To minimise the number of estimated parameters due to a limited sample size, IQ was used as the observed measure of neurocognition. IQ is a recognised measure of global cognition and showed significant relationship with the outcome measure (Table 7.1) making it suitable for both the basic and mediation models. Furthermore, IQ was significantly associated with all CANTAB measures which had a significant relationship with the social outcome variable. The only exception to this was for the simple RTI release time. The basic model shows the direct relationship between IQ and functional outcome (SOFAS). There was a statistically significant path between the two variables (standardised $\beta = .40$, $p = < 0.001$), accounting for 16% of the variance in outcomes. The path between social cognition and social functioning was also significant (standardised $\beta = .47$, $p = 0.008$). Confirmatory factor analysis revealed moderate to high factor loadings of the remaining variables on the latent social cognition variable, which were all statistically significant (standardised regression weights: AIHQ: $\beta = -.26$, SAT-MC: $\beta = .71$, and ERT: $\beta = .83$).

7.3.2 Mediation Model

The mediation model was used to evaluate the relationship between neurocognition and social functioning once taking into account the effect of social cognition (Figure 7.3). None of the social cognition indicator variables had issues of multi-collinearity. In the mediation model, social cognition was significantly predicted by neurocognition (standardised $\beta = .88$, $p = < 0.001$) and once controlled for, meant that neurocognition

no longer significantly predicted social functioning and its predictive value was close to 0 (standardised $\beta = -.06$, $p = 0.913$). This is in keeping with full-mediation. However, once controlling for the direct effect of IQ on the SOFAS, the relationship between social cognition and the SOFAS was no longer statistically significant (standardised $\beta = .50$, $p = 0.337$). Although much stronger than the direct path, without a significant b path, it is not possible to conclude mediation. The reasons for this are explored in the discussion section. The mediation model explained 21% of variance in social and occupational function outcomes with an indirect effect (ab) of $\beta = 0.44$. Indices of model fit showed a good model fit for the data as shown by a non-significant chi-square ($\chi^2 = 10.340$, $df = 9$, $p = 0.324$). Additional indices of model fit support this (CFI = .97, RMSEA = .08: PClose = .26).

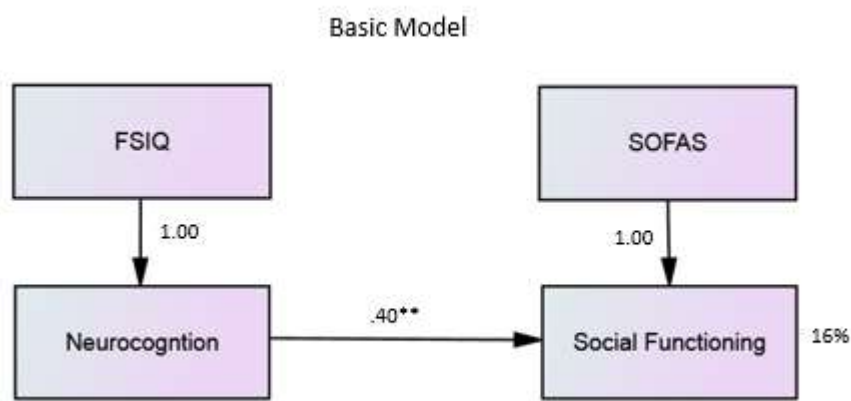


Figure 7.2: Basic model of the relationship between neurocognition and social functioning
 Rectangles indicate observed variables. Numbers on uni-directional arrows represent standardised regression weights.

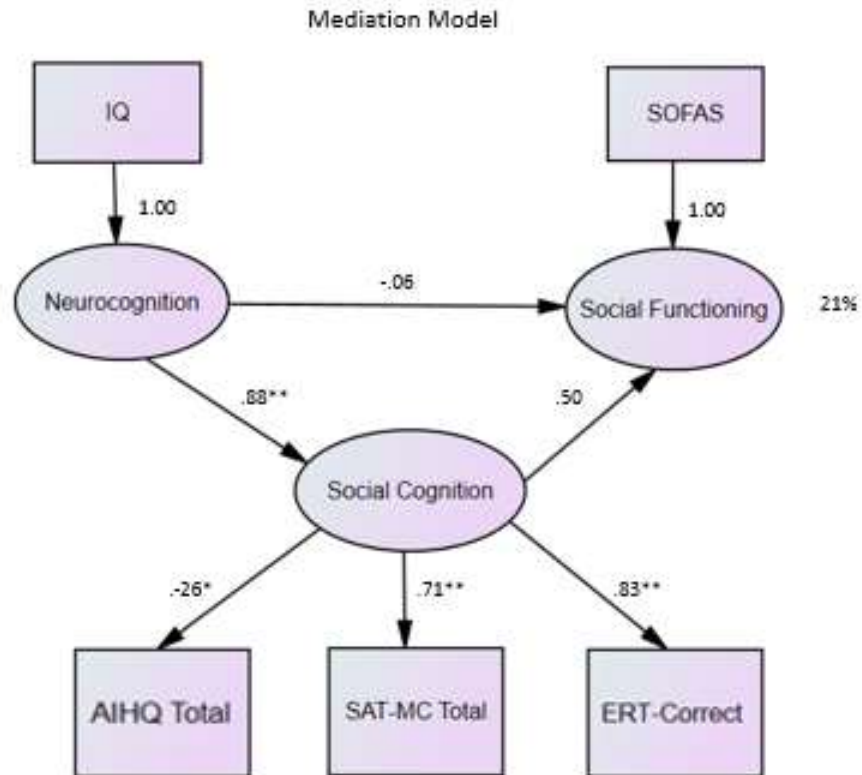


Figure 7.3: Mediation model accounting for social cognition as a potential mediator of the direct relationship between neurocognition and social functioning.

