The Effects of Antipsychotics on Social Cognition

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A thesis submitted for the degree of Doctor of Philosophy.

I, Zoë Joanne Haime, 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.

Signed: Zoë Haime

Date: 28/02/2023

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Abstract

Despite the perceived importance of social cognition in determining social functioning outcomes for patients with schizophrenia, it has received limited attention in clinical trials. Furthermore, the impact of antipsychotic medication (which is the primary treatment for schizophrenia) on social cognition has not been thoroughly investigated, and existing studies lack consistent results.

A systematic review and research study were conducted to investigate the effects of antipsychotics on social cognition in patients with schizophrenia. The study recruited 73 patients with schizophrenia and 37 healthy volunteers, to take part in a social cognition assessment, as part of a sub-study of a larger-scale randomised controlled trial of antipsychotic reduction/discontinuation vs. maintenance.

Narrative results from the systematic review of sedative psychiatric medication effects on social cognition revealed diazepam impairs emotion processing in healthy volunteers. It also showed the extent to which studies of antipsychotics on social cognition have been limited by design. For the analysis in this thesis, cross-sectional results showed impaired social cognition in patients compared to healthy volunteers. Although, antipsychotic dose was not significantly related to any social cognition domain after controlling for confounders. The longitudinal results showed temporary dips in some social cognition domains and social functioning performance at 12-months after being in the antipsychotic reduction/discontinuation group, but improvements at 24 months, although the group x time interaction was only significant for the Theory of Mind domain.

Results from these studies should be interpreted with caution due to limitations including unequal group sizes, high attrition, and poor measure reliability. However, the results suggest that relationships between social cognition and antipsychotic reduction may exist, although the associations are complex and require more investigation. Further studies with larger sample sizes over long-term periods are needed, particularly in healthy volunteers, to establish relationships between variables.

Impact Statement

In order to improve social functioning and quality of life for patients with schizophrenia-spectrum disorders, greater understanding and awareness of social cognitive impairment is needed. More effective treatment options that target social cognition deficits may improve individual outcomes, whilst also reducing costs to society and family/caregiver burden.

This thesis made progress in comprehending the relationships between social cognition domains and the use of antipsychotic medication as a treatment method. The results from this thesis identify impaired social cognition in patients with schizophrenia compared to healthy volunteers. This highlights the importance of addressing social cognitive dysfunction as a target for interventions in the development and course of schizophrenia. Additionally, studies highlighted potential relationships between antipsychotic dose, age, ethnicity, symptomology, and social cognition performance. Further research into understanding these relationships may potentially affect patient functioning outcomes, and therefore inform future treatment strategies. Additionally, this thesis has been able to emphasise several methodological factors that may improve the validity of research in this field and shows the need for accurate, dependable, and consistent social cognitive testing in this population. It also identifies the need for creation of novel or improved assessment tools.

The studies presented in this thesis underwent ethical review and were able to recruit a diverse range of participants through an NIHR-funded RCT (Research into Antipsychotic Discontinuation and Reduction – RADAR). This not only ensured a representative sample of patients across the UK, but also allowed for valuable public and patient input, involving a panel of lived experience service users and carers. This has hopefully resulted in a research design that incorporates patient perspectives which may have otherwise been missed, leading to more inclusive outcomes.

Results of this thesis have been disseminated to clinicians, academics, and service users through conference presentations and posters, and for the systematic review, via peer-reviewed scientific publication. This review publication has received citations, indicating it as a valuable source for current and future work in this area. Additionally, this thesis study and results have been discussed with school children through public engagement online, and the author ZH won an award for this work. Disseminating the results of this thesis is important, increasing visibility and accessibility of the findings and allowing others to consider future research needed in this area. Therefore, there will also be an aim to publish the cross-sectional and longitudinal analysis in thesis, in peer-reviewed journals.

Contents

Glossary

WHO	World Health Organisation
APA	American Psychological Association
ICD	International Classification of Diseases
DSM V	Diagnostic and Statistical Manual of Mental Disorders – 5th Edition
NHS	National Health System
RADAR	Research into Antipsychotic Discontinuation and Reduction
RCT	Randomised Controlled Trial
NIHR	National Institute for Health Research
CMHT	Community Mental Health Teams
NELFT	North East London NHS Foundation Trust
ELFT	East London NHS Foundation Trust
BEH	Barnet Enfield and Haringey Mental Health NHS Trust
C&I	Camden and Islington NHS Foundation Trust
CNWL	Central and North West London NHS Foundation Trust
SPFT	Sussex Partnership NHS Foundation Trust
GHC	Gloucestershire Health and Care NHS Trust
OHFT	Oxford University Hospitals NHS Foundation Trust
KMPT	Kent & Medway Social Care Partnership Trust
CPMS NHS	Central Portfolio Management System NHS
LEAP	Lived-Experience Advisory Panel
SD	Standard Deviation
AP	Antipsychotic
PANSS	Positive and Negative Symptom Scores
SFS	Social Functioning Scale

Chapter 1: Introduction & Background

1.1 Introduction

This chapter provides an outline of the current knowledge and understanding of social cognition in people with a schizophrenia-spectrum disorder. Additionally, the chapter will conclude by providing an outline of the studies that have been conducted as part of this thesis and how these relate to current evidence, including rationale, aims, and a background to the thesis development.

1.2 What is Schizophrenia?

In present day, schizophrenia (F20 – ICD 10, or 6A20 – ICD 11) is widely considered the most debilitating mental illness due to its resulting personal and societal costs, as well as early mortality rates (Fasseeh et al., 2018). Schizophrenia has been classified most recently in the ICD 11 as a psychotic disorder comprising of the following symptom domains: delusions, hallucinations, disorganised thinking, disorganised or abnormal motor behaviour, or negative symptoms. Symptoms must occur with sufficient frequency and intensity that the persons experiences deviate from societal or cultural norms (WHO, 2019). Descriptions of the symptom domains can be seen in **Table 1**.

Table 1.
Domains and Descriptions of Symptoms in Schizophrenia according to the ICD-11 and DSM-5 (WHO, 2019; APA, 2013).

Symptom Domain	Description	Case Study Example
Delusions	Delusions are fixed beliefs that are held with conviction by the person experiencing them, despite conflicting evidence from third parties (APA, 2013).	"*I started to believe people were talking about me wherever I went, as if they were plotting something against me. I believed the televisions in my house had secret cameras to spy on me and my family, as well as television hosts sending me hidden messages to stop taking drugs and start playing sport again. I had the firm belief police were after me due to my illicit drug use and that they had a warrant for my arrest."* (Hanley, 2016).
Hallucinations	Hallucinations are the experience of a sensory event in the absence of a real external stimulus being present (APA, 2013).	*"One moment, the voice in my head said to me 'go and sit up'. I sat up, I sat up and saw my reflection. And then the same voice said, 'go and look again'. And I didn't see a reflection anymore, but I saw blood flowing everywhere."* (Moernaut et al., 2018)

Disorganised Thinking	Disorganised thinking includes linguistic deficits such as, thought block (where a person suddenly stops speaking in the middle of a sentence), word salad (when a person uses seemingly random words or phrases during speech), tangentiality (speaking about loosely associated subjects unrelated to the main topic of conversation), pressured speech (accelerated speaking), poverty of speech (a lack of spontaneity of conversation), and creating neologisms (creating new words or expressions) (Andreasen, 1979; APA, 2013).	Neologisms or non-words: "I got so angry I picked up a dish and threw it at the *geshinker*" or "So I sort of *bawked* the whole thing up." (Andreasen, 1979)
Disorganised or Abnormal Motor Behaviour	Disorganised or abnormal motor behaviour can include motor skill deficits, including abnormal involuntary movements, impaired coordination, slowed fine motor execution, rigidity, and catatonia (Abboud et al., 2017).	'Ms. A is asking for coffee at the breakfast table. The nurse gives her a cup. Ms. A takes the cup and starts to move it around on the table. She then leaves the cup, looks out of the window, and reaches out for a knife, reaching it to the nurse and starts to serve herself jam with the fingers.' (Bakken et al., 2009)
Negative Symptoms	Negative symptoms include inattentiveness, low mood, anxiety, difficulty in abstract thinking, blunted affect, loss of interest in enjoyable activities, poverty of speech, asociality, and lack of motivation (Kay et al., 1987; Andreason, 1984; Overall & Gorham, 1962; Blanchard & Cohen, 2006)	'He seems to have excessive internalization of feeling that he would prefer to externalize, leading to anxiety.' (Yadav, 2017)

1.2.1 What is a Schizophrenia-Spectrum Diagnoses?

The chapter in the ICD 11 that includes schizophrenia is titled 'Schizophrenia or other primary Psychotic Disorders'. The other diagnoses included are therefore considered a schizophrenia-spectrum disorder, and are listed in **Table 2**, with their characteristic features. Many studies including patients with schizophrenia will implicitly include participants with a combination of these diagnoses. The 'Research into Antipsychotic Discontinuation and Reduction' (RADAR) study (introduced in Chapter 1, Section 1.10) also included participants with a range of schizophrenia-spectrum diagnoses (F20-F29 in ICD10; WHO, 1993). Therefore, throughout this thesis, the term 'patient/s with schizophrenia' will be used interchangeably for 'patients with a schizophrenia-spectrum disorder', where this is not necessarily stated. The eligibility criteria for the participants recruited into studies in this thesis will be specifically discussed in Chapter 3, section 3.3.4.2.

Table 2.
Diagnosis and Characteristic Features in the ICD 11 Chapter Titled 'Schizophrenia or other primary Psychotic Disorders'.

Diagnosis	**Features**
Delusional Disorder	One or more delusions with no other psychotic symptoms.
Schizotypal Disorder	Characterised by 'abnormal' behaviour and deficits in cognition and affect, however no definite symptoms of schizophrenia exist.

Schizoaffective Disorder	Psychotic symptoms last at least 2 weeks in the absence of mood symptoms, symptoms during most of the illness duration meet criteria for a mood episode.
Acute and Transient Psychotic Disorders	Acute onset of psychotic symptoms such as delusions or hallucinations, with a complete recovery usually within a few months, weeks, or days.
Substance/Medication Induced Psychotic Disorder	Psychotic symptoms resulting from consumption of a substance or medication.
Other/Unspecified Nonorganic Schizophrenia Spectrum and Other Psychotic Disorder	Other psychotic disorder not meeting criteria for another disorder or psychotic symptoms due to unknown or undetermined causes.

1.2.2 Why is Cognition Important in Schizophrenia? – Symptom or Side Effect

Cognitive deficits have also been considered an identifying factor of patients with schizophrenia and are now considered a core domain symptom of the disorder in the ICD 11 (WHO, 2019). Neurocognitive deficits include problems with general intelligence, memory, verbal fluency, attention, and/or executive functioning (Bowie & Harvey, 2006). Evidence has shown that impairments in cognition can exist in children and adolescents who develop schizophrenia (Mesholam-Gately et al., 2009), and at first episode of psychosis stage (Bilder et al., 2000; Woodberry et al., 2010). While some studies show that this cognitive decline stabilises after illness onset (Heaton et al., 2001; Lewandowski et al., 2011), others show improvements in cognition, thought to be related to psychotic symptom alleviation (Bozikas & Andreou, 2011). Few studies have managed to investigate neurocognitive change over the life-course of schizophrenia, however population-based studies have shown IQ-based declines from childhood to adulthood in those later diagnosed with schizophrenia (Kremen et al., 2010). A recent study by Zanelli et al (2019) also showed a decline in IQ, verbal knowledge, and memory of patients with schizophrenia after illness onset, with a stabilisation of processing speed and executive functioning.

In developing antipsychotic medications, pharmaceutical companies began to identify the potential of treating neurocognitive deficits. As a result of this the industry used cognitive enhancement as a supposed benefit of taking second generation, compared to first generation antipsychotics (Hill et al., 2010; Kane et al., 1988). However, pharmaceutical companies failed to backup these claims with evidence, and the so-called cognitive benefits were dropped from future marketing (Keefe et al., 2007). Although few longitudinal studies exist that investigate the effects of antipsychotic medication on neurocognition whilst accounting for symptom reduction (Bozikas & Andreou, 2011) some RCT designs, and antipsychotic reduction research allow us to explore the evidence. Meta-analysis has revealed several studies show improvements to cognition when taking antipsychotics (Baldez et al., 2021), some show mixed effects of first-generation compared to second-generation antipsychotics (Veselinovic et al., 2019), and some studies show that cognitive functioning may be impaired by antipsychotic medication (Harrow et al., 2012; Husa et al., 2017; Takeuchi et al., 2013). Specifically, the study by Takeuchi et al (2013) identified improvements in patients' neurocognition scores following discontinuation of antipsychotics, signifying neurocognition may be a viable treatment target. With contrasting evidence, it is important to note research into neurocognition in patients with schizophrenia often suffers from common study design flaws, including a lack of consensus between which neurocognition measures are used across studies, short follow-up periods inducing practice effects, reliance on old measures, and a lack of

specificity in neurocognition measures (e.g., the trail making test is sensitive to multiple cognitive domains including attention, visual searching, and motor coordination (Salthouse, 2011)).

In the DSM-V, there are recommendations that clinicians conduct clinical neuropsychological assessment of patients to guide diagnosis and treatment, although it is unclear how this should affect treatment decisions. The manual suggests neuropsychological testing of different cognitive domains should be administered and scored by trained personnel, but if unavailable, clinicians should 'use the best available information to make a judgment' (APA, 2013). Similarly, the ICD 11 recommends using validated, standardised neurological assessments of cognitive domains 'when available', but, where measures are unavailable, to use best judgment on a severity rating scale (WHO, 2019). The DSM-V and the ICD 11 recommend the use the WHODAS 2.0 as a general measure of mental functioning, which includes six neurocognition-related questions.

1.3 Social Cognition in Schizophrenia

1.3.1 A Brief History of Social Cognition

Social cognition describes the process of understanding and interpreting one's own, and others' actions, beliefs, emotions, and thoughts (Wyer & Carlston, 2018). Various constructs have been identified within social cognition that represent a range of abilities that allow people to perceive and interpret social situations and stimuli. In the theoretical model of social skills first proposed by Wallace et al (1980) the 'three-process' model postulated the three steps of social interaction: (1) receiving social information (e.g., perception of social cues), (2) processing social information (e.g., interpreting and selecting a response to social cues), and (3) responding to social information (e.g., using verbal and non-verbal responses to react and interact). The sequential pattern of this model suggests that social cognition is necessary for the first two steps, with social skills determining the third step outcome. Therefore, social cognition and social skills together, contribute to a person's overall social functioning, or the ability to carry out every day social responsibilities and tasks (Yager & Ehmann, 2006).

Social cognition research first came to prominence by social psychologists in the 1960s, with scientists beginning to explore familiar concepts of schemas and heuristics within social decision-making (Newman, 2001). Developmental psychologists, in their studies of child perspective-taking, began to develop and use false-belief tasks to identify whether children were able to understand others' beliefs (Flavell et al., 2002). Research found that this social cognitive ability - 'Theory of Mind' (ToM) - usually developed around the age of 4-5 years (Wellman et al., 2001). Identifying life-course markers of social cognition resulted in neurodevelopmental scientists detecting that pronounced social cognition deficits in children were often associated with autism, and that these deficits were usually maintained in adulthood (Baron-Cohen, 1995). As cognitive psychologists became more prominent over time, interest began to rise in neuro – and social- cognitive performance deficits apparent in other psychological disorders, such as in people with disordered eating, neurodevelopmental disorders, post-traumatic stress disorder, and mood disorders (Billeke & Aboitiz, 2013; Hortnagl et al., 2014; Nazarov et al., 2014).

Despite this rise in prominence of cognitive research in psychological disorders during more recent times, late 1950s research around 'Expressed Emotion' (EE) may mean the study of social cognition in schizophrenia was being conducted considerably earlier, by a different name (Amaresha & Venkatasubramanian, 2012). Brown (1959) attempted to investigate why symptomatically stable patients with schizophrenia on chlorpromazine discharged from psychiatric hospitals, experienced relapses. The study identified that the type of home that male patients were discharged to was the most significant predictor of relapse, notably they were more likely to relapse if they went home to their parents or wives, over living alone or with their siblings. Brown recognised the need to measure these relationships and did so through assessing the emotions portrayed between families/caregivers and patients in audio recordings. This work resulted in the conceptualisation of EE, which included measurement of patients' and family/caregivers' relationships through counts of critical comments, hostility, emotional overinvolvement, positive remarks, and warmth. Findings from this research showed that higher EE in families led to increased rates of relapse in patients with schizophrenia. It was postulated that one reason for higher EE in families/caregivers was as a response to patients' inability to interpret verbal and non-verbal social cues. This research began to emphasise the importance of social processing on outcomes of patients with schizophrenia, whilst also considering interpretation of emotions as an important factor in the pathway of the disorder. This signified the beginnings of a social cognitive perspective of schizophrenia. However, it is important to note that the current concept of social cognition extends beyond this interpretation and encompasses a broader range of domains, which reflect the complex processes involved in understanding social interactions and stimuli.

1.3.2 Critical Assessment of the Concept of Social Cognition

The emergence of social cognition as a distinct domain of study, separate from neurocognition, marked a significant advancement in understanding social processes in various populations; however, it became evident that notable overlaps between these domains exist, challenging the clear demarcation between them. Social cognition may be influenced by neurocognition processes such as perception, attention, memory, executive functioning, and language. Difficulties with these domains may hinder ones' understanding of social cues, limit their social communication, and prevent attention to relevant stimuli in interpreting their own or other emotions or actions.

However, research in the field of developmental psychology has provided evidence supporting the existence of social cognition as a separable domain to neurocognition. In particular, studies examining ToM have focused on comparing the performance of individuals with autism who often exhibit deficits in ToM alongside relatively high IQ, with individuals diagnosed with Down Syndrome who typically have lower IQ but intact ToM abilities. These studies have found that despite individuals with Down Syndrome having lower overall neurocognitive abilities, their ToM skills remain relatively intact. In contrast, individuals with autism, despite often having higher IQs, demonstrate notable impairments in ToM (Shojaeian, 2021; Yirmiya et al., 1996). This contrast provides support for the notion that ToM represents a distinct cognitive domain that operates independently of general cognitive abilities and has been supported by factor analysis studies identifying

social cognition domains as separate from neurocognition (van Hooren et al., 2008; Fett et al., 2011).

1.3.3 Social Cognition Domains and Schizophrenia

From the 1960s, research into social cognition and schizophrenia grew, with measures typically implemented to evaluate performance of patients with autism. As a range of literature in the field was available in the early-2000s, four domains considered central in identifying social cognition deficits in schizophrenia emerged (Green et al., 2008). These included emotion processing, social perception/knowledge, attribution bias, and theory of mind (Pinkham et al., 2014). Additionally, higher order concepts, including empathy and emotional intelligence, were recognised as identifiers of social cognition deficits in patients with schizophrenia (Arioli et al., 2018). Definitions of each of these domains can be viewed in **Table 3**.

Table 3.
The Definitions of Social Cognitive Domains Commonly Impaired in Patients with Schizophrenia.

Social Cognition Domain	Definition
Emotion Processing	The process of recognising and interpreting others' emotions from visual/audio cues. (Hamann & Canli, 2004)
Social Perception/Knowledge	The process of making inferences about social situations based on cues and context. (Bellack et al., 1996)
Attribution Bias	The process of assigning cause to a (positive or negative) social event. (Law & Falkenbach, 2018)
Theory of Mind (ToM)	The process of understanding others' thoughts, beliefs and action intentions. (Frith,1995)
Social/Emotional Empathy	The process of sharing and responding to others' emotional states. (Melloni et al., 2014)
Cognitive Empathy	The process of accurately understanding how someone else is feeling and thinking. (Smith, 2006)
Emotional Intelligence	The process of understanding our own and others' emotions accurately and adaptively. (Kee et al., 2009)

Social cognition domain definitions represent distinct aspects that contribute to our understanding of others' mental and emotional states (Montag et al., 2011). However, this categorisation may ignore overlaps that are present across social cognition domains. For instance, ToM involves interpreting others' beliefs and attributing mental states to them (Singer et al., 2009), and cognitive empathy emphasises the reflective process of understanding others' emotional experiences (Bernhardt & Singer, 2012). Although these definitions differ, cognitive empathy has been identified as mediating the relationship between affective ToM and social functioning (Canty et al., 2021), indicating that affective ToM may be a prerequisite of cognitive empathy. Additionally, separate studies have identified a significant positive relationship between cognitive empathy and emotion recognition of surprise and disgust in adolescents (Moret-Tatay et al., 2022), and a significant positive correlation between cognitive empathy and facial emotion recognition (Lui et al.,

2015). Therefore, the categorisation of empathy as a separate social cognition domain remains unclear, with evidence showing connections with both ToM and emotion processing domains. Additionally, although some view cognitive and affective empathy as separate components (Blair, 2005), others argue that in most cases cognitive and affective empathy co-occur and cannot be disentangled (Baron-Cohen & Wheelwright, 2004), with categorisation in studies often varying dependent on the theoretical framework employed (Preston & de Waal, 2002).

This identification of overlapping domains poses challenges when interpreting specific deficits within social cognition. Despite research evidencing domain-specificity in social cognition through factor analysis (Mancuso et al., 2011), few existing studies have included domains of empathy or emotional intelligence, and therefore their placement is still unsubstantiated. Within this sub-study, the concepts of empathy and emotional intelligence have been included as separate domains, as they were measured individually. To address these challenges in future research, studies should aim to examine where these concepts fit within existing social cognition domains, or if they represent a separate domain altogether, through factor analysis.