Rectangles indicate observed variables. Elipsis represent latent variables. Numbers on uni-directional arrows represent standardised regression weights.

7.3.3 Summary of Results

The AIHQ, ERT and SAT-MC were all significantly related with social and occupational functioning but there was no significant correlation between the Hinting Task and the SOFAS. The majority of neurocognitive measures were also related to social and occupational outcomes, and of a similar strength (weak to moderate) to the significant social cognition measures. RTI was the exception, with no significant relationship between the simple release or reaction time, or the 5-choice release time and the SOFAS. IQ was the variable most strongly correlated with social and occupational functioning.

Basic and mediation models found both IQ and a latent social cognition variable comprised of 3 domains were significant predictors of outcomes, and of similar magnitude. Multicollinearity between IQ and social cognition meant that in the mediating model, once accounting for social cognition, IQ no longer significantly predicted social and occupational outcomes, but social cognition also became non-significant. The model including both IQ and social cognition explained more of the variance in outcomes than IQ alone (21% vs 16%).

7.4 Discussion

The aim of this study was to investigate the relationship between neurocognition, social cognition and social and occupational outcome in a FEP group. This study also aimed to establish whether social cognition mediates the relationship between neurocognition and social function. There is a growing consensus that social cognitive impairments in FEP are similar in magnitude to those in established schizophrenia (Green et al., 2012a,

Healey et al., 2016) and research has shown that social cognition mediates the relationship between neurocognition and social outcomes in established schizophrenia samples (Schmidt et al., 2011).

As commonly found in this population (Green et al., 2000), the majority of neurocognitive measures were significantly associated with social and functional outcomes, with the exception of the CANTAB simple and five-choice reaction times and five-choice release time. IQ score was significantly related to social and occupational outcomes (SOFAS) and has the additional advantage of being adjusted for age. To reduce the number of parameters and therefore increase the power of the model, IQ was used as the only measure of neurocognition. In a basic model, IQ was shown to be a significant predictor of social and occupational function. A latent social cognition variable comprised of tasks measuring 3 different social cognition domains was also significantly related to social and occupational functioning and comparable to that of IQ. SEM was used to test the hypothesis that a latent measure of social cognition mediates this relationship between IQ and social and functional outcomes in FEP. The Hinting Task was not found to be related to social and functional outcome and was therefore not included in the model. This finding was surprising given that the Hinting Task was considered to have good psychometric properties as a measure of theory of mind (Pinkham et al., 2016b, Pinkham et al., 2017). This finding is also contrary to findings of some other studies, which found a significant relationship between the Hinting Task and interpersonal and social skills performance (Pinkham et al., 2017, Pinkham and Penn, 2006). The lack of a significant relationship in the current study may be due to the use of a single outcome measure with a wide range of possible scores and therefore variance. Despite not being found to significantly differ from healthy controls in the

earlier study (see section 6.3.3) the AIHQ did show a significant relationship with outcomes, as did the ERT and SAT-MC. These correlations were all either small or moderate and individually weaker than the relationship between IQ and outcome. As previously stated, other studies have found the relationship between social cognition measures to have stronger correlations than measures of global cognition. Stronger relationships between social cognition and the SOFAS were not found in this study. This may be due to the need for social cognition impairments to be present for longer periods of time before they have a significant negative impact on functioning and may require longitudinal studies for detection. Alternatively, using a social functioning outcome measure which can be used in both healthy controls and patients (e.g. Time Use Survey) would allow the assessment of differences in functioning and the contribution of social cognition variables.

The three constructs; neurocognition (IQ), social cognition (AIHQ, SAT-MC, ERT) and social and occupational functioning (SOFAS) were all significantly related, warranting their inclusion in the mediation model. Once controlling for social cognition, there was no longer a significant relationship between IQ and social and occupational outcomes. Baron and Kenny (Baron and Kenny, 1986) state that this is necessary to conclude that 'causal steps' mediation has occurred. However, they also state that there must be a significant relationship between the mediator and outcome variables after controlling for the direct effect of the predictor variable. In this study, despite a relatively strong β coefficient, once controlling for the direct effect of IQ on SOFAS, the relationship between social cognition and SOFAS was no longer significant. As a result, it is not possible to conclude that social cognition acts as either a full or partial mediator between neurocognition and functional outcomes in this model.

One potential explanation for this finding is that the relationship between neurocognition and social cognition (a path) is very strong and there is therefore high collinearity between these variables. Paradoxically, the power to detect the effects of mediation can decline as a result of increase in ab effect size, when the a path is substantially larger than the b path (Beasley, 2014). Significant collinearity leaves little unique variance for the mediator to explain outcomes and causes inflation of the variance of the b path. As a result a large standard error negates the increase in the effect size of the overall path (ab) due to a loss of statistical power (Beasley, 2014). Counter-intuitively (Beasley, 2014), given that social cognition had such a strong relationship with neurocognition in this study, a larger sample size is required to detect mediation than if social cognition had a weaker relationship with neurocognition. Others have argued it is not necessary to control for the direct relationship (c path) when calculating the b path coefficient as this creates an impossible condition for deterministic models (James et al., 2006, Shrout and Bolger, 2002). The relationship between neuro- and social cognition requires further exploration to determine whether this relationship should be considered deterministic and guide the type of mediation analysis employed.

The results of this study show that whilst including social cognition may improve the amount of variance explained in social and functional outcomes, social cognition and neurocognition are not fully independent. Conceptually, this is likely to be the result of neurocognition having a downstream effect on social cognition which, taken together, suggests that both are having an influence on functioning.

Zero-order correlation analysis to determine where the relationships between neurocognition and social cognition are greatest revealed that IQ had a small

relationship with attributional bias, but moderate-large relationships with measures of theory of mind, social perception and emotion recognition. The Hinting Task and the AIHQ both include vignettes, and performance could therefore be affected by verbal deficits, also assessed by the IQ measure. However, the Hinting Task also had significant associations with 4 of the language independent computerised cognitive tasks, (OTS, PALS, RVP and SWM) which includes those requiring higher-order executive functions. These findings are in keeping with those of Lindgren et al., (2018) who found a large proportion of variance in the Hinting Task performance was explained by general cognitive deficits including non-verbal measures. The AIHQ was unrelated to any of the individual neurocognitive measures. This may be due to attributional bias being related to clinical symptoms such as paranoia and delusions (Sanford and Woodward, 2017, Pinkham et al., 2016a), which could lead to greater variance and weaken the relationship with neurocognition.

The relationship between IQ and emotion recognition and social perception is likely to be due to the need for broad range of cognitive abilities for their successful completion. The findings of this study suggest that both these tests are related to a broad spectrum of cognitive tasks. Performance on the ERT is particularly strongly associated with tests of visual attention, spatial working memory and spatial planning. This may reflect an impairment in visual attention and the reliance on lower-order neurocognitive processes for successful emotion recognition. The SAT-MC was most strongly associated with tests of spatial planning and sustained attention and may reflect the need for both higher-order and lower-order neurocognitive abilities to perform well on this social perception task. Visual attention and executive functions have been shown to be some of the most impaired domains in individuals with schizophrenia and remediation of

these functions may result in subsequent improvement in social cognition performance. This is in keeping with the view that social cognitive tasks require neurocognitive functions, such as visual attention or executive functions, to be intact for their successful completion. There is need for further research, however, as there are few studies and little evidence to date that neurocognitive gains transfer to social cognitive performance (Genevsky et al., 2010). Alternatively, the link between neuro- and social cognition may be the result of global and widespread brain pathology or a shared genetic cause. Attributional bias appears to be distinct from neurocognition, whereas ToM, social perception and emotion recognition overlap with neurocognitive processes. Some have argued, however, that attribution bias is related to clinical symptoms and should not be considered a measure of social cognition (Buck et al., 2016). Other studies have shown neurocognition and social cognition are at least partly separable and may be affected by other factors such as disorganisation (Hardy-Bayle et al., 2003), paranoid (Frith, 2000) or negative (Sergi et al., 2007) symptoms. Using a broad range of validated neurocognitive tasks, the current study found stronger relationships with neurocognitive processes than those of a meta-analysis (Ventura et al., 2013) and indicate significant overlap between neurocognitive and social cognitive tests in this FEP population.

Including tests of social perception and emotion recognition in addition to tests of neurocognition may give a better understanding of the variability in outcomes following a first-episode of psychosis. Cognitive remediation strategies should focus on neurocognitive functions to improve and maintain social and occupational function, which may result in simultaneous or subsequent improvements in social cognition over the years following the onset of illness. However, given that the mediation model

explained more variance in outcomes than the basic model alone and that social cognition is a similar predictor of social functioning, social cognition may also be a suitable target for remediation in addition to neurocognition, or for those unresponsive to neurocognitive remediation therapy alone.

7.4.1 Methodological Considerations

This study is the first to assess whether a latent social cognition variable comprised of all 4 social cognitive domains mediates the relationship between neurocognition and social and occupational function in a FEP group. However, the findings of this study are limited by the sample size. Studies vary in their recommendations of sample size for SEM. Some suggest that 5 participants for each estimated parameter is adequate (Hair, 2019), suggesting SEM was suitable in this study, whereas others recommend minimums of at least 100 (Kline, 2016). As previously mentioned, in this study there was a strong relationship between global neurocognition and a latent social cognition variable, resulting in the need for a larger sample size in order to test mediating effects. It may, however, be the case that neuro- and social cognition overlap to the extent that it is not possible to separate their effect on variance in social and occupational outcomes. This study is further limited by having only one outcome measure. The SOFAS has a range from 0 – 100, meaning that variance in outcomes can be large and provides a measure of general outcomes. Different or additional measures of functioning may demonstrate stronger or differential relationships with neuro- or social cognition variables. It may have also been preferable to use several different measures of neurocognitive domains, rather than IQ alone, to evaluate neurocognitive performance. A latent or factor solution may provide a more precise estimate of intelligence, due to the score resulting from

multiple tests. IQ relies to some extent on language, which may affect the overlap between neuro- and social cognition, but due to the sample size of this study it was important to limit the number of parameters estimated to maximise the power of the study to detect mediating effects and therefore individual neurocognitive measures were not included in the mediation model.

This study was also cross-sectional and has the limitation that it is not possible to draw conclusions as to the temporality of the relationships between variables. Associations between both neuro- and social cognition have been shown to be more strongly predictive of outcomes over longer follow-up periods and future longitudinal studies are necessary to establish the temporal effect of cognition on social and occupational outcomes. In addition, correlations between individual neurocognitive, social cognitive and functioning scores were not controlled for multiple comparisons. This was to avoid type 2 errors when selecting the most appropriate variables for inclusion in the mediation analysis, but must be treated with caution, given the possibility of subsequent inflated type 1 error rates.