1.3.4 Social Cognition and Mental Health – Current Perspective

More broadly, when considering social cognition and mental health, social cognitive scientists have identified two main areas of focus in current mental health research. Firstly, the relationship between social cognition deficits and mental health symptoms, and secondly, the role of social cognition in attributing to other functional outcomes.
An integral review showed the transdiagnostic prevalence of significant social cognition deficits across developmental, neurological, and psychiatric disorders (Cotter et al., 2018). The authors suggested that social cognitive deficits in patients should be considered as clinically meaningful and a target for therapeutic intervention in much the same way neurocognitive deficits are approached. Unfortunately, similarly to many pieces of research in this field, the review was only able to focus on two domains of social cognition (ToM and emotion recognition) due to the lack of research available in additional domains. Further evidence for the prevalence of social cognition deficits in psychiatric illnesses comes from research by Santamaria-Garcia et al (2020). Their study used structural equational modelling to determine the relationships between social cognition, physical determinants of health, and mental health symptoms. When comparing their findings to the relationships between mental health symptoms and classical psycho-physical predictors (demographic, physical, and cognitive factors) they found that emotion recognition skills alongside social adverse factors and cognitive functioning were the best predictors of mental health symptoms, with social cognition emotion recognition skills showing higher predictive values of symptoms than any of the classical psycho-physical factors.

1.4 Schizophrenia, Social Cognition, and Social Functioning

Impairments have been found in social cognition domains amongst chronic, remitted, and first episode/recent-onset patients with schizophrenia (Achim et al., 2012; Edwards et al., 2002), which may suggest stable deficits in social cognition over the

course of the disorder. However, this evidence has largely been attributed to studies on emotional processing and ToM (Green et al., 2019), with far fewer studies conducted in the other domains of social cognition. Many studies of this nature have also failed to account for methodological issues already prominent in the neurocognition and mental health research, such that social cognition studies in schizophrenia often use old measures developed for other populations, do not account for practice effects, and lack a consensus in measures to be used for each domain (Green et al., 2008).

1.4.1 What Is Social Functioning?

Broadly, social functioning has been described as an ability to function in different societal roles such as homemaker, student, worker, family member, or friend. This definition may rely on an individuals' own satisfaction in their role, and the extent of their leisure and recreational activities (Priebe, 2007), or it may be defined more objectively through enquiry into or observation of someone's level of activity (Bjornestad et al., 2019; Long et al., 2022). In early depictions of schizophrenia, diagnostic descriptions by Kraepelin (1919) and Bleuler (1950) identified deficits in social functioning as part of the condition, including difficulties with independent living, interpersonal relationships, and occupational function (Hooley, 2010; Jablensky, 2010). Early beliefs suggested that improvement of positive symptoms in schizophrenia would lead to improvement in social functioning, however evidence now shows that negative symptoms are more likely to predict social functioning, with higher negative symptom scores resulting in lower social functioning scores (Juckel & Morosini, 2008; Kaneko, 2018; Robertson et al., 2014). It is important to consider however, that negative symptom measures encompass factors such as social withdrawal, poor rapport, and lack of flow of conversation, which may overlap with factors on social functioning measures, meaning that interpreting correlations can be problematic as some items are ultimately measuring the same thing. Long-term social functioning deficits continue to be significant in schizophrenia resulting in financial, health, and social burdens, not only for patients, but also for families, friends, caregivers, and the wider society (Knapp et al., 2004). Therefore, modern treatment strategies frequently consider targeting social functioning deficits as one of the most important parts of clinical recovery in patients with schizophrenia (Juckel & Morosini, 2008).

1.4.2 How Does Social Cognition Relate to Social Functioning in Patients with Schizophrenia?

Relationships have been identified in patients with schizophrenia between social functioning and neurocognition, as well as between social functioning and social cognition, with evidence for at least as large if not larger effect sizes in the latter relationship (Couture et al., 2006; Hoe et al., 2012; Schmidt et al., 2011). This was further demonstrated in a meta-analysis by Fett et al (2011) where researchers found that social cognition accounted for 16% of variance in community functioning, compared to 6% variance for neurocognition, suggesting that social cognition may be a more valuable treatment target over neurocognition when aiming to improve social functioning outcomes. Fett et al (2011) also found that ToM had stronger associations with community functioning than other social cognitive and neurocognitive domains, indicating that ToM may be more closely related to social

performance in real-world situations. However, there were also some limitations associated with this research. Firstly, only one research study was identified that investigated the association between attribution bias and social functioning (Lysaker et al., 2004), therefore the domain could not be included in the meta-analysis. Additionally, the authors noted that due to under-reporting of important potential moderating variables including symptom history, pharmacological treatment, and diagnostic comorbidity, their impact on the relationship between social cognitive domains and social functioning could not be established.

In addition to this meta-analysis, research was published by Schmidt et al (2011) investigating relationships between social functioning, social cognition, and neurocognition in patients with schizophrenia. The authors undertook both a systematic review of the current literature and a structural equation modelling (SEM) analysis on a sample of 148 patients with a schizophrenia diagnosis. They found that 14 out of 15 studies in their review supported the hypothesis that social cognition plays a mediating role between neurocognition and social functioning. This finding was also supported by their own SEM analysis, implying that a deficit in neurocognition may have an adverse effect on social cognition, which then impairs social functioning ability. However, again, the studies in this review included only the domains of social perception/knowledge and emotion processing, and the authors replicated this in their own study. Further, in their analysis they combined the domains of social perception/knowledge and emotion processing to provide one overall social cognition score. This means, in failing to investigate the distinct multidimensional constructs of social cognition, they were unable to identify the separate mediating pathways each domain may have within the relationship between neurocognition and social functioning. A more recent update to this review by Halverson et al (2019) found similar results, with social cognition accounting for more variance in social functioning then neurocognition, and evidence that social cognition mediated the relationship between neurocognition and social functioning. However, the review noted similar limitations, with an emphasis on the need to measure all independent social cognition domains ‘in a way that is accurate, reliable, and standardized’.

1.5 Social Cognition Associations with Particular Schizophrenia Symptoms

Particular symptoms associated with schizophrenia have also been linked directly to social cognition deficits. Research into these relationships have largely identified significant associations between paranoia and persecutory delusions, or negative and disorganised symptoms and the social cognitive domains. Below, a selection of the available research between social cognition and symptoms of schizophrenia is summarised.

1.5.1 Paranoia, Persecutory Delusions, and Social Cognition

1.5.1.1 Attribution Bias

In attribution bias, generally people assign causation of positive events to themselves (internalising bias), and of negative events to external situations (externalising bias) or other people (personalising bias). Research has shown that patients with schizophrenia have an excessively high self-serving bias (attributing positive events or successes to themselves) in comparison to healthy volunteers; as well as a greater likelihood of a personalising bias (Kinderman & Bentall, 1997; Martin & Penn, 2002; Randall et al., 2003). Bentall et al (2001) explained that this heightened personalising bias in patients with schizophrenia may lead to a belief that others are deliberately seeking to harm them or that they hold negative views about them, and this may then result in symptoms of schizophrenia including persecutory delusions or paranoia.

Studies into participants with paranoid vs. non-paranoid symptoms have shown mixed results with some clinical and non-clinical (paranoia studies on the general population) research demonstrating that those with greater levels of paranoia show a higher likelihood of personalising bias (Kinderman & Bentall, 1997; McKay et al., 2005), and some studies showing no significant difference between paranoid and non-paranoid participants (Kaney & Bentall, 1989; Martin & Penn, 2002). Further exploration by Janssen et al (2006) of symptoms related to attribution bias found a significant association between heightened externalising bias and the presence of persecutory delusions in patients with a non-affective psychosis. Additionally, this study found two groups at high-risk of psychosis did not show significantly high externalising bias, suggesting that attributional bias impairments are likely not a trait indicator of a vulnerability to psychosis, but instead may be more closely linked to the presence of 25ositivt psychotic symptoms. Similarly, Valaparla et al (2017) found a significantly higher externalising and personalising bias in patients with schizophrenia at an acute stage of illness compared to healthy volunteers. At a follow-up of 3 months, when patients had significantly lower levels of psychotic symptoms, the significant differences between patient and healthy volunteers scores on externalising and personalising bias no longer existed. This study did though fail to account for the effects of antipsychotic medication as well as other potential confounding variables on patients' attributional bias scores, and the short time between assessments may have caused practice effects.

1.5.1.2 Emotion Processing

In emotion processing, an early study by Lewis and Garver (1995) demonstrated a significant difference in the ability of paranoid vs. non-paranoid patients with schizophrenia, with the former performing better at a facial expression recognition task. Authors suggested impairments in non-paranoid patients with schizophrenia may be related to generally poorer neurocognition performance in the group, especially in short-term memory/recall. The authors also theorised that patients' experiencing symptoms of paranoia may be hypervigilant, and this could result in better emotion recognition ability. Similar studies have supported this theory, showing that patients with schizophrenia living with paranoid symptoms are more accurate at recognising emotions than those with non-paranoid symptoms (Huang et

al., 2013), and sometimes they even outperform healthy volunteer controls (Combs et al., 2006). Delusion-prone individuals have also specifically been shown to outperform others on recognition of angry faces (Arguedas et al., 2006), and to have a greater likelihood of 26ositive26ing anger to neutral faces. This finding supports the theory that individuals experiencing delusions having a higher significance of personal threat, which may lead to symptoms of paranoia.

1.5.1.3 Theory of Mind

In healthy individuals, an intact ToM allows people to represent and contextualise others' mental states, to understand their beliefs and intentions. A study by Harrington et al (2005) found that when testing paranoid and non-paranoid patients with schizophrenia, and healthy volunteers, only patients with paranoid schizophrenia experiencing persecutory delusions showed deficits in ToM. This relationship between paranoid symptoms and ToM deficits has also been supported by other studies including Drury et al (1998) and Corcoran et al (2008). This research has resulted in the 'Hyper ToM' hypothesis, where researchers hypothesise that patients with persecutory delusions or paranoia 'over-generate' thoughts about what others believe or think, not having a conceptual deficit with ToM but applying it in a biased way (Dorn et al., 2021). However, other researchers have found no difference between paranoid and nonparanoid groups in ToM performance (Langdon et al., 2006; Randall et al., 2003), and therefore the relationship remains unclear.

1.5.1.4 Social Perception

There is less support for a relationship between social perception and paranoia/persecutory delusions as other social cognitive domains. In a study by Seidman (1983), researchers found that patients with paranoid schizophrenia diagnoses performed significantly better on the social perception task than those with non-paranoid schizophrenia. The authors of the paper speculated that this result may be due to patients with paranoid schizophrenia being generally less cognitively impaired than patients with non-paranoid schizophrenia (Seidman, 1983). However, this difference in cognitive skill has been contested in a review by Zalewski et al (1998) showing no significant differences in neurocognition in paranoid vs. non-paranoid patients with schizophrenia groups, and no further recent studies have investigated the relationship between paranoid symptoms and social perception.

1.5.2. Negative and Disorganised Symptoms and Social Cognition

1.5.2.1 Attribution Bias

Studies of attribution bias and symptoms in schizophrenia are in their infancy and have shown contradictory reports. One study by Lysaker et al (2004) indicated that higher negative symptom scores were associated with poorer attribution stability with resultant deficits in social functioning, including fewer frequent social contacts and less community participation. However, a more recent study by Vidarsdottir et al (2019) in early psychosis patients demonstrated strong positive associations between hostility and blame attributions and positive symptoms. They also showed a weak relationship between higher negative symptom scores and lower aggression bias. The authors of this paper proposed that as scores were based on participant

self-report, relationships between negative symptoms and aggression represented better self-awareness in participants, which they attributed to better social cognition. They therefore concluded that attribution bias deficits were likely more strongly associated with positive symptoms in patients with schizophrenia.

1.5.2.2 Emotion Processing

A study investigating patients with psychosis found a significant negative association between emotion recognition and subclinical negative symptoms (Fett et al, 2013). This finding was also shown in a study of facial emotion recognition in patients with schizophrenia by Kohler et al (2003), where there were significant negative correlations between negative symptoms and emotion recognition, suggesting patients experiencing high negative symptom severity have poorer emotion recognition outcomes. However, an earlier study (Kee et al, 1998) showed no correlations between negative symptoms and facial emotion processing, although this was with a small sample and the facial emotion recognition measure was old, lacking ecological validity.

1.5.2.3 Empathy & Emotional Intelligence

When investigating the relationship between clinical symptoms and empathy in schizophrenia, results have been inconsistent. Achim et al (2011) and Montag et al (2007) found no significant associations. However, Haker and Rossler (2009) and Smith et al (2012) found negative correlations between negative symptom scores and self-reported empathy scores. Differences in studies likely emerge from methodological issues. One such issue was recruiting participants at different stages of their illness, as age is known to be a critical indicator of empathetic ability, with healthy older adults showing poorer cognitive empathy than younger adults (Bailey & Henry, 2008). Additionally, Achim et al (2011) and Montag et al (2007) investigated patients with chronic schizophrenia and therefore their results may have been confounded by dosage and duration of antipsychotic medication use.

Studies have also shown evidence for an association between emotional intelligence and negative symptoms, as well as emotional intelligence and disorganised symptoms (Kee et al., 2009; Mao et al., 2016). However, again more research is needed to reliably support the significance of these relationships.

1.5.2.4 Theory of Mind

ToM has been most widely studied as a developmental deficit evident in children with autism. As we see similarities in negative symptoms between autistic individuals and patients with schizophrenia, including stereotyped behaviours, social withdrawal, and poverty of language, Frith (1995) theorised that negative symptomology in schizophrenia would predict severe deficits in ToM. This has been shown in several studies evidencing an association between more severe negative or disorganised symptoms and poorer ToM ability (Kelemen et al., 2005; Mazza et al., 2001; Sarfati et al., 1999). Evidence from Fett et al (2013) also showed that in patients with psychosis, poorer ToM performance had the strongest significant associations with disorganised symptoms, however it was also significantly associated with negative and positive symptoms.

1.5.2.5 Social Perception

Literature has suggested task performance on social perception measures is often unrelated to particular symptoms in patients with schizophrenia (Appelo et al., 1992; Penn et al., 2002). However, in two studies (Toomey et al., 2002; Chapellier et al., 2022) testing non-verbal social perception in patients with schizophrenia, results showed that social perception scores were significantly correlated with conceptual disorganisation, and with blunted affect and avolition, respectively, which may provide scope for further research in this area.

1.6 Schizophrenia Treatment and Social Cognition

1.6.1 Pharmaceutical Treatments and Social Cognition in Schizophrenia

The most common treatment approach for patients with schizophrenia is a pharmacological intervention, with antipsychotics as the primary recommended drug. Evidence suggests that antipsychotics have efficacy in treating acute psychotic episodes (Horst et al., 2005). However, significant proportions of patients with schizophrenia (up to 40%) taking antipsychotic drugs continue to show moderate to severe symptoms of psychosis (Kelly et al., 2008; Sacco et al., 2009), and many also experience associated side effects of the medication. These side effects can include sedation, weight gain, sexual dysfunction, emotional blunting, changes in sense of self, and parkinsonism (Thompson et al., 2020). In response to these issues evidence has emerged showing that some patients can cope well in the long-term without antipsychotic medication (Harrow et al., 2017), and that some psychosocial interventions can be beneficial to patients without simultaneous antipsychotic use (Francey et al., 2020; Morrison et al., 2012).

A randomised antipsychotic discontinuation study by Faber et al (2012) has shown evidence that both neurocognition and social functioning may be improved following antipsychotic reduction (Faber et al., 2012; Wunderink et al., 2013). Less research currently exists investigating the effects of antipsychotic use on social cognition. However, a review of 15 existing studies by Kucharska-Pietura and Mortimer (2013) found mixed evidence for the efficacy of antipsychotic use on social cognition. Findings showed that some evidence exists for antipsychotics improving social cognition, although no studies in the review accounted for symptom changes in their analysis, where improvements in symptoms may lead to better performance in social cognition. Other studies included in the review showed evidence for antipsychotic use resulting in declines in social cognition, although again some studies failed to account for confounding factors such as age, illness duration, or neurocognitive ability, which may be associated with worsening social cognitive performance in the population. The authors of the review attributed the inconclusive findings thus far on inconsistences in study designs due to factors such as variability in baseline medication dosage, heterogeneous social cognition measures, and short or no follow-ups.

Recently, there has been a renewed optimism for the potential of the neurohormone oxytocin in the treatment of schizophrenia (Gibson et al., 2014; Woolley et al., 2014). Particularly, researchers have stressed the potential benefits on cognition as well as

on positive and negative symptoms, with fewer adverse side effects from the treatment (Tan et al., 2018). However, reviews into the effects of oxytocin on patients with schizophrenia show that the results are mixed across studies, and specifically, effects on social cognition domains continue to vary significantly (Bukovskaya & Shmukler, 2016; Erdozain & Penagarikano, 2019).

1.6.1.1 Antipsychotic Medication Actions

First-generation antipsychotics (FGAs) were developed to address the symptoms of schizophrenia. However, the serious side effects associated with the drugs, such as extrapyramidal symptoms (EPS) including parkinsonism and tardive dyskinesia, led to the development of second-generation antipsychotics (SGAs). While some theorise FGAs work by blocking dopamine D2 receptors in the brain, reducing dopamine activity, and alleviating positive symptoms of schizophrenia such as hallucinations and delusions (van Kammen & Marder, 1995), there is ongoing research to explore their impact on other neurotransmitter systems (Robbins, 2022). On the other hand, SGAs are known to affect various neurotransmitter systems, including dopamine and serotonin, which likely contribute to their broader efficacy in managing positive and negative symptoms of schizophrenia. (Robbins, 2022). Although SGAs have a lower risk of causing EPS, they still have side effects including weight gain and increased risks of cardiovascular issues (Zhang et al., 2013).

It is important to note that within the categories of FGAs and SGAs, there are multiple individual medications that may vary in their pharmacological properties, potentially leading to differences in their mechanisms of action. Additionally, these mechanisms of action do not account for individual differences amongst people taking antipsychotics, such as genetic variations that can influence the effectiveness of a medication. Previous research has associated social cognitive functioning with dopamine, serotonin, and oxytocin, and a social cognitive network in the brain has been established (Rosenfeld et al., 2011; Rushworth et al., 2013). Therefore, considering that FGAs and SGAs may act on various neurotransmitter systems in the brain, which may be intrinsically involved in social cognitive processes, it is crucial to better understand the underlying relationships between antipsychotics and social cognition.

1.6.2 Psychological Treatments and Social Cognition in Schizophrenia

Potential psychological treatment interventions for social cognition deficits including social cognitive remediation (SCR) and social cognitive interaction training (SCIT) have been explored in the research context for patients with schizophrenia (Fernandez-Sotos et al., 2019). Remediation and training approaches are based on behaviour, and rely on the concept of neuroplasticity, or the brain changing to develop new skills through learning. A meta-analytic review by Kurtz and Richardson (2012) conducted on social cognitive training in schizophrenia studies found that facial affect recognition and ToM were improved following training programmes with moderate to large effect sizes. However, they also found that there were no significant effects of the training on attribution style or social perception measures. This review also identified moderate-large effect size improvements in observer-rated community functioning and institutional functioning following the training,

showing improvements in social functioning, however they found no significant changes in positive or negative symptoms. There were though some limitations present with studies in this review. Namely, only 19 studies were included in the analysis, with a small number for each social cognition domain, meaning some of the analyses were likely underpowered. Additionally, some studies included combined findings from both cognition and social cognition training, and this may have biased results. Another review, conducted by Kurtz et al (2016) on social cognition training and social cognition interaction training in schizophrenia identified 16, largely pilot studies. They found large effect size improvements in facial affect, social perception, and ToM studies. Modest significant improvements were also shown in negative and general symptom domains. The studies in this review were regarded as high quality due to their randomisation procedures, relatively large sample sizes, and active control comparison groups. However, this review also identified several limitations with their identified studies, including the fact that under half of the studies included blinded outcome raters. Additionally, most of the studies failed to report if participants-maintained treatment fidelity, and as such it was difficult to assess if participants fulfilled the criteria of accessing social cognition training.

In the most recent NICE guidelines, they consider evidence for cognitive remediation as a treatment method in schizophrenia (NICE, 2014). Although some studies they evaluated included social cognitive domains in cognitive remediation interventions, they did not consider social cognitive remediation interventions separately. NICE found limited evidence of efficacy for cognitive remediation in improving interpersonal functioning in the studies they reviewed and considered methodological inconsistencies problematic in the interpretation of findings. The current recommendation by NICE therefore is for further research to be conducted using adequately powered RCTs of cognitive remediation interventions with long-term follow-ups for all cognitive domains including social cognition.

1.7 Recovery in Patients with Schizophrenia

1.7.1 Views on Recovery in Schizophrenia

For many years the dominating belief in psychiatry was that a patient with a schizophrenia diagnosis would not recover, and that their deterioration over time was inevitable (Frese et al., 2009) . The introduction of antipsychotic medications in the 1950s, and reintroduction of patients into community living, bought new hope to the field. Despite the initial optimism of this movement, it was soon found that those with serious mental illness could not easily reintegrate into society, partly due to ongoing/persistent positive and negative symptoms, as well as difficulties with occupational and social functioning (Jacob, 2015). Over time, shifts in views of recovery occurred, and now multiple definitions of recovery are utilised in the clinical space. A recent review on recovery from schizophrenia (Huxley et al., 2021) emphasised that there is not a singular predictable outcome for a patient with schizophrenia, and this has been supported by evidence that some recover from schizophrenia with little to no input from mental health systems (Davidson et al., 2005; Harrow & Jobe, 2007).