7.4.2 Clinical Implications

Social cognition does not mediate the relationship between neurocognition and social and functional outcomes in this FEP group. However, there is a strong relationship between neurocognition and social cognition and the mediation model explains additional variance in outcomes than the model with neurocognition alone. The findings of this study, however, would suggest that given the strong relationship between neuro- and social cognition, remediation of neurocognitive processes could have a direct effect on improvements in social cognition and functional outcomes. Alternatively it may be

just as effective to target social cognition with interventions directly. There is evidence from controlled studies that social cognition interventions have significant effects on social functioning (Kurtz et al., 2016) and these may be suitable alternatives or boosters for individuals who are unresponsive to neurocognitive remediation strategies, although there is a need for methodologically rigorous studies before this can be recommended (Grant et al., 2017). The evidence is currently stronger for CRT interventions, which are also supported by stronger assessment measures. Given that the mediation model explains more of the variance in outcomes, combinations of neurocognitive and social cognitive interventions may be preferable to optimise social outcomes. Interestingly, these findings suggest that theory of mind in particular should not be a remedial target. Poorer emotion recognition and social perception may be considered as future add-on targets for cognitive remediation interventions, but given the evidence of this study, have smaller associations with functional outcomes than global measures of neurocognition and may themselves be secondary to neurocognitive impairment. Cognitive remediation strategies should focus on neurocognitive gains early in the course of illness, and their subsequent effect on social cognition. However, social functioning is difficult to positively impact in this population and is likely to require a holistic approach including treatment of positive, negative and comorbid symptoms such as anxiety and depression in addition to neuro- and social cognition, which can all impact motivation and quality of life.

7.4.3 Conclusions

Social cognition, comprised of 4 key social cognitive domains, was not shown to mediate the relationship between neurocognition and social and occupational outcomes in this

FEP group. Including social cognition in the model did explain a small amount of additional variance than neurocognition alone, but the study was limited by the large overlap between social cognition and neurocognition, resulting in large shared variance in outcomes. Neurocognition overlaps with performance on social cognition tasks, except for attribution bias. Social cognition was found to be somewhat separable from neurocognition but relying to some extent on lower and higher order neurocognitive processes.

Future studies in larger FEP samples should include additional and more specific measures of functional outcomes and neurocognition variables made up of performance on a wide range of neurocognitive tests. A large amount of variance in outcomes remains unexplained and additional variables such as motivation and symptoms may be candidates as other mediators and moderators of outcomes.

8 General Discussion

8.1 Summary of Work

This thesis investigated the characteristics of neuro- and social cognition in FEP and the relationship these domains have with one another and with outcomes in this population. The empirical studies report on: the existence of IQ derived subtypes and their differential relationships with clinical and social functioning both cross-sectionally and at 1-year follow-up; their potential brain structure and blood-based inflammatory markers; the linear relationship between general and specific indices of neurocognition with global and social function; the characteristics of social cognitive impairment early in the course of illness; and the role of social cognition in mediating the relationship between neurocognition and social function.

This chapter synthesises the findings, reflects on limitations and clinical implications, and provides recommendations for future research on cognition in FEP populations.

8.2 Summary of Main Findings

8.2.1 Cognitive Deficits Are a Core Feature of FEP

In two separate FEP cohorts and in keeping with previous research, the studies in this thesis shows that patients have significant impairments in neurocognition relative to controls. Despite a well-established link between low premorbid IQ and risk for schizophrenia, Study 1 found no difference between patients and healthy controls groups in estimated premorbid IQ, indicating this study may include relatively high-functioning individuals. The significant difference between premorbid and current

global and specific neurocognition provides evidence that there is a decline in neurocognitive ability prior to, or at the time of illness onset. Study 2 showed there is no further deterioration or improvement relative to healthy controls in global cognition over a 12-month follow-up period. This indicates relative stability of neurocognitive function after illness onset and is in agreement with the majority of longitudinal studies in established schizophrenia (Hoff et al., 2005, Szoke et al., 2008), though others have argued the need for follow-up periods of decades to detect further decline (Zanelli et al., 2019, Meier et al., 2014, Fett et al., 2019). Study 4 showed that cognitive impairment in FEP extends to domains of social cognition; specifically, social perception, theory of mind and emotion recognition but not attribution bias.

8.2.2 Indices of Global Neurocognition Obfuscate Specific Cognitive Deficits

In a large FEP group, Study 1 shows that having a preserved IQ relative to healthy controls does not preclude the presence of neurocognitive deficits. Superior performance on preserved cognitive domains may offset poorer performance on impaired or deteriorated cognitive functions, such as processing speed and verbal learning. Caution should be taken when using IQ tests, particularly short-forms, as indices of cognitive performance or proxies of cognitive reserve in schizophrenia. General measures of intelligence may obfuscate the presence of core deficits and fail to capture the full breadth of cognitive impairment (Gray, 2013) which may impact clinical and social function outcomes. Studies using IQ as a measure of neurocognitive functioning in this population should include analysis of individual subtests in order to assess specific domains of cognitive impairment which may impact social functioning. Processing speed and verbal learning may be considered core impairments, present

even in those with IQs within the normal range, and relative impairment or preservation of other neurocognitive domains may reflect later onset or lesser severity of pathological process than those with impairment in all domains.

8.2.3 Neurocognitive Subtypes May Reflect a Linear Continuum Rather Than Distinct Phenomenological Groups

Study 1 used unbiased clustering analysis to identify the presence of three IQ trajectory-based subtypes early in the course of illness, detectable before potential confounding effects on cognition such as long-term antipsychotic use. As consistently found in other studies (Carruthers et al., 2019), the majority of patients, including those with below average estimates of premorbid IQ, showed statistically significant decline from previous cognitive function. These subtypes are useful in demonstrating those likely to have more persistent negative symptoms one-year after illness onset (Study 2) but show minimal discrimination of social and global functioning. Data from the 12-month follow-up demonstrate the relative success of early intervention services at treating positive symptoms but that global and social functioning trajectories remained poor. Cognitive subtypes are valuable guides for those at risk of poor outcomes, but the use of global neurocognition measures may be too broad to identify sharp boundaries reflecting etiologically or biologically distinct subgroups. Global cognition measures are useful determinants of prognosis for some individuals, but still leave a large amount of variance in outcomes unexplained. Clinical and biological differences between subgroups may simply reflect subdivisions of relationships on a linear continuum, rather than independent mechanisms of illness.

8.2.4 A Compromised Subgroup Is Separable on Biological Elements

In addition to showing less tractable negative symptoms at 12-month follow-up, a compromised subgroup of patients with premorbid and current IQ below the average range showed biological measures distinct from those with preserved IQ and, in some cases, from those with premorbid average IQ which subsequently deteriorated. Study 1 found compromised subgroups had smaller intracranial volume than those with preserved IQs and smaller absolute total brain volume than those with preserved or deteriorated but average premorbid IQ. These findings suggest that compromised patients may have early neurodevelopmental deficits (or cerebral hypoplasia) resulting from an early pathological process which causes, or confers greater risk for, schizophrenia. Furthermore, the compromised individuals had higher levels of hsCRP than the preserved group, suggesting early neurodevelopmental deficits may have a relationship with an inflammatory process and more severe negative symptoms over time. The fact that the deteriorating subgroup have mean scores between those of the preserved and compromised groups on measures of brain volume and inflammation suggest that the relationship between cognition and these potential biomarkers is likely to lie along a continuum. It is not wise to consider subgroups as having sharp and distinct biological profiles, but rather points to the manifestation of a linear relationship between neurocognition and global brain volume, and perhaps more surprisingly, a linear relationship between neurocognition and the non-specific marker of inflammation: hsCRP.

8.2.5 Cognitive Reserve Has a Modest Relationship with Social Functioning

Study 3 found that neurocognition at baseline was consistently a significant predictor of employment status cross-sectionally and that verbal fluency was the best predictor of global and social functioning but explained only a modest proportion of the variance in outcomes. Baseline cognition, measured soon after illness onset, was also a significant predictor of social and global functioning at 12-month follow-up, with verbal fluency and premorbid IQ being the most consistent predictors on a range of measures. Baseline processing speed was the best predictor of employment status at 12-months, having implications for targeting this core deficit even in those with apparently preserved cognitive function (as shown in Study 1). The range of correlations across different neurocognitive domains with different social function measures indicates that intact global intelligence may be necessary to maximise social function outcomes. Premorbid IQ was the best predictor of total social functioning scores and was a better predictor of social functioning across several domains than current full-scale IQ. In line with findings of Van Winkel (van Winkel et al., 2007) and in contrast to those of Leeson et al., (2011), this finding supports the cognitive reserve hypothesis that higher premorbid intelligence can help to compensate for illness onset. The model of cognitive reserve is complex in schizophrenia and may be moderated by influences on outcome such as negative symptoms, and metacognition.

8.2.6 Social Cognition Is Impaired as a Function of Neurocognition

Study 4 showed that patients were impaired on domains of social cognition relative to healthy controls, with the exception of attribution bias which may be more closely linked

to symptoms. However, differences between controls and patients no longer existed after controlling for current IQ. Study 5 further supported this view, showing that a latent measure of social cognition comprised of three social cognition domains was strongly related to IQ. These findings suggest that social cognition and measures of IQ share the same underlying cognitive processes, and that that current measures used to capture social cognition rely, at least in part on basic neurocognitive skills. It is also possible that they are unable to trigger the emotional component necessary for distinct measures of social cognition. There was no evidence that social cognition has a stronger relationship with social functioning than neurocognition, and it is therefore not clear that social cognition interventions should be preferred over neurocognitive remediation strategies.

8.2.7 Social Cognition and Neurocognition are Multicollinear in SEM

Study 5 showed that a latent social cognition variable does not mediate the relationship between IQ and social function in a FEP group. Studies in people with established schizophrenia have found individual domains of social cognition mediate the relationship between singular measures of neurocognition and social functioning (see Schmidt for a review) (Schmidt et al., 2011), but this was not found in an UHR group (Barbato et al., 2013) or in the FEP population in this thesis. The lack of mediation in Study 5 is unlikely to be the result of a weaker relationship in FEP than established schizophrenia, and more likely to be due to methodological issues due to the overlap and between IQ and social cognition. Global neurocognition may have a deterministic relationship on global social cognition, which cannot be detected by traditional mediation analysis (Shrout and Bolger, 2002, James et al., 2006). However, given the

close association between neuro- and social cognition and their subsequent relationship with social and occupational outcomes, remediation of either neuro- or social cognition is likely to have comparable benefits on social functioning and a combination of the two approaches may provide the greatest benefit.

8.3 Methodological Considerations

While methodological considerations are discussed in each experimental chapter, there are some broader methodological points which can affect the interpretation of the findings of research in FEP populations and which warrant further mention.