1.7.2 Service User Perspectives of Recovery in Schizophrenia

Importantly, a movement towards considering service user definitions of recovery has been highlighted. A review of qualitative studies on antipsychotic treatment in schizophrenia found that participants were largely positive about medication as an acute treatment but were sceptical about long-term use (Bjornestad et al., 2020). An integral research paper on service user definitions of recovery from psychosis was published by Law and Morrison (2014). Authors used a Delphi study of people with lived experience of psychosis, to determine how to conceptualise the term 'recovery'. The study found high consensus amongst participants on a range of items they deemed important in defining recovery, including 'the achievement of a personally acceptable quality of life', and 'feeling better about yourself'. When asked about factors that show a person has recovered; 'when the person can trust themselves to make good decisions and positive changes in life', 'when the person feels in touch with their own emotions again', and 'when the person finds places and situations where they can make friends' were rated amongst the higher items. Factors deemed to help the recovery process included 'having the support of others', 'having a good understanding of your mental health problems', and 'being able to develop positive relationships with other people'. Within the factors that hinder recovery, higher rated items included 'when a person feels isolated or alone even when with family or friends', and 'when a person feels lost or hopeless for much of the time'. Notably, medication was only rated amongst the lower items in factors that help recovery and was also rated in the factors that hinder recovery section as something that can affect concentration and memory, although there was also mention that deliberately stopping medication can also hinder recovery. The study had several limitations including localised recruitment to the north-west of England, meaning it was not representative of other regions, or countries.
This approach has significant implications for clinical practice by highlighting the importance of considering someone's personal priorities and social context and not just focusing on symptom reduction. Additionally, social functioning, self-esteem, and quality of life were considered the most important aspects related to recovery by service users, and therefore these factors should be regularly measured in clinical services and research interventions developed to target their improvement.

1.8 Rationale for This Thesis

In 2004, at the National Institute of Mental Health on Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) programme, a sub-committee meeting dedicated to social cognition took place. The conference attendees agreed at that time that emerging evidence in the field showed that social cognition was a highly valuable construct and needed a greater future research focus to contribute to understanding the nature and disability of schizophrenia. During the meeting they recommended that social cognition measures should be included in all clinical trials investigating interventions on patients with schizophrenia (Green et al., 2008).

Although research into social cognition in patients with schizophrenia has clearly continued, and more evidence has emerged signifying the importance of relationships between social cognition domains and social functioning, gaps remain

in the literature. These gaps are largely due to under researched domains, non-heterogeneity of measures and methodological issues in studies (e.g., reliance on cross-sectional or short-term follow-up studies, small sample sizes, and practice effects). In addition, the question of how antipsychotics effect social cognition has received relatively little attention and remains unresolved, including whether medication effects on social cognition are mediated by symptom reduction, and whether antipsychotics effect the relationship between social cognition and social functioning.

Social functioning deficits are seen consistently across mental health disorders, and, notably, previous research has highlighted that social cognition may directly impact social functioning outcomes. Additionally, as well as being a clinically important factor, research involving patient accounts has identified social functioning as a primary target in recovery. Despite evidence linking social cognition and social functioning, the mechanisms behind poor social functioning outcomes in mental health patients remain unclear with additional factors also potentially affecting this relationship, including symptomology, stigmatisation, neurocognitive deficits, and psychiatric medication. To gain a comprehensive understanding of the relationship between social cognition and social functioning in patients with mental health disorders, it is crucial to evaluate the effects of these factors.

Therefore, in this thesis a systematic literature review was conducted exploring the prevalence of social cognition deficits related to psychoactive medications with sedative effects. Considering potential relationships between psychiatric drugs, emotional blunting and sedation, the review was considered an important step in identifying patterns and themes in social cognition outcomes for both healthy volunteers and mental health patients. This review provided valuable insights into areas where further research can be conducted in a more robust manner. The findings of this study could help improve the understanding of the impact of psychiatric medications, particularly benzodiazepines on social cognition and inform clinical decision-making and future research in this area.

The review was followed with two studies, one cross-sectional and one longitudinal to gain a better understanding of the effects of antipsychotic medication on patients with schizophrenia specifically. The first study was a cross-sectional study comparing healthy volunteers and patients with schizophrenia on social cognition measures. This study aimed to build upon previous research that showed deficits in patients compared to healthy volunteers on emotion processing and ToM tasks. By including more neglected domains of empathy, emotional intelligence, attribution bias, and social perception, this study hoped to provide a more comprehensive insight into social cognition ability between the two groups. Additionally, the cross-sectional analysis of patient data enabled a closer examination of the relationships between antipsychotic usage (dose and duration) and symptoms of psychosis, social functioning, and social cognition domains. This insight into domain-specific findings may be important for future prognosis and targeted pharmaceutical or psychosocial treatment of schizophrenia.

As well as the cross-sectional study, a longitudinal study was conducted to investigate the long-term effects of antipsychotic treatment vs. a gradual supervised reduction in patients with schizophrenia. The study utilised a randomised controlled

trial (RCT) method to compare groups social cognition outcomes. This provided high quality, replicable data on the relationships between changes in antipsychotic treatment and changes in social cognition and symptoms, over time. The insights from this study will be important for understanding the effects of antipsychotic treatment on social cognition, potentially informing future treatment options.

1.9 Aims

This thesis aims to:

(1) Assess the existing literature on the effects of psychoactive medications on social cognition in both health volunteers and patients with schizophrenia.
(2) Explore the differences in social cognitive ability between healthy volunteers and patients with schizophrenia and examine the relationships between antipsychotic usage – dosage (AP dose) and duration of use (AP duration), psychosis symptoms, social functioning, and social cognition in patient participants.
(3) Explore the relationship between changes in social cognition domain scores over a 24-month period and randomised controlled trial (RCT) group, whilst considering potential confounding variables such as symptom changes.

1.10 Background to This Thesis

1.10.1 The RADAR Study

The Research into Antipsychotic Discontinuation and Reduction (RADAR) study was a multi-centre, pragmatic, two-arm, open, parallel group, single-blind, individually randomised controlled trial (RCT). It was a six-year research programme funded by the National Institute for Health Research (NIHR) which began in 2016. From 2016-2017 those working on the trial conducted a feasibility study, interviewing patients concerning their participation in a trial such as RADAR. I started working on the study as a researcher in early 2017 at the beginning of recruitment to the RCT.

RADAR aimed to evaluate the risks and benefits of reducing and discontinuing antipsychotic dose in a supported programme compared with a continuous maintenance antipsychotic treatment, in adults with multiple episode schizophrenia-spectrum disorder diagnoses. This thesis will use research data collected as part of the RADAR study, including demographic data, Positive and Negative Symptom Scores (PANSS), Social Functioning Scale (SFS) scores, and neurocognition data, as well as data collected in the social cognition sub-study, designed, and added to the RADAR data collection tools as part of this PhD. Additionally, data has been collected on a healthy participant population independently from the RADAR study, for comparison analysis as part of this PhD.

1.10.2 Implementing Social Cognition Measures into the RADAR Study

From working on the RADAR study, I became interested in knowing more about the effects of antipsychotics in areas where deficits have been identified in patients with schizophrenia. I have a background of studying social cognition during both my undergraduate degree and my masters, and therefore I was interested in

investigating the effects of antipsychotic medication on social cognition in patients with schizophrenia-spectrum diagnoses.

To explore this, I began by discussing the process of implementing social cognition measures into the RADAR study with my supervisory team. I identified appropriate questionnaires for each social cognition domain and sought permission for their use in the trial, where necessary. Following this, I created a social cognition questionnaire pack, consisting of six measures representing the separate social cognitive domains for the RADAR participant assessments at baseline and longitudinal follow-ups. I helped draft a substantial amendment for the RADAR study in order to add the measures, answering questions from the Medicines and Healthcare products Regulatory Agency (MHRA) and Health Research Authority (HRA) to justify their inclusion. Sites already enrolled in RADAR were approached to decide if they were willing to conduct the social cognition assessments, as there would be an additional time burden on both participants and researchers conducting assessments. Future sites recruited to RADAR were trained in the social cognition measures as a standard process. Eleven of the nineteen sites involved in RADAR recruited participants to the social cognition sub-study: North East London NHS Foundation Trust (NELFT), East London NHS Foundation Trust (ELFT), Barnet Enfield and Haringey Mental Health NHS Trust (BEH), Camden and Islington NHS Foundation Trust (C&I), Central and North West London NHS Foundation Trust (CNWL), Sussex Partnership NHS Foundation Trust (SPFT), Livewell Southwest, Gloucestershire Health and Care NHS Trust (GHC), Southern Health NHS Foundation Trust, Oxford University Hospitals NHS Foundation Trust (OHFT), and Kent & Medway Social Care Partnership Trust (KMPT).

1.10.3 Personal Contribution to the RADAR Study

During the four years that I worked on the RADAR study (Jan, 2017-Dec, 2021) I contributed a significant amount. In my role as a study researcher, I initially had responsibility for recruiting and consenting patients into the trial. This involved liaising with consultant psychiatrists and other members of community mental health teams (CMHTs) to identify eligible patients for the study, initiate contact with those patients, and create ongoing communication pathways between clinicians and the RADAR study team. I consented participants into the RADAR study from four of the trial sites (NELFT, BEH, C&I, and SPFT). I also had significant involvement in data collection, completing baseline and follow-up assessments across five sites, including NELFT, BEH, C&I, SPFT, and CNWL as part of my ongoing blinded researcher role. Additionally, I had unblinded researcher responsibilities at four sites, BEH, CNWL, C&I, and ELFT. Within this role I extracted data from medical notes, conducted safety reporting, organised participant follow-ups, and tracked intervention fidelity.

During my time on RADAR I was also involved in additional tasks including; assisting with site initiations, training researchers in collecting data and using outcome measures, site file management, data entry and cleaning, attending clinical meetings, completing consorts, trial social media and website content management, and contributing to the upkeep of recruitment figures and current research progress via the EDGE research management system, CPMS NHS, and clinicaltrials.gov. Additionally, I presented and discussed my PhD progress in programme

management group meetings and RADAR conferences to grant holders, researchers, and lived-experience advisory panel (LEAP) members. Finally, I also co-produced the bi-annual newsletter with members of the RADAR LEAP. I also continue to be involved with upcoming manuscripts as part of the RADAR trial dissemination.

6.1.2 Social Cognition Sub-Study

Alongside my blinded and unblinded research roles on RADAR, I led the social cognition sub-study from conception through to completion, including in the time between 2020-2022 when I left my research role with RADAR. Within this role I was responsible for creating the assessment packs, organising printing and dissemination of the packs, and training researchers across all sites. I also liaised with researchers on any queries regarding the social cognition sub-study and managed and monitored the social cognition data collection. Additionally, I was responsible for the data entry and cleaning, as well as analysis of all social cognition sub-study data.

Chapter 2: Systematic Review and Meta-Analysis into The Effects of Psychiatric Medications on Social Cognition

This chapter presents the systematic review and narrative synthesis titled 'A systematic review of the effects of psychiatric medications on social cognition', and will report the study design, method, results, and discussion. The current chapter will expand on the published manuscript by Haime et al (2021) in the peer-reviewed journal *BMC Psychiatry*. This review followed the PRISMA guidelines for reporting systematic reviews (Moher et al., 2009) and the protocol for the review can be read on the PROSPERO registry, ID: CRD42018092883.

While previous research has suggested that psychiatric medications may impact social cognition, there is still a need for a comprehensive and systematic review of the existing evidence to fully understand the nature and extent of these effects. The findings of this review can inform clinical decision-making, treatment planning, and future research in this area.

2.1 Introduction: Narrative Synthesis

2.1.1 Social Cognition and Social Functioning in Patients with Mental Health Disorders

Individuals experiencing mental health difficulties and social cognition deficits often show a significantly poorer ability to establish and maintain social relationships, greater social withdrawal, and present with poorer social skills in general. Research has predominantly shown these associations in patients with schizophrenia, but there is evidence social functioning deficits may be transdiagnostic when social cognition deficits are present, with literature supporting this in patients with bipolar disorder, major depressive disorder and anorexia (Knight & Baune, 2019; Robertson et al., 2014; Tiller et al., 1997; Van Rheenen & Rossell, 2014). Additionally, social cognitive deficits have been associated with higher rates of suicide, poorer quality of life, and lower levels of employment across mental health conditions (Hambrook et al., 2012; Lee et al., 2013; Szanto et al., 2012; Weightman et al., 2014)

2.1.2 Psychiatric Treatment in Mental Health Disorders

Medications with sedative effects including antipsychotics, benzodiazepines, (some tricyclic) antidepressants, antiepileptics, and z-drugs are commonly prescribed in the treatment of mental illnesses. In a study by the British Pharmacological Society (BPS) running from 2006 – 2009 a list of the most commonly prescribed drugs in the UK was produced, and examples of each of these sedative medications were found to be featured in the top 100, showing the extent of their administration (Audi et al., 2018). Research also shows an increase in the amount of off label prescribing for psychiatric drugs, where they have been administered for conditions they were not originally evaluated for. In antipsychotics, originally approved for psychotic disorders, there is frequent off-label prescribing for conditions including dementia, depression, and personality disorders (Weiss et al., 2000). Whereas, in antidepressant

prescribing, originally approved for depression treatment, there is use in conditions including chronic pain, and insomnia (Everitt et al., 2018; Urits et al., 2019). Additionally, frequent polypharmacy in evident in mental health patients (Kukreja et al., 2013). In the NICE guidance for antipsychotic prescription, advice states 'Do not initiate regular combined antipsychotic medication, except for short periods (for example, when changing medication)', with consideration for the addition of a second antipsychotic only being introduced after a patient shows a treatment-resistant response to clozapine (NICE, 2014). However, the concurrent use of more than one antipsychotic is seen frequently in the treatment of schizophrenia-spectrum disorders and bipolar disorder (Langan & Shajahan, 2018; Mojtabai, 2010; Roberts et al., 2018). In these mental health disorders, we are also likely to see sedative medications such as tricyclic antidepressants or benzodiazepines prescribed alongside an antipsychotic to treat nonpsychotic symptoms such as agitation, or for negative symptom control (Baandrup, 2020).

2.1.3 Sedative Effects of Psychiatric Medications

Sedative properties of psychoactive drugs refer to their abilities to induce drowsiness in individuals, resulting in a calming effect, relaxation, reduced anxiety, and sometimes slowed cognitive processing. Psychiatric medications exert their sedative actions through multiple mechanisms, influenced by their effects on neurotransmitters in the brain. For instance, benzodiazepines and z-drugs enhance gamma-aminobutyric acid (GABA) effects, promoting relaxation and sedation (Atkin et al., 2018). Tricyclic antidepressants primarily inhibit the reuptake of serotonin and norepinephrine, which can result in sedation (David & Gourion, 2016). Additionally, antipsychotics can block histamine and dopamine receptors, contributing to drowsiness (Miller, 2004; Hermes et al., 2013). These sedative properties may directly impact social cognition by influencing processes in the social cognitive brain network involved in perceiving and understanding social information, such as the amygdala or fusiform gyrus (Krendl & Betzel, 2022). Alternatively, medications may indirectly affect social cognition by impairing neurocognitive processes such as attention, processing speed or executive functioning (Arioli et al., 2018). Understanding the effects of sedative medications on social cognition is important in identifying potential adverse or unexpected treatment outcomes.

2.1.4 Previous Review on The Effects of Antipsychotics on Social Cognition

Evidence shows that sedative drug prescribing, off-label prescribing, and polypharmacy is relatively common in psychiatry, however little research has discussed how taking these drugs may affect social cognition. As a potential predictor of social functioning, and therefore a crucial treatment target it is integral to establish the consequences of these psychiatric medications on social cognition. One previous review conducted by Kucharska-Pietura & Mortimer (2013) explored the effects of antipsychotics on social cognition in patients with schizophrenia, and whether effects differed depending on typical vs. atypical antipsychotic type. Authors conducted searches of two databases and found 15 studies corresponding to their inclusion criteria. Findings from this review suggested that the studies conducted to this point produced inconclusive results of the effects of antipsychotic drugs on social cognition in schizophrenia. Additionally, the authors noted criticisms of study designs, with non-randomised approaches, small sample sizes, and inadequate

control of clinical variables such as standardising medication doses. This review demonstrated problems that exist in social cognitive research in mental health, however, it failed to undertake a systematic approach and provided inadequate details of their own review process. The search undertaken only included two databases, and terminology used to represent social cognition domains was not exhaustive, meaning it is likely the search failed to identify all relevant papers. Additionally, no quality assessment measure was used, nor were any inter-rater reliability scores calculated on agreement for inclusion of articles. Finally, a narrative approach was taken for the analysis, although no details were given on the methodology for this. The inconclusive results of this review support the need for a more comprehensive and up-to-date exploration of the effects of antipsychotic medication on social cognition. However, only considering antipsychotics ignores the potential effects of additional psychiatric drugs on social cognition that have gone unexplored in previous studies. Therefore, this review aimed to take a systematic approach to investigate the effects of psychiatric medications on social cognition in all populations.

2.2 Method

2.2.1 Search Strategy

During theory development key papers in the field were identified. These papers included those by authors well-known in the field of social cognition and schizophrenia whose work considering medication effects was already known to the authors of this review (Harvey et al., 2006; Kucharska-Pietura, et al., 2012a; Maat et al., 2014; Penn et al., 2009; Wölwer et al., 1996). Studying these key papers guided the searches, and aided decisions on search terms.

Searches were carried out in several databases, including MEDLINE (OviD), Embase, Psychinfo, Web of Science, and Scopus, as well as grey literature databases greylit.org and opengrey.eu. Searches included terms for 'social cognition' AND 'mental disorders' AND 'psychiatric medications'. MeSH terms specific to databases, and related synonyms were included to make the searches as broad as possible. An attempt to find additional studies was also made through backward reference searches of papers identified.

An example of the search strategy is included in Appendix A**.**

2.2.2 Screening

Citation manager 'Mendeley' (Foeckler et al., 2008) was used during this review. Citations were imported from databases, and duplicates were removed. All citation titles and abstracts were screened by ZH for their relevance to the inclusion criteria set out in **Table 4**. The remaining papers (n=170) were then screened in full by ZH, and any uncertainties for inclusion were discussed with the second reviewer (AJW).

Table 4.
Systematic Review Inclusion and Exclusion Criteria.

Inclusion Criteria	Exclusion Criteria
Longitudinal or cross-sectional study designs	Studies were published in a non-English language

Participants received a psychiatric medication with sedative properties (antipsychotics, benzodiazepines, Z-drugs, barbiturates, tricyclic antidepressants, mirtazapine, pregabalin, and trazadone)	Studies were qualitative, theoretical, or systematic review or meta-analysis
Population includes healthy volunteers, animals, or humans with mental health disorders	
Studies investigating a social cognition measure or task.	
Papers present in search of the following dates: inception of database to 10/08/2018, and 10/08/2019-30/12/2019.	

2.2.3 Animal Studies

At the point of screening, ZH and the second reviewer (AJW) were uncertain about the inclusion of animal studies, because they used outcome measures and study designs far removed from that used to measure social cognition in humans. For example, fear conditioning studies would use a foot-shock at the same time as a cue (normally an auditory tone). After several iterations of this pairing, the rat would learn that the tone meant a shock was coming, usually resulting in a fear reaction. In rats, fear was measured either observationally or through neuronal recordings of brain regions associated with fear, such as the amygdala. However, evidence shows fear conditioning is better thought of as a neurocognitive mechanism than a social cognitive one, as it is believed to evidence the learning mechanism and memory process, rather than any emotional processing ability (Hamm & Weike, 2005). Furthermore, although evidence from social interactions suggests that social cognition exists in animals, accurate and transferable measures between humans and animals do not currently exist (Seyfarth & Cheney, 2017). Therefore, it was decided to exclude all animal studies from the review.

2.2.4 Quality Assessment Process

Following the exclusion of papers not meeting the inclusion criteria, 40 full papers remained. To rate the quality of the remaining papers the Downs and Black Checklist (Downs & Black, 1998) was adapted and used. ZH rated all 40 papers against the checklist, and the second reviewer (AJW) rated 20% of the papers independently. Reviewers then met to discuss their ratings and resolve any discrepancies.

2.2.5 Categories of Quality Assessment Rating

The Downs and Black checklist (Downs & Black, 1998) was chosen as a data quality tool because of its versatility. The papers garnered from the search included non-randomised and randomised trials, and there were cross-sectional and longitudinal studies, covering a large variety of study designs. It was recognised that the Downs and Black checklist allows for quality assessment of all these papers, and it is also comprehensive in its criteria.

Categories rated by the Downs and Black checklist include reporting (10 questions), external validity (3 questions), internal validity – bias (7 questions), internal validity – confounding (5 questions), and power (1 question). The final question (Q.27) under the power category was adapted from the original Downs and Black checklist for this

review. In the original checklist the question stated, ‘Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?’, for this review this was changed to, ‘Did the study perform a power calculation?’. This decision was made due to reports suggesting post hoc power analysis should not influence significance (Hanney et al., 2016). Instead, evaluating if a study conducted a power analysis (yes=1 and no=2) before it began was decided to be a significant rating of study design quality.

2.2.6 Narrative Synthesis Approach

A narrative synthesis approach was utilised in the reporting of findings from this review. Popay et al (2006) produced guidance on the process of narrative synthesis in systematic reviews. The authors acknowledged the lack of consensus in the methods and reporting of previous narrative reviews and the need to utilise a systematic and transparent approach to synthesising data and avoiding bias. In conducting this review, the guidance by Popay et al (2006) was followed, using the four iterative elements: 1. Theory development; 2. Preliminary synthesis of findings; 3. Exploration of study relationships; 4. Assessment of synthesis robustness.

2.2.7 Meta-Analysis

A meta-analysis was conducted as part of this review. The outcome measures across papers were highly heterogeneous, however four papers reported scores for all emotion recognition categories and therefore the meta-analysis was completed on the basis of these results. Requests for further data were made to 6 authors who used similar emotional facial expression recognition outcomes, but no responses were received. As the four papers included in the meta-analysis did not use the exact same measure, score totals were different for each. Therefore, scores were converted into percentages to allow the analysis to be completed. The ‘metafor’ statistical package was used in ‘R’ (RCoreTeam, 2017; Viechtbauer, 2010) to conduct the meta-analysis. Further sensitivity analysis in R to identify outliers was completed, and the meta-analysis was re-conducted after their removal. As the results of this meta-analysis were consistently heterogenous, a decision was made not to include them in the final manuscript submitted for publication as they failed to add any information about the papers to the overall review.

2.3 Results

The search process to identify eligible papers is presented in the PRISMA flow chart in **Figure 1**. 40 total papers were identified for qualitative analysis, and four of these papers were used in the meta- analysis.

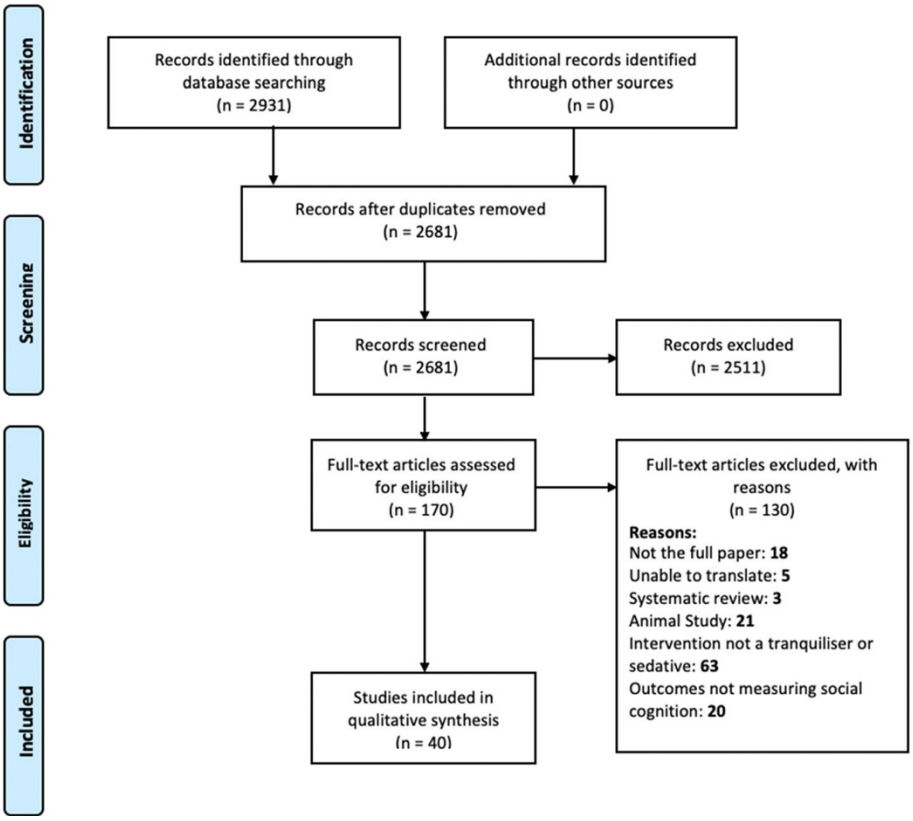

Figure 1. PRISMA flowchart for systematic review.

2.3.1 Results of the Quality Assessment

A Kappa coefficient of 85% suggested interrater reliability between reviewers was good on the data quality scoring of included papers.

The study team decided to keep all the 40 papers for the narrative synthesis despite their differing quality scores. This decision was made because of the relatively small number of papers, and due to the lack of 'excellent' and 'good' rated papers in the data quality check, issues with the papers that made them majority poor or fair ratings are considered in the discussion. All papers selected for analysis in this review can be viewed in **Table A1 (**Appendix B**).**

2.3.2 Narrative Synthesis

2.3.2.1 Theme Selection

In this review results showed only two types of psychiatric medication (antipsychotics or benzodiazepines) were used in the articles discovered. Themes in the narrative synthesis were dictated by the medication type (benzodiazepine/antipsychotic), the study design (longitudinal/cross-sectional), and the population (patients/healthy volunteers). Several neuroimaging studies for each medication type were also found and are discussed separately.

2.3.2.2 Benzodiazepine Studies

Benzodiazepine studies conducted in healthy volunteers showed significant impairments in emotion recognition tasks following diazepam administration (Coupland et al., 2003; Pringle et al., 2016; Zangara et al., 2002; Zurowska et al., 2018). A study investigating a lower dose of diazepam found a significant impairment on the recognition of angry expressions only (Blair & Curran, 1999). One of these papers also incidentally investigated the effects of 42ositive4242, a beta-blocker with mild sedative effects, on emotion processing and found no significant effects (Pringle et al., 2016). One further benzodiazepine study by Nilsonne et al (2018) showed no effect of the benzodiazepine oxazepam on a measure of empathy.

The study conducted by Zurowska et al (2018) aimed to investigate whether benzodiazepine withdrawal affected social cognition in those addicted to the medication, as they recognised that the sedative effects may impair complex cognitive functions. The study included three groups of participants: those who had already withdrawn from benzodiazepines at an addiction treatment unit; those who were currently undergoing withdrawal at an addiction treatment unit; and a comparative healthy volunteer group. Patients who were withdrawing from benzodiazepines were significantly impaired in recognising negative emotions compared to healthy volunteers, suggesting benzodiazepine use causes emotion recognition dysfunction. No differences were shown in social cognitive performance post-detoxification (testing negative for benzodiazepines in the blood after withdrawal) compared to those still undergoing withdrawal, which may also suggest that impairments in emotion recognition ability associated with benzodiazepine use may create longer-term social cognition performance deficits, compared to those who had never taken benzodiazepines.

2.3.2.3 Neuroimaging Studies

fMRI and EEG studies included in this review compared social cognition before and immediately after administration of a benzodiazepine. Del-Ben et al (2012) in a study of healthy volunteers, showed that when reacting to fearful faces a single dose of diazepam resulted in attenuated right amygdala activity, with no similar evidence when responding to angry faces. Another healthy volunteer study by Paulus et al (2005) found lorazepam attenuated activity in the amygdala and insula, and that the activation was significantly lower after 1mg compared to 0.25mg. This suggests a dose-dependent response in limbic brain regions when taking lorazepam. Another study in which lorazepam was administered was conducted on patients with ‘catatonic’ schizophrenia and patients with bipolar disorder (Richter et al., 2010). In ‘catatonic’ patients with schizophrenia lorazepam induced brain signal decreases in the occipital cortex and medial prefrontal cortex (MPFC) whilst they undertook a negative emotion recognition task. These results showed blood oxygen level dependent (BOLD) signal patterns resembling those of healthy volunteers taking a placebo during the task. However, at the time of the fMRI task all patients with a psychosis-related diagnosis were taking either antipsychotic or antidepressant medications in addition to the administered lorazepam. Another healthy volunteer study (Olofsson et al., 2011) showed no interaction between oxazepam and brain

activity, when performing a social cognition outcome measure, similarly to non-imaging study findings (Nilsonne et al., 2018).

2.3.3 Antipsychotic Studies

2.3.3.1 Healthy Volunteers

Two studies were found that tested the effects of antipsychotics on social cognition in healthy volunteers, which demonstrates the lack of overall research investigating the effects of antipsychotics in healthy volunteers. A cross-over study by Lawrence et al (2002) found that sulpiride, an atypical antipsychotic, reduced recognition of angry faces but did not affect the recognition of any other emotions, and that a placebo had no effect. Interestingly, sulpiride is often used clinically as an anti-aggressive agent, which may suggest a link between emotion recognition and emotion production ability. The other study identified investigated antipsychotic effects on social cognition in healthy volunteers via a randomised parallel group trial of quetiapine vs. placebo (Rock et al., 2016). The research found no effect of the drug on facial expression recognition, though dropout rates in the drug arm were high (25%) and may have masked an effect.

2.3.3.2 Patient Studies

A universal finding of studies in this review comparing the effects of antipsychotics on patients with schizophrenia and healthy volunteers was that patients performed less well on social cognition tasks, whether they were taking antipsychotics or not (Behere et al., 2009; Daros et al., 2014; Gaebel & Wolwer, 1992; Herbener et al., 2005; Lewis & Garver, 1995; Mizrahi et al., 2008; Mizrahi et al., 2007; Olivier et al., 2015; Shi et al., 2016; Zhou et al., 2017).

Most of the longitudinal studies in patients with schizophrenia showed improvements in social cognition performance over time (Behere et al., 2009; Fakra et al., 2009; Gaebel & Wolwer, 1992; Gultekin et al., 2017; Kee et al., 1998; Mizrahi et al., 2007; Olivier et al., 2015; Penn et al., 2009; Roberts et al., 2010; Shi et al., 2016; Zhou et al., 2017), or found no effect (Harvey et al., 2006; Herbener et al., 2005; Lewis & Garver, 1995; Maat et al., 2014; Mizrahi et al., 2008; Sergi et al., 2007; Wolwer et al., 1996). Of these studies, five had pharmaceutical company funding (Maat et al., 2014; Penn et al., 2009; Roberts et al., 2010; Sergi et al., 2007; Shi et al., 2016), and for one the drugs used in the study were also provided (Sergi et al., 2007). Two of these longitudinal studies involved patients who were drug naïve prior to research commencement. Behere (2009) found improvements on an emotion processing task and Mizrahi (2008) found no effect of the medication. Most studies involving patients who were required to have a drug-free period prior to taking part found improvements in social cognition (Fakra et al., 2009; Gaebel & Wolwer, 1992; Lewis & Garver, 1995; Mizrahi et al., 2007; Zhou et al., 2017). Other studies described participants switching antipsychotics at the baseline assessment (Gultekin et al., 2017; Harvey et al., 2006; Herbener et al., 2005; Maat et al., 2014; Olivier et al., 2015; Penn et al., 2009; Roberts et al., 2010; Sergi et al., 2007; Shi et al., 2016; Wolwer et al., 1996), and one had no description of treatment status prior to participation (Kee et al., 1998). In these studies where participants changed to an

antipsychotic rather than starting treatment the results only reflect the effect of changing antipsychotic type on social cognition.

Only one longitudinal study of antipsychotics in patients with schizophrenia showed a decline in social cognition performance (Daros et al., 2014). This study included 29 patients with schizophrenia and 28 patients with bipolar disorder and aimed to explore dose-response relationships between antipsychotics and emotion recognition across groups. Findings showed that patients with schizophrenia on higher doses of antipsychotics showed deficits at recognising sad and neutral faces compared to patients with schizophrenia taking lower antipsychotic doses. In patients with bipolar disorder, antipsychotic dose was unrelated to emotion recognition.

The majority of longitudinal studies included in this review were likely limited by practice effects. One study accounted for practice effects by not revealing baseline performance to participants, this meant participants were unable to recognise their errors and correct for them purposefully at follow-up (Behere et al., 2009). However, all patients in this study were also taking anticholinergic medication, which may also have influenced social cognition.

Studies comparing different atypical vs. typical antipsychotics also produced inconsistent results. Some research found that patients taking atypical antipsychotics performed better than those taking typical antipsychotics (Fakra et al., 2009; Gultekin et al., 2017; Kee et al., 1998; Roberts et al., 2010; Savina & Beninger, 2007), and some found no differences between different types of antipsychotics (Harvey et al., 2006; Koshikawa et al., 2016; Kucharska-Pietura et al., 2012a, Kucharska-Pietura et al., 2012b, Maat et al., 2014; Sergi et al., 2007).

2.3.3.3 Neuroimaging

Sumiyoshi et al (2009) explored the effect of the antipsychotic 44ositive4444e on social cognition in patients with schizophrenia. Conducting EEG before drug administration, and six months after use, whilst participants completed a social perception task, they discovered an increase in P300 ERP activation in the left pre-frontal cortex (PFC), alongside performance improvements in social perception. Another study on social cognition in healthy volunteers found after antipsychotic medication participants had decreased BOLD responses in the amygdala when viewing negatively valenced stimuli and increased activation in the PFC (Takahashi et al., 2005). However, they also found minimal changes to behavioural performance on an emotion processing task.

Finally, a cross-over EEG study was conducted with healthy volunteers administered bromocriptine and the antipsychotic haloperidol in one condition and a placebo in the other condition, authors found no significant difference in emotion-related ERPs compared to baseline activations in either condition. However, this study used low doses of antipsychotic medications, and some participants were also prescribed domperidone to treat nausea.

2.3.4 Meta-Analysis

A meta-analysis was conducted using three studies investigating the effects of benzodiazepines on social cognition, and one study investigating the effects of an antipsychotic (Blair & Curran, 1999; Murphy et al., 2008; Rock et al., 2016; Zangara et al., 2002). These studies were included because they all reported the accuracy score of success on a facial emotion recognition task with means and standard deviations (SDs) for each emotion category. As each paper used a different number of trials in their emotion processing task, means for accuracy were calculated as percentage scores, so they were comparable between papers. Initially, the meta-analysis pooled all results for each emotion category in the four papers, for which the results showed high heterogeneity (I2^ = 96.66%) (Higgins et al., 2003). Then sub-group analysis was conducted for each different emotion category, with results also indicating high heterogeneity amongst all sub-groups represented (**Table 5**).

Table 5.
Subgroup and Sensitivity Analysis of Accuracy for Emotion Categories.

Emotion Subgroup	I^2	I^2 after outlier removal
Surprise	92.58	92.58
Happiness	98.36	81.31
Sadness	98.41	65.04
Anger	96.19	96.19
Fear	85.29	85.29
Disgust	91.00	91.00

2.3.4.1 Sensitivity Analysis

A sensitivity analysis was conducted to find any outliers in the initial meta-analysis. Two results were discarded following this, the happiness accuracy result in the Blair and Curran (1999) paper, and the sadness accuracy result in the Murphy et al (2008) paper. The resulting papers again when pooled showed high heterogeneity (I2^ = 91.04%). Subsequent sub-group analysis also showed high heterogeneity across emotion categories in all domains (**Table 5**). Analysis of the included benzodiazepine papers only, after removing the study by Rock et al (2016), also resulted in high heterogeneity (I2^ = 96.91).

2.4 Discussion

2.4.1 Summary of Narrative Synthesis Findings

Impairments in social cognition domains have been consistently linked to social functioning deficits across mental health disorders, and the effects of medication on these impairments have yet to be explored in a systematic way. It is possible that psychiatric drugs impair social cognition due to sedative effects. However, studies included in this review did not measure sedation, and therefore, it is still uncertain if these drug actions directly impact social cognition. Furthermore, it is also possible psychiatric medications by influencing symptoms of psychiatric disorders or neurocognitive functioning, indirectly affect social cognition.

Findings from this review show that benzodiazepines can impair emotion recognition in healthy volunteers. This relationship was shown most consistently for emotion processing with the drug diazepam, although this was also the most well-studied benzodiazepine type. Two neuroimaging studies also showed alterations to social cognitive related brain regions following lorazepam administration. Attenuated activity in the amygdala was found in the Del-Ben et al (2012) study, and evidence of a dose-dependent interaction, with higher lorazepam doses resulting in attenuated activity in the amygdala was shown by Paulus et al (2005). However, Paulus et al (2005) did not find any significant behavioural changes in their emotion recognition task and Del-Ben et al (2012) only found an impairment in the recognition of fearful female faces. This finding provides insights into the intrinsic intentions of benzodiazepines, specifically their ability to modulate emotion recognition which likely promotes a sense of calmness and relaxation in users, diminishing fearful responses. By dampening recognition of emotional stimuli, these medications may alleviate symptoms of anxiety.

In contrast, only two studies measured the effects of antipsychotics on social cognition in healthy volunteers, and findings from these were inconsistent. Further research is therefore required to clarify effects of antipsychotics on social cognition in volunteers, especially considering the established evidence that antipsychotics impair neurocognitive performance (Singh et al., 2022). Additionally, the effect of benzodiazepines on other domains of social cognition should be established, and whether this influences individual's wellbeing.

Patient studies showed antipsychotic medication effects continue to be inconsistent across papers, with some showing improvements, and some showing no effect on social cognition performance. The studies included in the review suffered from common study design flaws including most studies failing to account for practice effects, failing to distinguish effects of medication from changes in symptoms, and failing to account for important covariates such as neurocognitive performance, education level, or age. One study was found to show a decline in social cognition after antipsychotic medication in patients with schizophrenia, with evidence of a dose-dependent response (Daros et al., 2014). However, in testing patients with bipolar disorder they failed to show a similar relationship between the antipsychotic and social cognition performance. The findings of this review did show that social cognition was consistently impaired in patients with a psychosis-related diagnosis before commencement of treatment, however there was not enough evidence to conclude if psychiatric medication then had a positive or negative effect on social cognitive performance on a long-term basis.

Neuroimaging research on the effects of antipsychotics on social cognition suggest that medication may be affecting related social cognitive brain processes. A reduced P300 ERP has been identified as a biological marker of schizophrenia (Chun et al., 2013; Mathalon et al., 2000), and Sumiyoshi et al (2009) found a P300 increase in patients with schizophrenia during a social perception task after antipsychotic administration. This P300 increase was also positively correlated with social perception performance on the task, which suggests the medication may be associated with social cognition related brain activity changes. However, only seven of 20 participants started the study drug-free, and eight participants dropped out after the baseline assessment, making it difficult to make solid conclusions. In an fMRI

study by Takahashi et al (2005) on healthy volunteers, results showed decreased BOLD responses in the limbic structure of the amygdala, and increased activations in the PFC following antipsychotic administration in healthy volunteers. Previous research shows the PFC attenuates amygdala activation during emotional processing (Banks et al., 2007) and therefore, it is possible antipsychotics are working directly on the PFC, and decreased amygdala signals are secondary to this. Behaviourally however, the authors showed minimal changes in social cognition performance. Overall, there remains little evidence that brain changes induced by medication affect social cognitive ability.

The findings from the meta-analysis in this review were not included in the published manuscript due to adding no further information to the results of the study. The meta-analysis however does highlight the heterogeneity in social cognition measures utilised in the scientific literature, as well as the diverse reporting style of results. This shows the need for more consistency in the social cognition measures that are used in mental health research and how they are reported, to allow for comparisons across studies.

2.4.2 Strengths and Weaknesses of the Review

This review was the first of its nature to establish the current literature on the effects of psychiatric medications on social cognition using a rigorous search strategy of published and unpublished work. An earlier review (Kucharska-Pietura & Mortimer, 2013) gave initial insight into the effects of antipsychotic medication on social cognitive ability, although the authors did not follow a systematic approach and their search was not as comprehensive in terms of scope, as the one presented here. This review aimed to include all psychiatric medications with sedative effects, all known terminology for social cognitive domains and measures, and all psychiatric populations in its search. However, with social cognition being a relatively new field, terminology for phenomena has been used interchangeably, creating difficulties in consensus in the literature. For example, the terms ‘emotion perception’, ‘affect recognition’, ‘affect perception’, ‘facial affect’, and ‘emotional valence’ represent the different ways that emotion processing has been discussed in the field. Examples of this can also be seen in the domain of ‘theory of mind’, which is often also referred to as ‘mentalising’ or ‘mentalizing’ dependent on country. This makes creating search terms in this area a complex issue, with the added problem that newer or novel terminology may not be included due to its relative lack of recognition, and again promotes the need for a consensus of glossary terms being used in the social cognition literature.

A strength of this review was that the relatively broad inclusion criteria established the current lack of healthy volunteer studies of antipsychotics and other sedative medications, and the deficiency of plausible animal models. Another important aspect of this review was the inclusion of neuroimaging studies in the search. This research allowed us to consider how psychiatric medication changed processing mechanisms in the brain, and to explore how these reflected changes in social cognition task performance.

Using the adapted Downs and Black Checklist (Hanney et al., 2016, Downs & Black, 1998) was also a strength of this review. The checklist allowed quality of both

randomised and non-randomised trials to be analysed. It was important to have a consistent way to rate the quality of papers in this review, and it gave us a good understanding of the multiple flaws evident in the studies. The breadth of poor-quality studies discovered in this review presents limitations in generalising the current findings. However, it also emphasises the problematic nature of study designs in this field and the need for improvements, specifically in sample sizes, randomised study approaches, and adherence to medication measures.

Another limitation of this review was exposed by the high heterogeneity in the meta-analysis that meant the results could not be interpreted meaningfully. The high heterogeneity may be due to including a small number of papers (n= 4). The inconsistencies in methodology employed by the papers in this meta-analysis, or the differences in their quality may also have influenced the heterogeneity of the findings. Additionally, studies used in the meta-analysis, like the rest of the review, involved small sample sizes and used different dosages and types of medications, suggesting these are important factors to control for in future investigations.