8.3.1 Clinical Trial Participants

The data collected and analysed in this thesis were from FEP participants taking part in large multi-site clinical trials of pharmacological (Studies 1, 2 and 3) or psychological (Studies 4 and 5) interventions. Whilst there is within-group heterogeneity in cognitive, clinical and social functioning in this population, there is the possibility that those willing and able to take part in a clinical trial may not be representative of the true breadth of individuals seen by clinical teams. This is a common limitation of clinical research studies. As a result, those recruited to clinical trials may have fewer clinical symptoms and better social functioning than the general population of those with the illness, particularly given that the desire to take part in a clinical trial can be adversely affected by the presence of symptoms such as suspiciousness, delusions or lack of motivation. The patient groups in all studies had relatively few positive symptoms, though this may reflect the success of EIS teams and pharmacological strategies. This is a broader issue

of clinical research and is not specific to those taking part in the studies included in this thesis.

In addition to this point, those in Study 2 were randomised to a pharmacological treatment or placebo. Whilst the treatment was shown not to be effective and data were adjusted for trial allocation in the analyses, taking part in an interventional study can have positive or negative effects on outcomes. Taking part in clinical trials can often lead to improved outcomes, even for those in placebo groups, but there is also the possibility of nocebo effects (resulting from negative expectations of a treatment) occurring in some individuals. These effects can influence outcomes which can result in clinical trial participants having different outcomes from those in seen in clinical settings.

8.3.2 Cross-sectional Studies

Studies 1, 4 and 5 used cross-sectional data. This is useful to distinguish relationships between variables but does not allow the establishment of causal relationships. It is also difficult to establish the directionality of relationships; for example, those with poorer social functioning could have worse social cognition as a result of having fewer social interactions. Cross-sectional research therefore relies to some degree on a priori determinism. Furthermore, the strength of relationships between variables may result from having had impairments for a longer period of time and therefore requires following-up over many years before relationships strengthen and become more apparent. Some researchers have argued, for example, that cognitive impairments in schizophrenia manifest over a long period, from birth to early adulthood, and therefore it is necessary to follow-up participants for decades after illness onset to establish their

stability (Zanelli et al., 2019, Meier et al., 2014, Fett et al., (Zanelli et al., 2019, Meier et al., 2014). Longitudinal studies are therefore preferable to establish the relationship between cognition and outcome trajectories.

8.3.3 Healthy Control Data

To determine whether cognitive deficits are specific to schizophrenia, it is important to collect healthy control data for comparison. This is particularly true for longitudinal studies, in order to account for practice effects of repeated cognitive testing. Practice effects relate not only to familiarity with the tests themselves, but also to familiarity of task instructions, environment and the researcher. This thesis includes two healthy control groups. The healthy control group used for studies 1 and 2 was collected at the same intervals as the patient group and used the same neurocognitive tests. This allows for useful comparison of performance and any differential change in these variables over time (Pantelis et al., 2009). Healthy control data were not available for the verbal fluency task or the biological variables making it difficult to interpret the relative trajectories of patients and limiting the ability to determine if cognitive subtypes are distinct from those unaffected by the illness on these measures. Furthermore, it is difficult when collecting healthy control data to include representative groups, due to bias in those who are willing to take part in research studies. Both healthy control groups (used in studies 1, 2 and 4) had significantly more females than the patient group, meaning it was important to appropriately control for these variables in the analyses.

8.3.4 First-episode Cohorts

The studies in this thesis include individuals early in the course of schizophrenia spectrum disorders. This has the advantage of being able to capture the fundamental features of the illness before potential confounders such as long-term medication use and social factors. These individuals were recruited from early intervention services after having had a “first-episode” of psychosis. However, since individuals were recruited within the first 5 years of presentation to services, it is possible, and even probable that some patients will have experienced multiple psychotic episodes. Without a reliable and valid measure of duration of untreated psychosis (DUP) it is also possible that some individuals had been unwell for longer periods before presenting to early intervention services. This is a difficulty in psychiatric research, particularly since even measures of DUP rely on accurate self/family report of an individual’s history. Early-intervention services aim to intervene early in the course of illness, but it is a practical issue of research that not all of those included will be considered to be true first-episode patients.

8.3.5 Measures

Studies are limited by the measures they employ, with the need to consider burden on the participant as well as reliability and validity of the measure. The measures used in this study were chosen to account for both, but some limitations are discussed below.

8.3.5.1 Cognition

The potential issues of using global measures to assess cognitive function are addressed above. It would undoubtedly be preferable to have a direct premorbid measure of IQ

assessed before illness onset, but this is not possible without large longitudinal cohort studies. In addition, the WTAR and subtests of the WASI-II rely to some extent on language ability and may handicap those without English as a first language. Though all participants were required to be fluent in English, whether English was the mother tongue of participants was not recorded and this is therefore a limitation of the studies. The Information subtest of the WAIS-III also includes questions which are culturally specific and may disadvantage those who were not educated in the UK. The unidirectional nature of current social cognition measures means they are unable to capture the full range of social processes of an individual and there is therefore need for the development of novel, bi-directional tasks (Gallagher and Varga, 2015, Schilbach, 2016). Furthermore, the AIHQ and the Hinting Task rely on understanding of vignettes and are likely to rely somewhat on language processing ability and may therefore underestimate social cognitive ability in some individuals. In addition, many of the scenarios in the Hinting Task include gender stereotypes and require updating.