Due to the lack of meaningful results from the meta-analysis, results were synthesised through narrative synthesis. Despite being a common approach for analysing and synthesising data in systematic reviews, the guidance on conducting narrative synthesis is considerably limited, drawing criticism on the methodology. However, where reviews do not produce enough quantitative evidence to analyse, or are predominantly investigating qualitative attributes of papers, narrative synthesis would be the recommended approach. Weaknesses of narrative synthesis that have been described include a lack of transparency (Dixon-Woods et al., 2005) and a lack of clarity on methodology and guidance (Mays et al., 2005). However, the guidance produced by Popay et al (2006) sought to overcome these issues by providing a detailed outline of how to conduct narrative synthesis in a transparent and systematic way. By following the guidance of Popay et al (2006) this review is comprehensive and clear in the steps and processes involved in the analysis.

Another major limitation of the literature uncovered during this review was the focus on emotion processing studies and the lack of research studies investigating the other domains of social cognition. 80% of included studies explored emotion processing tasks only. The other social cognition domains of attribution bias, theory of mind, and social perception were largely ignored in the literature and meant this review was unable to clarify the impact of psychiatric medications on these domains. This is a recurrent issue in studies investigating social cognition with a clear gap in the literature surrounding the other domains. A focus on the other domains may result in innovation in targeting treatments or interventions.

An additional limitation of the papers in this review was the lack of diversity of psychiatric medications tested. The studies identified examined antipsychotics and benzodiazepines only. No studies were found that assessed effects of the many other drugs with properties, such as those in the search terms. We also did not attempt to identify research on the effects of alcohol or other non-prescription psychoactive agents that may have an impact on social cognition, such as opiates and stimulants. Although this allowed this review to be focused on the medication effects discussed, it also showed the existing gap in psychopharmacology literature available.

A final limitation of this review was that the search was conducted in 2019, three years before the publication of this thesis, and therefore these results may have excluded important recent findings in the field. Therefore, an updated database search of two databases, Medline and Embase was conducted on 03/06/2023 of papers published since the last search. This resulted in a total of 41 results. Only one result was identified through these searches that would be eligible for inclusion in this systematic review if it were to be updated. This was a conference abstract by Lee et al (2023), who found no difference in social cognition performance by patients with psychosis with less than 4 weeks of antipsychotic exposure, compared to drug-naïve patients with psychosis. Suggesting that cognitive dysfunction may be present in the early stages of psychotic disorder before antipsychotic use, and that commencing antipsychotics may have no effect on social cognition performance.

One relevant systematic review was also found during this search, by Riccardi et al (2021) titled 'Pharmacological Treatment for Social Cognition: Current Evidence.' This review included studies on patients with a schizophrenia, schizoaffective or schizophreniform disorder diagnosis, undergoing a pharmacological treatment, being measured on at least one social cognition measure. Search terms for the Riccardi et al (2021) review were not as broad or comprehensive as those in the systematic review presented in this chapter. For example, authors only included the term 'social cognition' rather than individual domain names. Riccardi et al (2021) identified 13 papers that met their eligibility criteria, six of those papers, which investigated the effects of antipsychotics on social cognition, overlapped with papers discussed in this systematic review. One paper retrieved by Riccardi et al (2021) investigated the effects of glutamic acid decarboxylase 67, and the remaining six papers all explored the relationship between oxytocin and social cognition in patients with schizophrenia. These latter papers were not included in the presented systematic review as the psychoactive drug investigated did not fall into a sedative category. Therefore, it is evident few additional studies have been conducted on the relationship between social cognition and sedative psychiatric medications since the searches conducted for this review.

2.4.3 Impact of Review

With the present review, the goal was to bridge the gaps in the literature on the effects of psychiatric drugs on social cognition. Through identifying limitations with the majority of prior studies, the review has advanced our understanding of the field, and highlighted the need for more robust research to shed light on the relationship between psychiatric drugs and social cognition, both in healthy individuals and patients.
It is noteworthy that this review has already made a contribution to the field having been cited in a systematic review and meta-analysis protocol on 'investigating the effects of pharmacological interventions on social cognition impairments in schizophrenia' (Yamada et al., 2022), and recognised as an important study by others (Braak et al., 2022; Zetsen et al., 2022). It is hoped this review will continue to spur on research in this area, by drawing attention to the need for studies that account for practice effects and include diverse domains of social cognition.

Chapter 3: Method

This chapter will describe in detail the method undertaken for the experimental studies outlined in this thesis. The aims of this component of the PhD were to determine the effects of antipsychotic medication on social cognition, in patients with a schizophrenia-spectrum disorder. A flowchart of how the two experimental studies in this thesis were implemented is presented in **Figure 2.** The method chapter will detail the procedures of each study.

3.1 Introduction

Study 1: Cross-sectional Study – 'Social Cognition in Patients with Schizophrenia and Human Volunteers'

This study aimed to confirm if deficits exist across all the domains of social cognition in patients with schizophrenia compared to healthy volunteers. The study also aimed to explore if antipsychotic dose or duration, or schizophrenia symptoms were associated with social cognition, and whether there was a relationship between social cognition domains and social functioning.

Study 2: Longitudinal Study – 'RCT of the Effects of Antipsychotic Reduction/Discontinuation vs. Maintenance on Social Cognition in Patients with Schizophrenia.'

This study aimed to determine whether group allocation predicted changes in social cognition outcomes over time, whilst controlling for potential predictors such as symptom or neurocognition changes. The study also aimed to identify if changes in social cognition predicted changes in social functioning, and whether antipsychotic dose changes were related to social cognition changes.

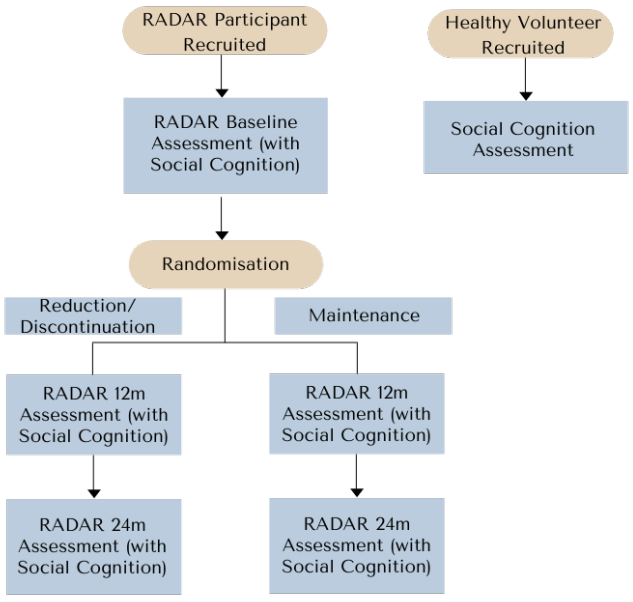

Figure 2. Flowchart demonstrating the process of the studies in this thesis.

3.2 Ethical Considerations

Specific ethical issues for participants were considered in undertaking these research studies. Patients with schizophrenia were recruited for the cross-sectional study and followed up in the longitudinal study, healthy volunteers took part in the cross-sectional study only. The main ethical considerations and how they were addressed are in **Table 6**.

Table 6.
Ethical Considerations When Undertaking Research Studies in This Thesis.

Ethical Concern	Solution
Voluntary Participation	● Participants were invited to be in the study on a voluntary basis. ● Participants had the right to withdraw from the study at any time, with no negative consequences to themselves.
Consent & Capacity	● Participants were provided with an information sheet. ● A capacity assessment was undertaken by the researcher before consent was given. **Patients with Schizophrenia-spectrum Disorders Only** ● Participants were encouraged to discuss the study with their family, friends, and clinicians. ● Researchers visited the participant to discuss the information sheet further, if requested.
Confidentiality and Anonymity	● Participants were given a participant ID on entering the study, so that their study data remained confidential. ● All personal data was processed according to General Data Protection Regulation (GDPR) and the UK Data Protection Act (DPA, 2018; GDPR, 2018).
Potential for Harm	● If a participant became fatigued during the social cognition tasks, they were given the option by the researchers to stop, or to take a break. ● If a participant became anxious or concerned about their performance on the social cognition tasks they were reassured by researchers. They were also given the option to stop completing the tasks, or to take a short break if they wished to do so. **Patients with Schizophrenia-spectrum Disorders Only** ● When entering the RADAR study, the risk of psychotic relapse was discussed with participants. This risk was minimised through study protocol considerations. ● Participants randomised to the reduction arm were seen or spoken to by a psychiatrist every two months during their reduction. ● At the initial appointment with their psychiatrist, participants in the reduction arm drew up an agreed care plan with their clinician. ● Electronic medical notes for all RADAR participants were checked every two months in order to identify any adverse or serious adverse events.
Monitoring	● When entering the study participants were made aware that data collected during the study may be reviewed by responsible individuals from UCL for monitoring or audit purposes.

	Patients with Schizophrenia-spectrum Disorders Only ● Data collected during the study could also be reviewed by responsible individuals from MHRA for monitoring or audit purposes.
Data Storage	**Patients with Schizophrenia-spectrum Disorders Only** ● Participants consented to their hard-copy data being kept in accordance with the Data Protection Act (2018) for at least five years. **Healthy Volunteers Only** ● Participants consented to their anonymised research data being used for future research until 1st October 2025. ● Participants were made aware that their questionnaire data would be digitised, and hard-copy data would be destroyed by 1st October 2020.
Communicating Results	● Participants had the option to consent to receiving copies of any dissemination regarding their study data.

3.3 Cross-Sectional Study: Social Cognition in Patients with Schizophrenia and Human Volunteers

This section will describe the aims, hypothesis, study design, study set-up, and procedures of the cross-sectional study.

3.3.1 Aims & Hypotheses

Aim 1: Determine if there are significant differences in social cognitive ability across domains, in patients with schizophrenia compared to healthy volunteers.

Hypothesis 1: There are significant differences in social cognitive ability, across domains, in patients with schizophrenia compared to healthy volunteers, with patients performing worse.

Aim 2: Determine if symptoms of schizophrenia, and AP usage can significantly predict social cognition outcomes, across domains.

Hypothesis 2: Symptoms of schizophrenia, and AP usage (dose and duration) will significantly predict social cognition outcomes, across domains. Higher symptom scores, and higher antipsychotic dosages and duration will result in poorer social cognition outcomes.

Aim 3: Determine if social cognitive domain scores can predict social functioning outcomes in patients with schizophrenia.

Hypothesis 3: Social cognitive domain scores will significantly predict social functioning outcome in patients with schizophrenia, with poorer social cognition scores resulting in poorer social functioning outcomes.

3.3.2 Study Design

A cross-sectional study design was utilised, incorporating baseline patient data collected via the RADAR study, and healthy volunteer data, collected separately. In

order to collect social cognition data from the RADAR study, I created an assessment pack. It included the six social cognition questionnaires listed in the 'measures' section of this chapter (section 3.5.1) The assessment pack was sent for ethical approval via a RADAR study amendment, through the Integrated Research Application System (IRAS), and it was approved in April 2018. The social cognition measures were then added as an optional component of the baseline RADAR assessment for participants, with 12- and 24- month follow-up assessments also added (for the longitudinal study set-up, see section 3.4.3 of this chapter).

3.3.3 Study Set-Up

In order to assess the differences between social cognitive ability in patients with schizophrenia, and healthy volunteers, I was required to set-up a separate study to collect data from healthy volunteers. This study was named 'Cognition in Human Volunteers'.

For the 'Cognition in Human Volunteers' study I created an assessment pack that included the social cognition measures, a neurocognition measure and a sociodemographic questionnaire, detailed information can be seen in the 'measures' (section 3.5 of this chapter). As part of the 'Cognition in Human Volunteers' study I also created additional documentation, including a long-form information sheet, screening form, and consent form. Copies of these documents can be viewed in Appendix C of the thesis.

Sections below (ethical approval, inclusion/exclusion criteria, sampling and recruitment, and procedure) outline the process that was utilised for the healthy volunteer participants in the 'Cognition in Human Volunteers' study. The same details are given for the RADAR participants who provided data for the cross-sectional study in (section 3.4 of this chapter), in order to also describe their participation in the longitudinal study. Below sections, 'sample size calculation' and 'data processing', describe processes in the cross-sectional study related to both sets of participants.

3.3.3.1 Ethical Approval

In order to gain ethical approval for the 'Cognition in Human Volunteers' study, procedural guidelines set out by University College London (UCL) were followed. Firstly, the study was registered with the data protection officer at UCL. Following this, a risk assessment was conducted by myself and my primary supervisor, Professor Joanna Moncrieff. The study was identified through this assessment as low-risk, and therefore a low-risk ethics application form was completed, which was co-signed by my primary supervisor (JM), and by my head of department (Psychiatry department at UCL), Professor David Osborn. Ethical approval was obtained in July 2019 from the UCL Research Ethics Committee with reference number 14171/001 for the 'Cognition in Human Volunteers' study.

Ethical approval steps for the RADAR trial are set out in section 3.4.3.1 of this chapter, and the published study protocol (Moncrieff et al., 2019).

3.3.3.2 Sample Size Calculation

In order to establish the number of participants required to perform a cross-sectional analysis between patients with a schizophrenia-spectrum disorder and healthy volunteers, a sample size calculation was conducted. The statistical power analysis was performed for sample size estimation, based on a standard deviation (SD) of 2.9 from published data by Charernboon and Patumanond (2017) comparing patients with schizophrenia to healthy volunteers on an emotional processing measure. The effect size in this study was 0.81 and considered large using Cohen (1988) criteria. With an alpha = 0.05, power = 0.90, and SD = 2.9, the projected sample size needed was N= 74. Thus, our proposed sample size was N= 74, with each group requiring N= 37 (schizophrenia-spectrum disorder patients, and healthy volunteers) (Rosner, 2011).

A larger sample of patients with schizophrenia spectrum disorders was required for the longitudinal study in order to conduct linear mixed model analysis (see section 3.4.3.2 of this chapter for sample size calculation). Therefore, the aim was to recruit a larger sample of patients with schizophrenia-spectrum disorder than was required for the cross-sectional analysis (e.g., n= >66).

3.3.4 Procedure

3.3.4.1 Recruitment

Recruitment of patient participants from the RADAR trial is detailed in section 3.4.4, of this chapter.

Recruitment materials for the 'Cognition in Human Volunteers' study were targeted to a wide population in order to fulfil the required sample size, however at the mid-point of recruitment purposive sampling was used to ensure diversity in the sample in age, gender, and ethnicity. Social media posts pre-approved via ethics were used to recruit, on 'Twitter' to access a varied audience. An advertising poster (Appendix C) was also used to recruit to the study, which was put up in the Division of Psychiatry university department at UCL, East London libraries (Canary Wharf and Poplar Idea stores), and in two blocks of flats in Tower Hamlets, London (after seeking permission from the required building managers). In addition to this I also recruited via referrals from personal and professional connections. All healthy volunteer participants were recruited from August 2019-March 2020, and details of the recruitment figures can be seen in **Table 7**.

Table 7.
Recruitment Figures for 'Cognition in Human Volunteers' Study.

Recruitment Method	Number of Recruits N (%)
Via Personal and Professional Connections	15 (40.5)
Snowball Sampling	9 (24.3)
Poster Recruitment	12 (32.4)
Twitter	1 (2.8)

3.3.4.2 Inclusion and Exclusion Criteria

To take part in the Cognition in Human Volunteers study all healthy volunteer participants were required to meet the eligibility criteria described below in **Table 8**. Criteria were confirmed by participants through self-report.

Table 8.
Inclusion and Exclusion Criteria for 'Cognition in Human Volunteers' Study

Inclusion Criteria	Exclusion Criteria
Participant is aged 18 years or older	Participant is not fluent in English Language
Participant has no current, and does not have a history of psychiatric diagnosis	Participant has a disability that prevents them from completing the measures included in the study (e.g., visual impairment)
Participant has no family history of serious mental illness (Manic Depressive Disorder, Bipolar Disorder, Schizophrenia-spectrum Disorder)	Participant is currently taking psychiatric medication (including anxiolytics, antipsychotics, tricyclic antidepressants, or mood stabilisers)
	Participant has had a diagnosis of a neurological disorder or has suffered any kind of head injury or systemic disease that might affect the central nervous system.

All patients recruited to the baseline component of RADAR met the eligibility criteria set out in the study protocol (Moncrieff et al., 2019). Details of this can be seen in section 3.4.4.1 of this chapter.

3.3.4.3 Screening, Capacity and Consent

Following initial contact between the researcher and the healthy volunteer, the researcher went through the screening form with the potential participant to ensure they met all eligibility criteria. Following this, the potential participant was provided with the information sheet which detailed the purpose and process of the study, whilst also highlighting the risks and benefits of taking part, how the findings from the research would be disseminated, and the procedure for withdrawing from the study. If, after reading the information sheet, the participant was still interested in taking part in the study, the researcher would assess their capacity recording their decision on a capacity assessment form.

Once eligibility and capacity were confirmed, the researcher and participant would read over the consent form together. The participant would initial each of the 19 points in the consent form that they agreed to. If the participant agreed to all 19 points, they would be asked to print their name, sign, and date the form to confirm their consent was given. The researcher would also then print their name, sign, and date the form. The participants could also choose to provide their contact details if they wished to be contacted about other UCL studies in the future, or if they wished to be informed of the results from this study, these were optional points. Participants were provided with a copy of the consent to take with them when they left the assessment.

If for any reason the participant did not give consent to any of the points on the form, they were thanked for their time and told that the assessment could go no further. Participants who completed the form were assigned a participant ID. The consent form was then scanned into the computer and saved into an encrypted drive. The

hard copy of the consent form was kept for the duration of the study in a secured filing cabinet in the Department of Psychiatry, Maple House, UCL. Following the closure date of the study (July 2020), the hard-copy consent forms were destroyed.

3.3.5 Data Collection

After consent, the participant was invited to take part in the assessment. For this study, all assessments took place straight after consent was given. Measures included in the assessment can be seen in section 3.5 of this chapter. The assessment took place in either the participants' home or in a private room on public premises (e.g., library room). The researcher guided the participant through the assessment pack which took on average 45 minutes. On each page of the assessment pack the participant ID was written, to ensure data could be traced back to the correct participant if they wished to withdraw at a later stage.

Following completion of the assessment, data were entered into an encrypted database. Hard-copy assessment packs were stored in the same room as the consent forms, in a separate filing cabinet at the Department of Psychiatry, UCL. The hard-copy assessment packs were destroyed following the study closure date (July 2020).

On completion of the assessment, participants were reimbursed with £10 cash for their time and participation in the study.

3.3.6 Data Processing

Once data collection was complete, I, as a trained researcher, checked and cleaned all data entries, and ensured it was in the correct format for analysis. To ensure interrater reliability, I was assisted by a Plymouth University MSc student to separately score the AIHQ items 1 and 5 for each scenario, and a kappa score was calculated. Following this, analysis of the data took place in R (RCoreTeam, 2021), following the data analysis plan (section 3.9.3 of this chapter). The following data packages were used in R for cross-sectional data analysis 'stats' (RCoreTeam., 2017), 'chlorpromazineR' (Brown et al., 2021), 'MICE' (van Buuren et al., 2021), 'tidyverse' (Wickham et al., 2022), and 'car' (Fox et al., 2022).

3.4 Longitudinal Study – 'RCT of the effects of Antipsychotic Reduction/Discontinuation vs. Maintenance on Social Cognition in Patients with Schizophrenia.'

This section will describe the aims, hypothesis, study design, study set-up, and procedures for the longitudinal study.

3.4.1 Aims & Hypotheses

Aim 1: Determine if there are significant differences in social cognitive ability across domains, in patients in the reduction/discontinuation group vs. the maintenance group at baseline.

Hypothesis 1: There are no significant differences in social cognitive ability in patients with schizophrenia in the reduction/discontinuation group compared to the maintenance group at baseline.

Aim 2:
To evaluate:

- Whether *changes* in social cognition domains between timepoints were significantly different between groups.
- Whether changes in social cognition domains between timepoints were significantly different, *across* both groups. To examine whether there are changes in social cognition, irrespective of group allocation, to understand whether there are general fluctuations in social cognition over time.
- To test for differences in social cognition change between groups and over time after controlling for potential predictors of social cognition change across groups and any relevant variables that differ between groups.
- Whether changes in social cognition are associated with changes in antipsychotic dose

Hypothesis 2: There are significant improvements in social cognition in patients with schizophrenia in the reduction/discontinuation group compared to the maintenance group, which are related to antipsychotic reduction. There are improvements between timepoints on all measures of social cognition across groups.

Aim 3: To determine whether changes in social cognition were related to changes in social functioning performance, and to identify other potential predictors of social functioning change.

Hypothesis 3: Social functioning performance changes are related to changes in social cognition performance, with improvements in social functioning reflecting improvements in social cognition.

3.4.2 Study Design

In order to investigate the relationship between reducing or discontinuing antipsychotic medication and social cognition in patients with a schizophrenia spectrum disorder, the social cognition assessment was incorporated into the research design of the RADAR trial.

RADAR was a randomised controlled trial of an antipsychotic maintenance treatment vs. a gradual antipsychotic reduction/discontinuation in patients with a schizophrenia-spectrum disorder. Data being used in this thesis that was collected as part of the RADAR assessments outside of the social cognition assessment pack is listed in the 'Measures' part of this chapter (section 3.5).