8.3.5.2 Social Functioning

Different measures of social functioning exist, including those scored by independent raters and those through self-report. The SFS used in studies 1, 2 and 3 has been shown to be reliable and sensitive to change but was validated in an established schizophrenia, rather than FEP group. Some of the items including independent living are likely to be applicable only to more chronic groups. Furthermore, 30 years after the scale was developed, some of the items require adaptation or updating to be relevant to individuals. Previous studies have found associations between neurocognition and the

SFS in schizophrenia groups (Addington et al., 2010) whereas others have found no associations (Addington and Addington, 1999).

The SOFAS used in studies 4 and 5 was shown to be related to both neurocognition and social cognition but is a relatively crude measure, scored by the researcher. The scoring is on a large scale and accounts for only one point in time, which can leave large variance in patient scores. It may be preferable for studies to use measures of quality of life relevant to patients themselves or those which account for time-spent over a period of time, such as the Time-Use Survey (Cella et al., 2016).

8.3.6 Concomitant Medication

All participants in study 1, 2 and 3 and the vast majority (94%) of patients in Study 4 and 5 were taking antipsychotic medication at the time of recruitment to the study. The type of antipsychotic medication and other concurrent medications were not adjusted for in the analysis due to large amounts of missing data. However, different antipsychotics are unlikely to have differential effects on cognition and the majority of evidence shows no consistent evidence of cognitive impairment associated with antipsychotics (Hill et al., 2010), with many studies finding that antipsychotics have a small beneficial effect on cognitive function (Keefe et al., 2007a).

8.4 Summary of Clinical Implications

Cognitive impairments are a core feature of schizophrenia and those presenting with early psychosis should undergo routine cognitive assessments, including assessment of relative strengths and weaknesses on individual cognitive domains. Cognitive difficulties

contribute to functioning, and early assessment may give an indication of extra support individuals need to achieve functional change. This may be particularly important in FEP individuals, as difficulties may not yet be established and therefore prove more malleable. Those with below average premorbid function should be considered at highest risk of refractory negative symptoms which may lead to more persistent functional impairments over longer time periods and require more intensive support to boost cognitive reserve. Psychological and pharmacological remediation strategies should target processing speed and auditory verbal learning impairments even in those with apparently preserved cognition, with a focus on transfer to real world functioning. Those with deterioration from average premorbid levels of intelligence may be most responsive to cognitive remediation interventions and subsequent improvements in some domains of social functioning.

Given the overlap with neurocognition and similar relationship to social functioning, there is insufficient evidence that targeting social cognition directly would show greater functional benefits than neurocognitive remediation. Theory of mind should not be considered as a primary target due to a lack of a relationship with social functioning, and attribution bias seems to be unimpaired relative to healthy controls. Social perception and emotion recognition deficits may be a risk factor for the development of schizophrenia, with effects on social functioning, but are likely to occur downstream of neurocognitive deficits. Emotion recognition and social perception could be considered as targets for social cognition training interventions, but more evidence as to their effectiveness in improving social outcomes is needed before this can be recommended as an alternative to cognitive remediation therapy. However, social cognition interventions may be suitable for use in combination with neurocognitive remediation

strategies to optimise outcomes, or for those who are unresponsive to neurocognitive remediation. A combination of neurocognitive and social cognitive assessment in high-risk groups may also be a useful way of identifying those at greatest risk of transition to psychosis and of poor social function, and reduce the development of mental health problems in the general population. Neurocognitive remediation strategies should be personalised and focus on neurocognitive gains in impaired functions early in the course of illness, with the aim of achieving subsequent benefits in social functioning. Social cognition interventions require more research, with more rigorous methodology and greater consistency in outcome measures. Routine neuro- and social cognitive assessment should be undertaken in those with psychosis to establish cognitive difficulties which may cause barriers to social and occupational functioning.

8.5 Future Directions

There is an urgent need for large longitudinal prospective cohort studies including comprehensive cognitive batteries consisting of reliable and valid neuro- and social cognition tests and additional measures of biological markers. This will provide information on which individuals experience developmental problems or decline in cognitive function, the affected domains, when they occur, and their temporal biological correlates. This information will provide valuable information about those at risk of poorest outcomes, and the development and application of targeted psychological and pharmacological treatment strategies to maximise functional gains and quality of life for individuals. As these studies are timely and expensive, an alternative way of assessing relative cognitive impairment is to calculate individual discrepancy from expected levels

of cognitive functioning using discordant twin studies. Future studies should include healthy control groups for accurate comparisons with those unaffected by illness. When grouping patients based on disrupted cognitive trajectories, it is important to keep in mind that between-group differences may be the result of relationships which exist along a linear continuum. In other words, groupings may be the result of forcing dimensional aspects into a category, which does not fully represent the complexity of the individual. There is further need for research into the relationship between hsCRP and cognition to establish the role in the pathophysiology of schizophrenia, or whether this is a non-specific marker due to higher levels of stress associated with the illness. There is a need to consistently control for potential confounders of inflammation, including BMI, smoking status and medication. Establishing the relationship between cognition, inflammation and brain function will be better served by the use of functional neuroimaging in preference to cruder measures of brain structure.

Before social cognition can be reliably assessed in this population, there is the need for the development of valid and reliable tests, which are validated through the observance of activation of distinct neural substrates from those of neurocognitive tasks. Ways of measuring social cognition domains which activate “hot” social processes, such as using dynamic and multi-agent tests (e.g. ultimatum game) are important to increase the discriminant validity of social cognition measures and should be considered for future studies. Ideally, social cognition should be measured in a social context and may benefit from the use of experience sampling methods. To better characterise the relationship between affective impairments and social functioning in schizophrenia, batteries assessing social cognition in this population should extend to measure other relevant aspects of affective cognition such as impulsivity and reward/motivation (Bland et al.,

2016). Future studies including such measures should use complex statistical models to account for additional mediating and moderating variables, such as negative symptoms, metacognition and recreational drug use in SEM analysis.