Patients in this study were recruited and took part via the procedure outlined in section 3.4.4 of this chapter. Patients who took part in the cross-sectional and the longitudinal study of this thesis completed the social cognition assessment pack during their baseline RADAR assessment and were followed up at 12- and 24-month assessments, where possible. The social cognitive component of the RADAR trial

was not added until the second year of trial recruitment and was not implemented at all sites. The social cognition measures were added to the RADAR assessments in May 2018. The social cognition questionnaires that make up the assessment pack are listed below in the 'Measures' section 3.5 of this chapter.

3.4.3 Study Set-Up

3.4.3.1 Ethical Approval

Ethical approval for the RADAR trial was obtained in October 2016 from the Brent Research Ethics Committee with the reference number 16/LO/1507, social cognition measures were added to the RADAR trial via a substantial amendment. The amendment went through HRA, MHRA, and Research Ethics Committee (REC) review and was approved on 30/04/2018.

3.4.3.2 Sample Size

The initial overall target sample size of the RADAR trial was 402 based on relapse difference, however this was revised to 218 based on the primary outcome of social functioning.

The target sample for the social cognition component of this study was based on the literature around the emotion processing measure, the Bell and Lysaker Emotion Recognition Test (BLERT). Taking a distribution-based approach, using the standard error of measurement, I calculated a minimum clinically important difference of 2.19 (Pinkham et al., 2016; Revicki et al., 2008). Using a conventional alpha of 5% (two-sided) and taking a SD of 3.62, based on the literature (Gordon et al., 2018), a sample size of 58 participants (28 per arm) was deemed necessary to provide 90% power (Sakpal., 2010). Considering a dropout rate of 15% (Moncrieff et al., 2019) a target sample size of 66 participants (33 per arm) was used.

3.4.4 Procedure

3.4.4.1 Participants and Eligibility Criteria

In the RADAR study, participants with a range of schizophrenia-spectrum diagnoses (F20-F29 in ICD 10; WHO, 1993) were included. Throughout this thesis, when referring to patient participants in this sub-study, the terms 'patients with schizophrenia' and 'patients with a schizophrenia-spectrum disorder' will be used interchangeably, unless explicitly stated otherwise. Including participants with schizophrenia-spectrum diagnoses offered insights into a broad clinical population, whilst also addressing the under-representation of certain diagnoses due to their lower prevalence in research. Moreover, this approach acknowledged the complexities observed in clinical settings, where shifts between diagnostic categories are not uncommon (O'Connor et al., 2022; Baca-Garcia et al., 2007). However, it is important to note that including multiple diagnoses may have limited the generalisability of the study's findings and posed challenges in determining the specific implications for individual disorders.

Eligibility criteria required for patients in the RADAR trial are listed below in **Table 9**.

Table 9.
Inclusion and Exclusion Criteria for Patients in the RADAR Study.

Inclusion Criteria	Exclusion Criteria
have a diagnosis of schizophrenia, schizoaffective disorder, delusional disorder, or other non-affective psychosis (F20-F29 in ICD 10)	lacking capacity to consent to the trial
have had more than one previous psychotic episode or exacerbation, or a single episode lasting more than one year	insufficient command of spoken English to understand the trial procedures
currently taking antipsychotic medication	subject to a section of the Mental Health Act that included a requirement to take antipsychotic medication
over the age of eighteen	their clinician considered them a serious risk of harm to themselves or others
	they were admitted to hospital or treated by the home treatment team or crisis team in the last month
	involved in any other investigational medicinal product (IMP) trial
	they were a pregnant woman or a breastfeeding woman
	they had a contraindication to antipsychotic medication

3.4.4.2 Sampling and Recruitment

The central site for conducting the RADAR trial was NELFT, and an additional 18 NHS trusts across the UK were enrolled to recruit for RADAR and conduct assessments in their locations. The following RADAR trial sites took part in the social cognition sub-study: NELFT, ELFT, BEH, C&I, CNWL, KMPT, Livewell Southwest, SPFT, OHFT, Southern NHS Health Foundation Trust, and GHC.

In order to identify potential participants to take part in the RADAR trial, psychiatrists in secondary mental health services were approached for their confirmation of eligibility regarding patients on their caseload fitting the requirements of the research. Once eligibility was formally confirmed researchers were introduced to potential participants through their clinical team (psychiatrist or care coordinator), unless the patient had given consent for research contact at a previous point in their care and this was recorded on their electronic record, which meant they could be contacted directly.

If potential participants were interested in hearing more about the study, they were given a long-form and a short-form information sheet about the research. Their eligibility to participate in the study was also assessed by a researcher through self-report by the potential participant and confirmatory checking of information via the patients electronic NHS record, this eligibility was recorded on a screening form. Any patients who then wanted to be involved in the study were assessed on their capacity to understand and take part in the research.

3.4.4.3 Informed Consent and Capacity

Capacity was judged by researchers throughout the recruitment process and during the trial, with a capacity assessment form being completed at the baseline appointment. The form was used to formally assess if the participant could retain information, weigh up their decision, and if they could make an informed choice to take part in the study. If a participant was deemed to have capacity to partake in the study, written informed consent was obtained from them prior to their participation. Each point on the consent form that a patient agreed to, they were required to write their initials next to. To take part in RADAR all points on the consent form required agreement. If participants agreed to take part in the study, they were required to print and sign their name, and date the form. The researcher would then print their name, sign, and date the same consent form. All participants were then given a copy of the consent form. Participants enrolled could withdraw consent at any time or withdraw consent for the intervention only – data for these participants was still used in analysis unless they requested otherwise.

3.4.4.4 Baseline Assessment

Participants took part in the RADAR baseline assessment with a researcher, with the assessment taking place either in their own home, or on NHS premises. Baseline assessments lasted between 1.5-2 hours, with social cognition measures being completed as the final component of the study visit. Where needed, assessments were split over two or three visits, to ensure participants were not experiencing over-burden or fatigue. Participants were free to withdraw from the assessment at any time, or to choose not to answer any of the questions presented to them. Following the assessment, participants were given £20 to thank them for their time and participation in the study.

Following the assessment, data entry for the RADAR baseline questionnaire was completed via the Sealed Envelope Redpill online system (SealedEnvelope., 2021). Redpill is a secure online database for entering and storing data on subjects from clinical trials. Once data entry was complete an unblinded researcher was informed so that randomisation could be completed. Baseline data has been utilised in the cross-sectional and longitudinal studies in this thesis. Data entry for the social cognition assessment pack was completed in a separate encrypted database using the same participant ID as assigned in the RADAR trial, in order to match data in future analysis.

Full procedures for the RADAR trial can be seen in the trial protocol (Moncrieff et al., 2019).

3.5 Measures

In the ‘Cognition in Healthy Volunteers’ healthy volunteer study participants were required to complete the social cognition, neurocognition, and demographics measures. In the RADAR trial, participants completed the social cognition, neurocognition, and demographic measures, as well as additional outcome measures including the social functioning scale (SFS), the medication adherence

report scale (MARS-5), and the positive and negative symptom scale (PANSS). All measures for patients were collected as part of the standard RADAR assessments.

3.5.1 Social Cognition Measures

The social cognitive measures used in this thesis were chosen due to the basis of their recommended use in studies of patients with schizophrenia by researchers in the Social Cognition Psychometric Evaluation (SCOPE) studies, who aim to validate measures for use in clinical trials of schizophrenia (Pinkham et al., 2018). Where measures veer from those recommended by Pinkham et al (2018) it is due to no known measurement of that domain that is adequate at this time, or in the case of emotional intelligence due to costs and training required to administer the recommended measure.

3.5.1.1 Attribution Bias: The Ambiguous Intentions Hostility Questionnaire (AIHQ; (Combs et al., 2007))

The AIHQ provides a measure of attributional style by assessing participants' responses to ambiguous social situations. The AIHQ was developed to examine whether social cognitive biases are more likely to result in hostile behaviour in paranoid individuals and has been validated in patients with schizophrenia.

The AIHQ consists of 15 short vignettes that reflect negative outcomes varying in intentionality (intentional, accidental, and ambiguous intentions). In the assessment pack created for this thesis only the five vignettes reflecting ambiguous intentions were used. This is because the ambiguous scenarios have been found to have a stronger relationship to paranoia and hostility than intentional and accidental situations when evaluating the psychometric properties of the AIHQ (Pinkham et al., 2014). This has resulted in only the ambiguous scenarios being used in the majority of research in patients with schizophrenia.

The AIHQ procedure is as follows: the AIHQ is introduced by a researcher instructing the participant to read each vignette and imagine it happening to them. The participant reads the scenario (e.g., "You walk past a bunch of teenagers at a shopping centre, and you hear them start to laugh"), and they are then required to give a written response to the question 'why did the person/s act that way towards you'. Two independent raters subsequently code the written response (from 1 – Accident to 5 – Unrealistically Hostile) in order to create a 'hostility bias (HB)' variable score. The interrater reliability for the hostility bias was $\kappa = 0.82$ at baseline, $\kappa = 0.85$ at 12m, and $\kappa = 0.81$ at 24m. The participant was then required to rate on Likert scales, whether the person/s did that to them on purpose (1- definitely no to 6 – definitely yes), how angry it made them feel (1 – not at all angry to 5 – very angry), and how much they would blame the other person/s (1 – not at all to 5 – very much). Finally, the participant gave a written response to the question "how would you respond to that situation?" Independent raters computed an 'aggression bias (AB)' variable score to this final question (from 1 – not at all aggressive to 5 – very aggressive). The interrater reliability score for the aggression bias was $\kappa = 0.78$ at baseline, $\kappa = 0.82$ at 12m, and $\kappa = 0.83$ at 24m.
To calculate a total Blame Score (BS) the average score was calculated for each vignette on all Likert scale items (purpose, anger, and blame), with a score for each

vignette between 1-5. Then each vignette score was summed and averaged for an overall total mean score (AIHQ-BS range 1-5). Thus, higher scores for the AIHQ-HB, AIHQ-AB, and the AIHQ-BS indicate greater social cognitive bias, and higher hostility, aggression, and blame of others.

3.5.1.2 Social Perception: The Social Attribution Task Multiple-Choice and The Social Attribution Task Multiple-Choice II (SAT-MC and SAT-MC II (Johannesen et al., 2018; Klin & Jones, 2006))

The SAT-MC/SAT-MC II are both based on the social attribution task (SAT) developed by Heider and Simmel (1944). The researchers initially created the SAT as a silent animation for experiments involving vision and perception. The SAT uses the visual cues of simple geometric shapes (triangles, rectangle, and a circle) presented monochromatically. Following the use of SAT in clinical population studies, limitations were identified concerning the measures reliance on verbal communication, and the rater errors associated with open-response tests. This resulted in the adaptation of the measure to include multiple-choice response scoring by Klin and Jones (2006). The SAT-MC was then further developed for use by including an alternative measure, the SAT-MC II (Johannesen et al., 2013). The aim of including the SAT-MC II in trials was to extinguish potential practice effects. The SAT-MC II follows a similar format to the SAT-MC, with geometric shapes displaying a new social scenario for participants to interpret.

The procedure for the SAT-MC is as follows: the SAT-MC consists of a 64-second animation of a silent social drama, enacted by a small triangle, large triangle, and a small circle. The animation is shown to participants on an electronic device twice in its entirety, then once more with pauses for questions on the relevant part of the video. The questions are read-aloud by an embedded recorded voice, and they are displayed in text format on the screen, alongside 4 multiple-choice answers (one describing the action with correct emotional intent, two describing the action with incorrect emotional intent, and one describing object motion without emotional intent). The participant is required to verbalise their answer to the researcher who records their score. In total, 19 questions are asked with possible total scores ranging from 0-19. A score of ‘11’ has been established as a cut-off for impairment based on distributions observed in schizophrenia (Bell et al., 2010). The SAT-MC-II consists of a 64-second animation depicting a silent social drama with geometric shapes, an oval, a rectangle, and a small triangle. The procedure remains the same as the SAT-MC. The social drama enacted by the shapes was changed from the SAT-MC by object motion. The SAT-MC II also has 19 questions with scores ranging from 0-19.

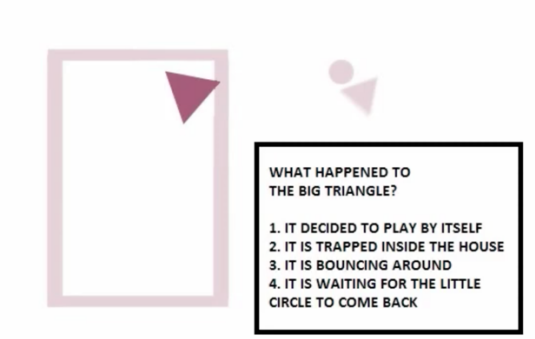

Figure 3. Sample items from the SAT-MC (Klin and Jones, 2006)

After the introduction of remote assessments (during Covid-19), participants were sent a private YouTube link to the relevant video for the time-point they were completing, depicting either the SAT-MC or SAT-MC II animation. They were then required to view the video whilst on the phone/video-conferencing software to the researcher and verbalising their answers to each question for the researcher to record.

3.5.1.3 Emotional Intelligence: Trait Emotional Intelligence-Short Form (TEIQue-SF (Petrides, 2009))

The TEIQue-SF is an adaptation of the full TEIQue (Petrides, 2001) and has been recommended as an appropriate assessment of trait emotional intelligence in circumstances where resources are limited. The use of the TEIQue-SF in this study was decided because its free of charge to academic researchers, there is no required training required for its administration, and because it can be completed in under five minutes. As the social cognition assessment pack was added to RADAR after the trial had been actively recruiting participants for one year there was sufficient insight into the average baseline assessment times when considering measures to add. Due to the relatively long assessments (~1.5 hrs) the most important requirements were for the social cognition measures to be easy to understand and non-demanding, and as such the TEIQue-SF fit into these specifications well.

The procedure for the TEIQue-SF is as follows: the TEIQue-SF is a self-report measure requiring participants to score themselves on facets of global trait emotional intelligence. The form consists of 30 questions (e.g., “I’m usually able to influence the way other people feel”, “I find it difficult to regulate my emotions”) and is derived from the full form of the TEIQue. Based on correlations between facets on the full form, the short form questions represent two items from each of the 15 facets. On each item participants are required to rate themselves on a scale of 1 (Completely Disagree) to 7 (Completely Agree). Items [2, 4, 5, 7, 8, 10, 12, 13, 14, 16, 18, 22, 25, 26, and 28] are reverse scored, all items are then summed and divided by the total number of items to produce a global trait EI score. The version (v.1.50) used in this research is available, free of charge from psychometriclab.com.

3.5.1.4 Empathy: Empathy Quotient Short Form (EQ-SF (Wakabayashi et al., 2006))

The EQ-SF used in this social cognition assessment pack is a shorter version of the EQ originally developed by Simon Baron-Cohen and Sally Wheelwright at the Autism Research Centre, University of Cambridge (Baron-Cohen & Wheelwright, 2004). The EQ was created as a response to the lack of measures that existed at the time to measure empathy explicitly. The EQ was designed with the intention of measuring the empathising-systemising theory in adults of normal intelligence. The theory postulates that abilities in both empathetic thinking and systematic thinking can be evaluated to create a 'brain type' profile. Baron-Cohen suggested that individuals with below-average empathy, and average or above-average systemising scores were more likely to experience Autism and Asperger syndrome, leading the measure to be used as a diagnostic identifier in research (Baron-Cohen, 2009). The original EQ has been translated and validated in many languages other than English and is used across clinical research, including in patients experiencing psychosis (Wakabayashi et al., 2006).

The procedure for the EQ-SF is as follows: The EQ-SF used in this assessment consists of 15 questions, and has been shown to have good psychometric properties (Wakabayashi et al., 2006). Responses to each question are given on a 4-point Likert scale (completely disagree, slightly disagree, slightly agree, completely agree) in a forced-choice format. Approximately half of the items were designed to extract a 'disagree' response and half to produce an 'agree' response in order to avoid response bias. The responses were scored according to a key, with items 1-5, 9, and 15 scoring 2 for 'completely disagree' answers, scoring 1 for 'slightly disagree' answers, and scoring 0 for agree options, and items 6-8, and 10-14 scoring2 for 'completely agree' answers, scoring 1 for 'slightly agree' answers, and scoring 0 for disagree options. All scores were summed to produce a total score, with higher scores indicating higher overall empathy. The EQ-SF is available, from www.autismresearchcentre.com.

3.5.1.5 Emotion Processing: Bell and Lysaker Emotion Recognition Test (BLERT (Bell et al., 1997))

Emotion recognition deficits have been a consistent feature associated with patients with schizophrenia, dating back to the times of Kraepelin (Jablensky et al., 1993). Research into emotion recognition largely relies on the Ekman facial action coding system (FACS) where the researcher proposed seven emotional expressions universal to humans (Ekman, 2003). Bell et al (1997) developed the Bell and Lysaker Emotion Recognition Test (BLERT) as a measure of emotion processing in patients with schizophrenia. The task examines the participants' audio-visual affect recognition skills to classify the seven emotional states set out by Ekman (fear, disgust, anger, sadness, happiness, surprise, and no emotion). Using this stimulus was thought to be more enriching than other available methods for measuring emotion recognition (such as stimulus cards or slides), and a more realistic task to situate participants in a real-world scenario.

The procedure for the BLERT is as follows: The video displays an actor's upper torso and face as they present one of three monologues aloud whilst visibly displaying a certain emotion. The three monologues are:

Monologue 1: "*I just received my job rating from my supervisor. He called me into his office and gave me a rating of adequate. He told me that I haven't made any serious mistakes lately.*"

Monologue 2: *"Our workload on the job has sure increased. Did you hear?... We're going to be asked to put in overtime this week. The supervisor says that this is a chance for our department to look good."*

Monologue 3: *"I heard that I'm being transferred to another department next week. I know some of the people there. My supervisor says that it might be permanent."*

The participant is required to use the visual cues from the actor's facial expressions and the audio clues from the actor's voice to determine which emotion is being most prominently displayed. A total of 21 (10 second) vignettes are shown with a predetermined combination of monologues. After each vignette is displayed the video is paused and the participant asked to select an emotion from the list. If they find the decision difficult, they are prompted to go with their gut feeling. The researcher scores the questionnaire on the basis of correct vs. incorrect answers. Total correct scores are recorded (scores ranging 0-21), as well as total correct positive emotion identifications (happiness and surprise, scores ranging 0-6), and total correct negative emotion identifications (fear and sadness, scores ranging 0-6). Higher scores indicate better emotion recognition.

After the introduction of remote assessments (during Covid-19), participants were sent a private YouTube link to the video. They were then required to view the video whilst on the phone/video-conferencing software to the researcher and verbalise their answers for the researcher to record.

3.5.1.6 ToM: Hinting Task (Corcoran et al., 1995)

Before the creation of the Hinting task by (Corcoran et al., 1995) there were no studies investigating theory of mind abilities in patients with schizophrenia. Therefore, on the assumption of Frith's model indicating patients with 'passivity symptoms' (e.g., delusions of control, thought insertion, and second person auditory hallucinations) were less likely to be able to monitor the intentions of others, the authors designed the measure to investigate simple inference skills (Frith, 1995).

Pinkham et al (2016) considered the Hinting task one of the strongest performing measures with adequate test-retest reliability, small practice effects, and significant differences between patient and healthy volunteers' ability. The task is considered good for use in clinical trials due to the speed of administration and being generally liked by patients. Pinkham et al (2016) also failed to find evidence of ceiling effects, although these have been evident in other trials, (Davidson et al., 2018; Klein et al., 2020).

The procedure for the hinting task is as follows: the hinting task examines the participant's ability to infer the true intent of a passage of indirect speech. Interactions between two characters are played out in ten different short scenarios, at the end of the speech one of the characters will drop a hint and the participant is asked what they really meant by that. If the first response by the participant is inaccurate, a second hint is given through another sentence of indirect speech, allowing participants to have another chance at answering the question. If the participant gets the answer first time they score two points, if they answer after the second hint they get one point, and if they fail to get a correct answer, they score zero and the researcher moves on to the next scenario. Total scores range from 0-20 with higher scores indicating more accurate responses.

3.5.2 Demographics

Demographic data collected included age, gender, ethnicity, first-language, country of birth, highest education level, occupation status, recreational drug use, and alcohol consumption for all participants. In the 'Cognition in Healthy Volunteers' study the participants were also required to record any prescribed medications taken for the last six months, for RADAR patients all medication use was recorded in the Client Service Receipt Inventory at baseline. In follow-up assessments for RADAR, patient data regarding medication was recorded from NHS electronic records by unblinded researchers.

3.5.3 Neurocognition Measure

3.5.3.1 Digit Span Forwards/Backwards -a sub-test of the Wechsler Adult Intelligence Scale (WAI– IV (Wechsler, 1958))

The Digit Span is a cognitive measure of attention and executive function. This task requires participants to repeat digits spoken to them by a researcher. Each set of digits (sets A-G) consists of two attempts at digits of a certain length. The digits increase in length at every set step (A > B > C). Participants continue until they get two attempts wrong in a set. Backwards Digit Span requires participants to complete the same task, however they repeat the numbers back to the researcher in reverse order. The scores for the Digit Span forwards and the Digit Span backwards tasks are summed to create a total Digit Span score. Higher total scores indicate better neurocognitive functioning.

3.5.4 Additional Outcomes (RADAR patients only)

3.5.4.1 Social Functioning Scale (SFS (Birchwood et al., 1990))

This questionnaire measures social activity and occupation by self-report. The questionnaire was used because of its specific focus on functioning, good reliability, and the ability to distinguish between different types of antipsychotic treatment in its analysis (Moncrieff et al., 2019; Long et al., 2022). This measure was the primary outcome for the RADAR trial.

The measure is scored on seven constructs of social functioning (engagement/withdrawal, interpersonal communication, independence (performance), recreation, prosocial, independence (competence), and (occupation/employment). Each of the seven constructs is summed depending on scoring for each relevant item in the questionnaire. The totals for each section were summed to create an overall social functioning score (scores ranging from 0-223), means of the summed scores were then calculated. Higher scale scores indicate higher levels of functioning.

3.5.4.2 The Positive and Negative Symptom Scale (PANSS (Kay et al., 1987))

This is a widely used clinical measure in research settings to give psychiatric ratings on three subscales: positive (score range 7-49), negative (score range 7 – 49) and general symptoms (score range 16 – 112) of psychosis. Each item is rated on a 7-point Likert scale (1= absent, 2= minimal, 3= mild, 4= moderate, 5= moderate severe, 6= severe, and 7= extreme). Ratings are based on a semi-structured interview with the participant, based on their last week. Participants are given total scores. Severity categories in this thesis were classified based on Leucht et al., (2005): mildly ill (<58), moderately ill (58-74), markedly ill (75-95), and severely ill (>96).

3.5.4.3 Medication Adherence Report Scale (MARS-5 (Chan et al., 2020))

This questionnaire is a self-report measure of medication adherence, with five questions. Items are rated on a 5-point Likert scale between 1 (all the time) to 5 (never) and summed to create a total score (score range 0-25). Higher scores indicate better adherence to medication. In the RADAR trial the MARS-5 was used to indicate participant adherence to their antipsychotic medication only.

3.5.4.4 Client Service Receipt Inventory (CSRI (Beecham & Knapp, 2001))

This questionnaire records information on resource use of health, leisure, financial support, and criminal justice services by the participant. It also records medication prescribed over the last six months to participants, including information on the medication name, dosage, method of administration, frequency of use, date started, and date ending, or ongoing use. Within this thesis I will be using information from the CSRI cross-referenced with data from patient records to accurately account for all medications participants were using at the time of assessment.

3.6 RADAR Randomisation

Randomisation was completed following the baseline assessment. Randomisation was conducted through an independent internet-based system linked with the database (https://www.sealedenvelope.com/randomisation/internet/) with 1:1 allocation. Randomisation group was blinded to outcome assessors but revealed to participants and clinicians and any unblinded study personnel (for site-specific participants). Participants were randomised to either an antipsychotic maintenance arm, by which they were instructed to take their medication as usual for the next two years unless clinically unable, or to a reduction/discontinuation arm.

3.6.1 Reduction/Discontinuation Arm

If participants were randomised to the antipsychotic medication reduction arm, an individualised reduction schedule was devised by clinical members of the RADAR research team, adjusted according to the participant's initial antipsychotic treatment. The dose was reduced incrementally every 1 or 2 months, focusing on one drug at a time where participants were taking more than one antipsychotic. This reduction process was undertaken with the participants' treating clinician or with the RADAR trial doctor, where this was requested.

Rate of reduction varied according to baseline dose, with most schedules aiming for discontinuation within a 12-month period, but some lasting longer where the baseline doses were higher. Treating psychiatrists were asked to see the participants randomised to antipsychotic reduction every 2 months for the duration of the reduction, to adjust medication and monitor mental state. Participants were offered the option to discontinue antipsychotic medication completely if the reduction progressed well, or to reduce to a very low dose. Reduction schedule guidance strategy stressed the need for flexibility and included a suggested protocol for the treatment of adverse reactions to withdrawal or symptom exacerbation.

3.6.2 Maintenance Arm

Participants randomised to the maintenance arm of the RADAR trial were requested to stay on their current dose and type of antipsychotic for the two-year duration they were enrolled in the study. Participants were reassured that if they experienced any side effects of the medication or were in any way concerned with their antipsychotic medication, they could continue their clinical care as usual and should speak to their psychiatrist about any issues. Psychiatrists with participants enrolled in the trial were able to make any changes to participant antipsychotic medication that they deemed clinically necessary.

3.7 Follow-up Assessments

RADAR trial assessments were completed at baseline, 6- months, 12- months, and 24- months. The social cognition sub-study data was collected at baseline, 12-months, and 24- month timepoints to avoid practice effects.

3.8 Data Processing

Once data collection was complete, I checked and cleaned all data entries. To ensure interrater reliability, I was assisted by a MSc student at Plymouth University to separately score the AIHQ items 1 and 5 for each scenario, and kappa scores were calculated. Next, analysis of the data took place in R (RCoreTeam, 2021), following the data analysis plan. The following data packages were used in R for data analysis 'stats' (RCoreTeam, 2017), 'chlorpromazineR' (Brown et al., 2021), 'MICE' (van Buuren et al., 2021), 'tidyverse' (Wickham et al., 2022), 'car' (Fox et al., 2022), and 'lme4' (Bates et al., 2022).

3.9 Data Analysis

The following section will outline the data analysis plan for both the cross-sectional and longitudinal studies described above.

3.9.1 Missing Data

Descriptive statistics were reported, and all other analyses were then completed after statistical inputting for missing data. A Missing Values Analysis was conducted using Little's test of Missing Completely at Random (MCAR) for each timepoint (Little, 1988). Data was also checked to confirm a reasonable assumption that data may be missing at random (MAR) through missing vs. non-missing tests of significance, reported in Appendix D.

Due to the relatively small proportions of missing data at each timepoint <10%, as well as recommendations for missing data in longitudinal clinical trials, multiple imputation was considered the least biased way of accounting for missingness in this dataset (Dziura et al., 2013; Little et al., 2012; Groenwold et al., 2014; Jakobsen et al., 2017). Nonmonotonicity in the missing data was checked using scatterplots, and a decision was made based on this to utilise monotone methods of multiple imputation. The MI method followed; random number generator fixed value = 950, 5 imputations, MCMC, maximum iterations = 50, and predictive mean matching (PMM) to account for sensitivity analysis (Kleinke, 2018; Stuart et al., 2009). Variables included in the MI model included the following, (at each timepoint where relevant); AIHQ blame, AIHQ aggression, AIHQ hostility, BLERT, SAT-MC, Hinting Task, TEIQue, EQ-CEF, EQ-SSF, age, gender, education level, ethnicity, Digit Span, SFS, MARS5, PANSS Positive, PANSS Negative, PANSS General, PANSS Total, CPZ Equivalents, and antipsychotic duration.

Complete case analysis (CCA) was also conducted on data as it is less prone to user error and should be used to check analysis after MI (Austin et al, 2021). However, as over 5% of data was missing at each timepoint in this dataset, it is likely CCA produced unreliable results. The CCA procedure and results for baseline data can be seen in Appendix D. Overall, CCA showed a highly biased sample, with the MI dataset providing a much larger and diverse sample at all timepoints.

3.9.2 Pre-processing

Dependent variable total scores and associated variables were checked for data normalisation. Where variables did not meet this assumption non-normal variables were transformed using the 'log10' command in R, where variables were transformed it is stated in the results, this occurred for the CPZ equivalent antipsychotic baseline dose and 24- month dose variables. Assumptions for each analysis method were also checked, and where they were unable to be met it is stated clearly in the results.

3.9.3 Cross-Sectional Study Analysis

3.9.3.1. Baseline Characteristics

The baseline characteristics of the included subjects were reported and shown in tables. The following characteristics were reported for those who completed social cognition measures: age (years), gender, education level (up to 18, and tertiary), ethnicity (white, non-white), substance use in last month, and alcohol use in last month. For the patients, inpatient admissions, age when first referred to mental health services, and length of time in contact with mental health services were reported, and name of antipsychotic, dosage of antipsychotic (CPZ equivalent), and administration of antipsychotic (LAI vs. oral) were also reported.

Categorical variables were summarised as a proportion of participants with the given characteristic. Continuous variables were summarised as mean with standard deviation.

3.9.3.2. Statistical Analysis:

Aim 1: Determine if there are significant differences in social cognitive ability across domains, in patients with schizophrenia compared to healthy volunteers:

a) T-tests and Chi-squares were used to compare demographic variables between groups (healthy volunteers vs. patients with schizophrenia).
b) To find any potential predictor variables associated with social cognition domains, linear regressions of each social cognition domain and demographic/illness-related variables (age, gender, education level, and ethnicity, and Digit Span as a measure of neurocognition) were conducted on all participant data. To identify any significant differences between groups on social cognition outcomes, t-tests and ANCOVAs were conducted on each measure, adjusting for predictor variables where they had previously been found significant, or as trending on significance.

Aim 2: Determine if symptoms of schizophrenia, and AP usage significantly predict social cognition outcomes, across domains.

a) Linear regressions were carried out between social cognition outcomes and PANSS, antipsychotic usage, and other potential predictor variables to identify any significant relationships. Where social cognition outcomes had a significant relationship with a symptom-related or AP-related variable as well as an additional predictor variable, multiple linear regressions were conducted to identify the impact of these predictors on the relationship.

Aim 3: Determine if social cognition domain scores predict social functioning outcomes.

a) Linear regressions were carried out between SFS scores and social cognition outcomes. To identify relationships with other potential predictor variables additional linear regressions were conducted between SFS scores and AP usage variables, PANSS variables, and other potential predictor variables.

Multiple linear regressions were then conducted where relevant to identify any significant relationships between SFS and social cognition domains that remained after adjusting for confounders.

3.9.4 Longitudinal Study Analysis

3.9.4.1. Intention to Treat

An intention-to-treat (ITT) analysis was conducted on the data from the longitudinal study. In the ITT analysis all patients were analysed according to their initially assigned study arm at baseline, regardless of adherence to study protocol.

3.9.4.2. Statistical Analysis:

Baseline characteristics were compared between those who completed the 24-month follow-up assessment, and those who did not, using T-tests and chi-squares, to assess for bias in the sample.

Aim 1)

To determine if there were significant differences in ability across social cognition domains, in patients in the reduction/discontinuation group vs. the maintenance group at baseline.

a) T-tests and Chi-squares were used to compare demographic variables between groups (reduction/discontinuation vs. maintenance) at baseline.
b) To find any potential predictor variables associated with social cognition domains at baseline, linear regressions of each social cognition domain and demographic/illness-related variables (age, gender, education level, and ethnicity, and Digit Span as a measure of neurocognition) were conducted on all participant data. To identify any significant differences between groups on social cognition outcomes, t-tests and ANCOVAs were conducted on each measure, adjusting for predictor variables where they had previously been found significant, or as trending on significance.

Aim 2)

To evaluate:

- Whether *changes* in social cognition domains between timepoints were significantly different between groups.
- Whether changes in social cognition domains between timepoints were significantly different, *across* groups.
- To test for differences in social cognition change between groups and over time after controlling for potential predictors of social cognition change across groups and any relevant variables that differ between groups.
- Whether changes in social cognition are associated with changes in antipsychotic dose

a) T-tests were conducted on mean change scores from baseline to 12- months, baseline to 24- months, and 12- to -24 months, between and across groups.
b) Linear regressions were undertaken to identify predictors of mean change score in social cognition variables, using potential predictor variables including the PANSS symptom, Digit Span, and relevant demographic variables.
c) Where significant relationships were identified between group mean change scores, or mean change scores across timepoints, repeated measure linear mixed models (RLMM) were used for further analysis. Any significant variables identified in linear regressions were added as random effects or covariates. Fixed effects were time (baseline=1, 12m=2, 24m=3), and group (randomisation variable), with time x group interaction. To account for baseline differences across individuals in social cognition scores, a random intercept for subject was included in the model. The model used significant predictor variables identified as covariates. When accounting for baseline differences in predictor variables (e.g., PANSS scores) they were included in the model as by-subject random slopes.
d) Additional linear regressions were conducted between social cognition change scores and antipsychotic dose change scores at 24- months.

Example R Code:

lmer (AIHQ Aggression ~ time + group + gender + age + panssposítive + time*group + (1+panssposítive|subject), data=dat)

Aim 3)

To determine whether changes in social cognition were related to changes in social functioning performance, and to identify other potential predictors of social functioning change.

- Spearman's correlations were conducted between social functioning mean change scores and social cognition domain mean change scores.
- Linear regressions were performed at 12- and 24- months to identify potential predictors of change in SF including symptom-related and demographic variables.
- Repeated measure linear mixed models (RLMM) were used for further analysis. Fixed effects were time (baseline=1, 12m=2, 24m=3), and group (randomisation variable), with time x group interaction, and any social cognition variables that had significant relationships with social functioning change. Any significant variables identified in linear regressions were added as random effects or covariates.

Example R Code:

lmer (SFS ~ EQ_CEF + AIHQ_Blame + BLERT + Age + EQ_CEF:Time + AIHQ_Blame:Time + BLERT:Time + Group:Time + (1|Group), data = data)

3.10 COVID-19 Implications

In late 2019 a novel coronavirus 'COVID-19' was identified in Wuhan, China. The virus rapidly spread around the globe and the World Health Organisation (WHO) officially declared a pandemic on the 11th March 2020 (Cucinotta & Vanelli, 2020). In the UK the first confirmed case of Covid-19 was identified on the 31st January 2020, and the first death was reported on the 5th of March (Ritchie et al., 2020). Over the time-course of 2020-2021 the Prime Minister of the UK imposed three lockdowns, these involved the closure of hospitality services, non-essential shops, cinemas, theatres, gyms, and leisure centres. The government advised people to only go outside during these periods to exercise, buy essential goods, or care for others. People were encouraged to work from home, and schools and universities were moved online to allow for remote learning. A break-down of key events related to Covid-19 are available on a timeline in Appendix E.

These strict restrictions in the UK overlapped with periods of data collection for the longitudinal component of the research in this thesis. This resulted in procedural changes to the study process, in order to keep both participants and researchers safe during the pandemic.

From March 2020, a protocol amendment allowed RADAR assessments to take place remotely across sites in the UK, including the social cognition measures. Measures could be completed on the phone, or via online video-conferencing software which became a popular communication tool during this period. Two of the social cognition measures that required participants to view videos whilst answering the questions (SAT-MC or SAT-MC II, and the BLERT) were adapted to be accessible for participants whilst maintaining social distancing practices. For these measures, the videos were uploaded onto YouTube and a private link was distributed to researchers at sites conducting social cognition measures. During the social cognition portion of RADAR assessments, researchers were able to share the private YouTube links with participants for them to view on an electronic device that had access to the internet. Participants were then able to watch the video whilst verbalising their answers to the researcher by whichever method they were using to conduct the assessment.

Due to the pandemic, there was a significant shift from in-person assessments to online assessments, this transition is portrayed in **Table 10**. These changes show how the study was adapted in response to the pandemic, allowing for continued data collection despite the challenges posed by the COVID-19 restrictions. Additionally, it is crucial to acknowledge the potential implications of this shift on the validity and comparability of the collected data. Notably, analysis in this thesis did not account for potential biases introduced by change in assessment format. Further sensitivity analysis may be necessary to thoroughly explore and address these potential biases.

Table 10

Number of Participant Assessments In-Person vs. Online at Each Timepoint

	In-Person N (%)	Online N (%)
Baseline Assessment	73 (100.0)	0 (0.0)

12- Month Assessment	16 (34.8)	30 (65.2)
24- Month Assessment	0 (0.0)	42 (100.0)

In addition to new procedural measures due to Covid-19 restrictions, it is important to note that the total global impact of Covid-19 is as yet unknown. When looking at the data collected during this period of the research it has been important to consider the potential impact of the pandemic on the participants involved in this study, emotionally, mentally, socially, and physically, and how this may have affected outcomes. These considerations will be discussed more in depth in the general discussion chapter of the thesis (Chapter 6).

3.11 My Role

Under the guidance of my supervisory team:

- I was responsible for the implementation of the social cognitive sub-study in the RADAR trial. This involved deciding on the RADAR assessment pack measures and completing a substantial amendment requesting ethical approval from the MHRA, HRA, and REC authorities, for which I had to answer additional questions related to the content of the measures.
- I was responsible for part of the data collection of the social cognition sub-study, assisted by fellow research assistants working across sites conducting the RADAR trial. In addition, I was a contact point for all social cognition queries up until the closure of the RADAR trial.
- I was responsible for training all researchers at all sites that took part in the social cognition sub-study.
- I was responsible for designing and conducting the 'Cognition in Human Volunteers' study. I completed an ethics form for the study, I recruited the participants, and I collected the data.
- I was responsible for all data entry and cleaning involving social cognition data.
- I was responsible for completing a statistical analysis plan for the cross-sectional and longitudinal studies, and for completing data analysis and write-up.

Chapter 4 – Baseline Results and Discussion

This chapter outlines the results from the cross-sectional analysis described in Chapter 3 (section 3.3). Findings are then discussed with reference to existing literature in the field related to social cognition relationships with symptoms, antipsychotics, and social functioning.

The purpose of the present cross-sectional study was to determine if differences exist in social cognition performance between healthy volunteers and patients with schizophrenia. Additionally, analysis was undertaken to determine any significant predictors of social cognition performance, including AP dose, AP duration, and symptoms. Finally, analysis explored whether any social cognition domains are significant predictors of social functioning.

A reminder of the aims for this chapter:

- To determine if there were significant differences in social cognitive ability across domains, in patients with schizophrenia compared to healthy volunteers.
- To determine if symptoms of schizophrenia, and AP usage significantly predict social cognition outcomes, across domains.
- To determine if social cognitive domain scores predict social functioning outcomes.

4.1 Participant Flow

A total of n=253 patient participants were recruited at baseline for the RADAR trial, with n=73 completing at least one of the social cognition measures. Reasons for non-completion can be seen in **Figure 4**. Recruitment of healthy volunteers was conducted as a separate study, with n= 37 participants consenting and taking part in at least one social cognition measure.

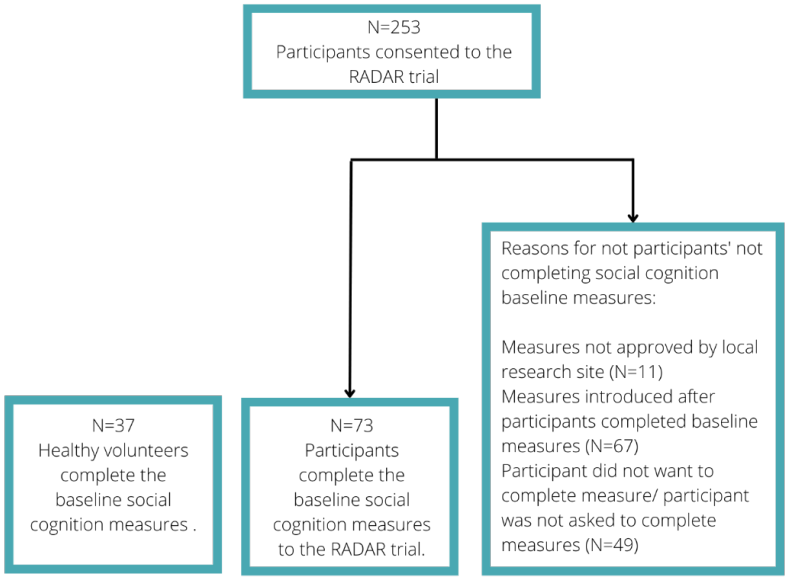

Figure 4. Flow-chart of recruitment for baseline social cognition measures.

4.2 Missing Data

Missing data for healthy volunteers and patient participants is presented in **Table 11**. No missing data was identified for demographic variables of age, gender, education level or ethnicity for patient or healthy volunteer participants. Additionally, number of mental health inpatient stays was available for all patients. However, data were missing for 10 patient participants on the number of years in contact with mental health services.

Table 11.
Table Showing Data for Measures Missing at Baseline.

Measure	Healthy Volunteers (n= 37) N (%)	RADAR Participants (n= 73) N (%)
Digit Span	0 (0.0)	0 (0.0)
SFS*	N/A	3 (4.2)
MARS5	N/A	0 (0.0)
PANSS*	N/A	13 (17.8)
AIHQ*	1 (2.7)	4 (5.5)
BLERT	2 (5.4)	5 (6.8)
Hinting	3 (8.1)	2 (2.7)
EQ-SF	1 (2.7)	3 (4.2)
TEIQue	3 (8.1)	6 (8.2)
SAT-MC/SAT-MC II	1 (2.7)	7 (9.6)

Notes:
*Refers to individual items on measure missing

For patient participants, positive and negative symptom data, recorded via the PANSS, was missing for 13 (17.8%) participants, on one item. Potential reasons for this missing data included patients refusing to answer the questions relating to their current symptoms, patients becoming too distressed to answer these questions, or because there was no time to complete the measure. There was also missing data for the SFS on one item for 3 patient participants.

On the AIHQ there were 5 missing responses on individual items (4 patient participants). On the BLERT there were 7 occasions of the measure being missed (5 patient participants). On the SAT-MC there were 8 missing measures (7 patient participants). On the EQ-SF there were 4 missing measures (3 patient participants). On the TEIQue there were 9 missing measures (6 patient participants), and on the Hinting Task there were 5 missing measures (2 patient participants).