8.6 Final Conclusions

The main findings of this thesis and take-home messages are listed below:

- There is great need to improve outcomes in those affected by FEP.
- There was substantial evidence of the existence of three cognitive subtype trajectories, with measures of global intelligence obscuring the observance of core neurocognitive impairments in high functioning patients.
- Processing speed and auditory verbal learning were impaired even in those with preserved IQs, relative to healthy controls, confirming neurocognitive impairments are a core feature of FEP.
- Those with compromised premorbid IQ showed markers of cerebral hypoplasia and the highest levels of inflammatory marker hsCRP.
- Evidence that deteriorated subtypes showed levels of hsCRP and brain volume intermediate between preserved and compromised groups indicate these measures operate on a linear continuum.
- After illness onset, cognition remains relatively stable over 1-year follow-up.
- Social cognition domains of emotion recognition, theory of mind and social perception are significantly impaired in patients with FEP, but these are likely to be largely downstream of neurocognitive impairments.

- Neuro- and social cognition are significantly, albeit modestly, related to social function and share significant overlap, such that it is not possible to determine that one has a stronger relationship with social outcomes than the other.
- Given the significant overlap it was not possible to establish if social cognition mediates the path between neurocognition and social function. A priori hypotheses about the temporality of the relationship favours that remediation strategies should focus on neurocognitive impairments, with the aim of leading to downstream improvements in social cognition and social function, and therefore quality of life.

9 References

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10 Appendix

Table A.1: Pearson Correlation between hsCRP and Olanzapine equivalent antipsychotic dose

		Olanzapine Equivalent Antipsychotic Dose
hsCRP	Pearson Correlation	.186
	Sig. (2-tailed)	.070
	N	96

hsCRP = high-sensitivity C-Reactive Protein

Table A.2: Average cognitive performance of entire patient group at baseline and 12-month follow-up

Variable	Baseline Mean (SD)	Follow-up Mean (SD)
FSIQ ^a	90.07 (13.89)	92.86 (14.24)
Digit Symbol ^a	6.10 (2.26)	6.49 (2.44)
Block Design ^a	9.45 (2.94)	9.89 (3.50)
Information ^a	10.14 (3.22)	10.67 (3.06)
Arithmetic ^a	8.37 (3.12)	8.68 (2.98)
AVLT Immediate ^a	5.06 (1.90)	5.55 (1.84)
AVLT Total ^a	38.26 (10.92)	42.15 (12.66)
Verbal Fluency	83.86 (24.48)	85.29 (21.83)

FSIQ = full-scale IQ, AVLT = Auditory Verbal Learning Test

Table A.3: Means and standard deviations of cognitive performance for healthy control and patient subtypes for those remaining in the study at 12-month follow-up

	HC (n=52) Mean (SD)	PIQ (n=35) Mean (SD)	DIQ (n=37) Mean (SD)	CIQ (n=16) Mean (SD)
Premorbid IQ	101.92 (8.32)	106.81 (6.73)	101.94 (7.14)	83.05 (8.77)
12m FSIQ	101.05 (11.83)	103.85 (10.91)	89.51 (9.55)	76.56 (9.69)
12m Digit Symbol	106.05 (13.03)	7.44 (2.69)	6.25 (2.13)	4.93 (1.52)
12m Block Design	11.23 (2.70)	12.00 (3.24)	9.13 (2.97)	6.93 (2.26)
12m Information	12.34 (2.42)	12.32 (2.36)	10.61 (2.83)	7.23 (1.88)
12m Arithmetic	10.23 (2.72)	10.64 (2.41)	7.89 (2.42)	6.23 (2.72)
12m AVLT Immediate	5.96 (1.58)	5.94 (2.01)	5.67 (1.63)	4.47 (1.58)
12m AVLT Total	47.82 (9.40)	46.72 (11.15)	41.43 (11.74)	33.76 (13.70)
12m Verbal Fluency	*	92.91 (20.78)	86.73 (17.38)	64.25 (21.38)

HC = Healthy controls; PIQ = preserved IQ; DIQ = deteriorated IQ; CIQ = compromised IQ. * data not available.

Table A.4: Means and standard deviations of clinical symptoms of cognitive clusters at 12-month follow-up

	PIQ (n=35) Mean (SD)		DIQ (n=37) Mean (SD)		CIQ (n=15) Mean (SD)	
	Baseline	Follow-Up	Baseline	Follow-Up	Baseline	Follow-Up
Positive Symptoms	16.66 (5.14)	13.16 (5.46)	17.18 (4.77)	14.66 (5.31)	16.13 (6.08)	13.63 (5.46)
Negative Symptoms	17.37 (4.78)	14.18 (5.52)	18.21 (6.49)	15.66 (5.60)	20.94 (7.79)	19.50 (6.70)
General Symptoms	33.92 (7.74)	28.82 (9.40)	34.61 (9.42)	31.00 (9.90)	34.19 (8.21)	30.44 (7.33)
Total Symptoms	67.95 (14.69)	56.16 (17.96)	70.00 (17.59)	61.32 (18.13)	17.08 (4.27)	63.56 (13.77)
Calgary Depression	5.92 (4.89)	3.42 (4.31)	5.26 (4.42)	3.36 (3.90)	3.18 (4.67)	2.31 (3.80)

PIQ = preserved IQ; DIQ = deteriorated IQ; CIQ = compromised IQ. * data were not available