Social cognition missing data at baseline in both patient and healthy volunteer participants was due to lack of time to complete all the measures, or participants not wishing to complete measures due to burden.

There was no missing data on additional variables used in the analysis, including the Digit Span, MARS5, antipsychotic duration, and chlorpromazine (CPZ) equivalent totals of antipsychotic dosage.

A missing values analysis indicated that Little's test of Missing Completely at Random (MCAR) was significant (X^2 = 42.60, DF =5 8, p = .035). When significant, this test suggests that the hypothesis that the data are MCAR can be rejected. Therefore, this suggests that the data were not MCAR. There was sufficient evidence in this dataset that other observed values may be associated with missing data (See Chapter 3, section 3.9.1). Therefore, multiple imputation (MI) was feasible. Analysis for this chapter was conducted after MI of the dataset.

4.3 Demographic Data

Demographic data for patient and healthy volunteer participants can be seen in (**Table 12).**

In total, 37 healthy volunteers were recruited for this study and provided data at the baseline visit. The sample was comprised of n= 25 men (67.6%) and n=12 women (32.4%). The ages of healthy volunteers ranged between 24 and 79, and the mean age was 45.46 (S.D. 12.79), with n= 25 (67.6%) identifying as a white ethnicity, and n=12 (32.4%) identifying as a non-white ethnicity. The mean Digit Span score, used to assess general cognition, was 17.46 (S.D. 3.89).

A total of 73 patients with a schizophrenia-spectrum disorder were recruited for this study and provided data at the baseline visit. The sample was comprised of n=54 males (74.0%) and n=19 females (26.0%). The ages of patients ranged between 26 and 68, and the mean age was 47.16 (S.D. 10.84), with n= 48 (65.8%) patients identifying as a white ethnicity, and n= 25 (34.2%) identifying as a non-white ethnicity. The mean Digit Span score was 15.40 (S.D. 4.65), and the mean social functioning score was 105.03 (S.D. 11.20).

Independent sample t-tests and chi-squares conducted between patients (n= 73) and healthy volunteers (n= 37) on age, ethnicity, education, and gender variables did not reveal any significant differences between groups at the .05 level of statistical significance. However, significant differences were evident between groups Digit Span performance, with a moderate effect size (Hedges g = -.465, p = .023), and there was a statistically significant association between group membership and marital status (X^2 = 12.90, p = .003) (**Table 12**).

Table 12.
Demographic Data and Significance Tests for Patient and Healthy Volunteer Participants, at Baseline Assessment.

Demographic Variable	Category	Patients (n=73) N (%)	Healthy Volunteers (n=37) N (%)	X^2	p value
Gender	**Male**	54 (74.0)	25 (67.6)	.202	.653
	Female	19 (26.0)	12 (32.4)		
Marital Status	**Cohabiting/Civil Partnership/Married**	8 (21.6)	15 (40.5)	12.90	**.003**
	Single/Widowed/Divorced	65 (78.4)	22 (59.5)		
Ethnicity	**White**	48 (65.8)	25 (67.6)	3.31	.069
	Non-White	25 (34.2)	12 (32.4)		
Education Level	**School up to 18 Yrs.**	39 (53.4)	21 (56.8)	.154	.695
	Tertiary/Further Education	34 (46.6)	16 (43.2)		
		Mean (S.D.)	**Mean (S.D.)**	**Hedges g**	**p value**
Digit Span		15.39 (4.65)	17.46 (3.89)	-.464	**.023**
Age		47.16 (10.84)	45.46 (12.79)	.147	.465
	21-30	5 (6.8)	2 (5.4)		
	31-40	14 (19.2)	14 (37.8)		
	41-50	22 (30.1)	7 (18.9)		
	51-60	24 (32.9)	9 (24.4)		
	61+	8 (11.0)	5 (13.5)		
Alcohol Use Over Last Month	**Once a Month or Less**	50 (68.5)	19 (51.4)		
	Two to Four Times a Month	10 (13.7)	14 (37.8)		
	Two to Three Times a Week	8 (11.0)	4 (10.8)		
	Four or More Times a Week	5 (6.8)	0		
Recreational Drug Use Over Last Month	**Yes**	8 (11.0)	1 (2.7)		
	No	65 (89.0)	36 (97.3)		

Notes:
Bold: P<0.05

4.4 Patient Participants with Schizophrenia

Demographic data related to mental health service use for the patients with schizophrenia sample in **Table 13.1,** shows that the median number of inpatient stays in mental health hospitals was 3.3 times (IQR= 4.00). Patient participants, n= 35 (48.0%) were referred to mental health services aged 20-30 years, n=14 (19.2%) were referred at under 20 years old, n= 14 (19.2%) were referred at 31-40 years old, n= 8 (11.0%) were referred at 41-50 years old, and n= 2 (2.6%) were first referred at over 50 years old. Around a third of patient participants n= 24 (32.8%) had been in contact with mental health services for more than 20 years, and another third for 4-10 years, n= 24 (32.8%). N= 8 (11.0%) patient participants were in contact for 16-20 years, n= 13 (18.0%) in contact for 11-15 years, and n= 4 (5.1%) in contact for 1-3 years at the time of their baseline assessment. Additionally, around one third (34.2%) of patient participants in the study had a schizophrenia-spectrum diagnosis, other than schizophrenia.

Table 13.1
Frequency Data on Mental Health Service Use of Patient Participants.

Mental Health Service Use Variable	Category	Patients (n=73) N (%)
Inpatient Admissions	**0-1 times**	23 (31.5)
	2-3 times	20 (27.4)
	4-5 times	18 (24.7)
	6-7 times	8 (10.9)
	8-10 times	4 (5.5)
Age when first referred to MH services	**Under 20 years**	14 (19.2)
	20-30 years	35 (47.9)
	31-40 years	14 (19.2)
	41-50 years	8 (11.0)
	Over 50 years	2 (2.7)
Length of time in contact with MH services	**1-3 years**	4 (5.5)
	4-10 years	24 (32.9)
	11-15 years	13 (17.8)
	16-20 years	8 (11.0)
	More than 20 years	24 (32.9)
Diagnosis		
	Schizophrenia	48 (65.8)
	Other Psychosis	25 (34.2)

Further information on patient participants can be seen in **Table 13.2**. The average total PANSS score was 48.0 (S.D. 14.36), which would suggest the participants in this study were placed in the less than 'mildly ill' category of the clinical thresholds proposed by Leucht et al. (2005). The average SFS score was 109.02 (S.D. 9.11). In the original Birchwood et al (1990) sample of patients with schizophrenia taking the SFS, the sample scored between 86-105, whereas the normal community sample scored between 116-135, this indicates that patients in this sub-study scored

relatively well at baseline social functioning, above the expected clinical thresholds, but below that of a healthy population. The average MARS5 score was 23.32 (S.D. 2.74), suggesting patients' self-reported good medication adherence at baseline. The median number of years for patient participants taking their current antipsychotic was 5 years (IQR = 9.05). Most participants were administered their antipsychotic via oral tablets n= 41 (56.2%), with n= 32 (43.8%) administered their antipsychotic via long-acting injection. The median CPZ equivalent dose of antipsychotic amongst patients at baseline was 300.00 (IQR = 208.00).

Table 13.2

Descriptive Statistics for AP Usage, Symptom, Social Functioning, and Medication Adherence Variables.

Variable	Mean (S.D)	Range
AP dose (CPZ Equivalent)	365.51 (275.00)	100.00-1800.00 mg
AP duration	7.21 (6.52)	0 – 26 years
PANSS negative	11.41 (4.91)	7-26
PANSS positive	11.38 (5.14)	7-35
PANSS general	25.21 (6.93)	28-44
PANSS total	48.00 (14.36)	30-100
SFS total	109.02 (9.11)	90.93-130.36
MARS5 total	23.32 (2.74)	13-25

4.5 Patient Participant Correlations

Spearman's correlations for patient participant variables can be seen in **Table 14.** Spearman's correlations were conducted due non-normality in Age, AP duration and AP dose variables, to identify any significant relationships between independent variables for the purposes of meeting regression assumptions. Higher positive correlations were found between the PANSS Total score and each of the three PANSS symptom dimensions, which in turn showed positive correlations with each other. PANSS Total correlation coefficients with other PANSS dimensions were all around .7 and therefore determined as strong, the measure was therefore removed from analysis due to multicollinearity. No significant correlations were evident between PANSS dimensions and Digit Span, or AP dosage. However, there was a weak correlation between PANSS Positive symptoms and AP duration. Additionally, there were no statistically significant relationships between AP dose or AP duration and Digit Span, suggesting no effect of Aps on general cognition. There were statistically significant correlations between age and Digit Span, gender and Digit Span, age and AP duration, age and AP dosage, education level and AP duration, age and ethnicity, and ethnicity and education level, however correlation coefficients were deemed small to moderate as they were all between .2 to .4.

Table 14.

Spearman's Correlations Between Patient Participant Variables.

	Digit Span r (p-value)	**AP duration r (p-value)**	**AP dosage r (p-value)**	**PANSS Negative r (p-value)**	**PANSS Positive r (p-value)**	**PANSS General r (p-value)**	**PANSS Total r (p-value)**	**Age r (p-value)**	**Gender r (p-value)**	**Ethnicity r (p-value)**	**Education r (p-value)**
AP duration	-.128 (.279)	-	-	-	-	-	-	-	-	-	-
AP dose	-.125 (.291)	.021 (.861)	-	-	-	-	-	-	-	-	-
PANSS Negative	-.189 (.109)	-.091 (.446)	.113 (.340)	-	-	-	-	-	-	-	-
PANSS Positive	-.041 (.733)	.235 **(.045)**	.097 (.416)	.383 **(<.001)**	-	-	-	-	-	-	-
PANSS General	.066 (.578)	-.033 (.779)	.091 (.444)	.451 **(<.001)**	.561 **(<.001)**	-	-	-	-	-	-
PANSS Total	-.027 (.820)	.039 (.745)	.135 (.253)	.687 **(<.001)**	.782 **(<.001)**	.878 **(<.001)**	-	-	-	-	-
Age	-.396 **(<.001)**	.239 **(.042)**	.304 **(.009)**	.089 (.457)	-.115 (.333)	-.073 (.540)	.036 (.762)	-	-	-	-
Gender	-.366 **(.001)**	.104 (.382)	.050 (.672)	-.102 (.388)	.132 (.265)	.075 (.528)	.049 (.691)	.067 (.575)	-	-	-
Ethnicity	-.024 (.840)	-.088 (.461)	-.202 (.087)	-.165 (.164)	.028 (.811)	-.274 **(.019)**	-.164 (.166)	-.433 **(<.001)**	.164 (.166)	-	-
Education	.251 (.136)	.004 **(-.332)**	.528 (-.075)	.899 (.015)	.929 (-.011)	.725 (.042)	.500 (.080)	.083 (-.204)	.937 (.009)	.252 **(.031)**	-

	Digit Span r (p-value)	AP duration r (p-value)	AP dosage r (p-value)	PANSS Negative r (p-value)	PANSS Positive r (p-value)	PANSS General r (p-value)	PANSS Total r (p-value)	Age r (p-value)	Gender r (p-value)	Ethnicity r (p-value)	Education r (p-value)
AP duration	-.128 (.279)	-	-	-	-	-	-	-	-	-	-
AP dose	-.125 (.291)	.021 (.861)	-	-	-	-	-	-	-	-	-
PANSS Negative	-.189 (.109)	-.091 (.446)	.113 (.340)	-	-	-	-	-	-	-	-
PANSS Positive	-.041 (.733)	**.235 (.045)**	.097 (.416)	**.383 (<.001)**	-	-	-	-	-	-	-
PANSS General	.066 (.578)	-.033 (.779)	.091 (.444)	**.451 (<.001)**	**.561 (<.001)**	-	-	-	-	-	-
PANSS Total	-.027 (.820)	.039 (.745)	.135 (.253)	**.687 (<.001)**	**.782 (<.001)**	**.878 (<.001)**	-	-	-	-	-
Age	**-.396 (<.001)**	**.239 (.042)**	**.304 (.009)**	.089 (.457)	-.115 (.333)	-.073 (.540)	.036 (.762)	-	-	-	-
Gender	**-.366 (.001)**	.104 (.382)	.050 (.672)	-.102 (.388)	.132 (.265)	.075 (.528)	.049 (.691)	.067 (.575)	-	-	-
Ethnicity	-.024 (.840)	-.088 (.461)	-.202 (.087)	-.165 (.164)	.028 (.811)	**-.274 (.019)**	-.164 (.166)	**-.433 (<.001)**	.164 (.166)	-	-
Education	.251 (.136)	**.004 (-.332)**	.528 (-.075)	.899 (.015)	.929 (-.011)	.725 (.042)	.500 (.080)	.083 (-.204)	.937 (.009)	**.252 (.031)**	-

Notes:
Bold: P<0.05

4.6 Antipsychotic Medication Use in Patient Participants

Patients were prescribed a variety of medications at baseline and there were no eligibility criteria excluding patients taking certain antipsychotics. Antipsychotics administered at baseline are shown in **Table 15**. Any patients who were taking more than one antipsychotic at baseline were given a total CPZ equivalent dose of all antipsychotics summed. Any patients who had been taking a different antipsychotic or different dosage of an antipsychotic during the last 6 months were given an average dose, from the CPZ equivalent for each antipsychotic based on days taken. Two patients were taking three antipsychotic medications at baseline, 15 were taking two antipsychotics at baseline, and all other patients were taking only one antipsychotic. CPZ equivalents were calculated using the 'chlorpromazineR' package in R, which uses the Gardner et al (2010) dosages as default. Where antipsychotic medications taken by patients were not included in the default equivalents, the Leucht et al (2016) and Leucht et al (2020) dosage equivalents were used.

Table 15.
Current Antipsychotic Medication Use in Participants with Schizophrenia.

Antipsychotic Name	Number of participants taking antipsychotic	Mean Daily Dosage (mg) – oral medication	Mean Daily Dosage (ml) – LAI medication
First-Generation Antipsychotics			
Chlorpromazine	1	350	
Haloperidol	1	4	
Flupenthixol Decanoate	7		82.14
Fluphenazine Decanoate	4		156.25
Second-Generation Antipsychotics			
Clozapine	14	317.86	
Amisulpride	1	150	
Aripiprazole	19	13.49	385.32
Cariprazine	1	3.0	
Olanzapine	7	12.93	
Paliperidone	5		137.6
Prochlorperazine	1	5	
Quetiapine	9	183.33	
Risperidone	16	3.5	31.56
Zuclopenthixol	4	125	291.67

4.7 Social Cognition Results

The following hypotheses were tested:

Hypothesis 1: There are significant differences in social cognitive ability, across domains, in patients with schizophrenia compared to healthy volunteers, with patients performing worse.

Hypothesis 2: Symptoms of schizophrenia, and AP usage (dose and duration) will significantly predict social cognition outcomes, across domains. Higher symptom scores, and higher antipsychotic dosages and duration will result in poorer social cognition outcomes.

Hypothesis 3: Social cognitive domain scores will significantly predict social functioning outcome in patients with schizophrenia, with poorer social cognition scores resulting in poorer social functioning outcomes.

The structure of this section is as follows; firstly, hypothesis 1 will be analysed through mean score comparisons of each social cognition domain between the patient group and the healthy volunteer group. Secondly, tests will be reported to identify any significant relationships between dependent variables and potential confounding variables for patient participants. Finally, each social cognitive domain will be analysed to test hypothesis 2 and 3 in patients with schizophrenia.

Tests were carried out to assess assumptions for all analysis. Due to multicollinearity, the PANSS total variable was dropped from analysis. Due to non-normality, the CPZ Equivalent Dose variable was log transformed. All other assumptions were met satisfactorily.

4.7.1 Comparison of Means

Linear regressions were conducted between social cognition outcomes and potential demographic and illness-related predictor variables across both groups of participants (**Table 16.1**). Where relationships between social cognition outcomes and predictor variables were significant, or trending on significance, those predictor variables were used as covariates in further analysis (**Table 16.2**).

Table 16.1

Linear Regressions Between Social Cognition Outcomes and Potential Predictor Variables.

Variable	AIHQ Blame		AIHQ Aggression		AIHQ Hostility		BLERT		Hinting Task		SAT-MC		EQ-CEF		EQ-SSF		TEIQue	
	Standardised Beta	p value	Standardised Beta	p value	Standardised Beta	p value	Standardised Beta	p value	Standardised Beta	p value	Standardised Beta	p value	Standardised Beta	p value	Standardised Beta	p value	Standardised Beta	p value
Gender	.220	.285	.216	.081	.342	.067	1.82	.054	.716	.244	.427	.662	.134	.261	.699	.352	.308	.086
Ethnicity	-.273	.163	.142	.231	-.078	.662	.432	.634	.156	.791	1.934	**.036**	-1.057	.356	.501	.488	-.075	.664
Age	.004	.617	-.005	.341	.014	**.050**	-.104	**.005**	-.016	.496	-.124	**<.001**	.006	.902	-.050	.092	-.016	**.019**
Education	-.110	.555	.193	.084	-.027	.875	.760	.377	.957	.084	1.137	.196	-.428	.694	.187	.785	-.043	.793
Digit Span	-.052	**.011**	-.018	.140	-.036	.054	.391	**<.001**	.042	.497	.177	.070	-.098	.413	.116	.123	.037	**.042**

Notes:
Bold: P<0.05

Comparison of means using t-tests and ANCOVAs showed significant differences between patient participants and healthy volunteer participants on all social cognition measures after controlling for the potential confounding variables identified above (**Table 16.2**). Across the AIHQ measures, patient participants had a higher mean score compared to healthy volunteers (higher scores showing a higher attribution bias). On all other social cognition measures patient participants had a lower mean score in comparison to healthy volunteers (lower scores showing a poorer social cognition performance on these measures).

Table 16.2

Outcomes of T-Tests and Ancovas in Patient Participants Vs. Healthy Volunteer Participants on Social Cognition Domains.

Social Cognition Measure	Patients Mean (SD)	Healthy Volunteer Mean (SD)	p value	95% Confidence Interval (CI)	
				Lower CI	Upper CI
AIHQ Blame[a]	2.36 (.911)	1.59 (.686)	**<.001**	.322	1.052
AIHQ Aggression	1.66 (.583)	1.35 (.538)	**.009**	.079	.533
AIHQ Hostility[b]	1.95 (.941)	1.38 (.594)	**.002**	.211	.879
EQ CEF	11.85 (5.39)	14.71 (5.52)	**.013**	-5.09	-.619
EQ SSF	4.97 (3.37)	8.47 (2.48)	**<.001**	-4.78	-2.22
TEIQue[c]	4.38 (.85)	4.84 (.76)	**.017**	-.734	-.073
BLERT[d]	12.44 (4.25)	17.51 (2.62)	**<.001**	-5.90	-3.02
Hinting	16.11 (3.22)	17.32 (1.89)	**.037**	-2.352	-.077
SAT-MC[e]	10.74 (4.49)	15.97 (2.11)	**<.001**	-6.55	-3.65

Notes:
[a] adjusted for Digit Span
[b] adjusted for age
[c] adjusted for age and Digit Span
[d] adjusted for age and Digit Span
[e] adjusted for age and ethnicity
Bold: P<0.05

Spearman's correlations for social cognition variables can be seen in **Table 17**. AIHQ Blame, Hostility, and Aggression show positive associations, showing higher levels of attribution bias tend to co-occur. BLERT, Hinting Task, SAT-MC, EQ-CEF, EQ-SSF,

and TEIQue exhibit both positive and negative correlations, suggesting complex relationships between variables. Of the statistically significant correlations, EQ-SSF and AIHQ Blame have the strongest negative association, while EQ-SSF and TEIQue have the strongest positive correlation. Findings may suggest grouping AIHQ variables into one attribution bias factor, and EQ variables into one empathy factor, to reduce multiple testing, however this was not completed as part of this analysis as the approach was to focus on relationships between predictors and individual social cognition variables.

Table 17.
Spearman's Correlations Between Social Cognition Variables.

	AIHQ Blame r (p-value)	**AIHQ Hostility r (p-value)**	**AIHQ Aggression r (p-value)**	**BLERT r (p-value)**	**Hinting Task r (p-value)**	**SAT-MC r (p-value)**	**EQ-CEF r (p-value)**	**EQ-SSF r (p-value)**	**TEIQue r (p-value)**
AIHQ Blame	-	-	-	-	-	-	-	-	-
AIHQ Hostility	.058 **(<.001)**	-	-	-	-	-	-	-	-
AIHQ Aggression	.349 **(<.001)**	.248 **(.002)**	-	-	-	-	-	-	-
BLERT	-.019 (.809)	-.035 (.655)	.102 (.196)	**-**	-	-	-	-	-
Hinting Task	-.055 (.491)	.002 (.976)	-.004 (.961)	.202 **(.010)**	**-**	-	-	-	-
SAT-MC	-.018 (.823)	-.131 (.096)	. 049 (.537)	.393 **(<.001)**	.111 (.160)	**-**	-	-	-
EQ-CEF	-.066 (.404)	-.138 (.081)	.085 (.284)	-.238 **(.002)**	.132 (.094)	-.126 (.113)	-	-	-
EQ-SSF	-.409 **(<.001)**	-.307 **(<.001)**	-.096 (.225)	.080 (.316)	.093 (.242)	.074 (.350)	.314 **(<.001)**	-	-
TEIQue	-.421 **(<.001)**	-.380 **(<.001)**	.063 (.495)	.008 (.933)	.125 (.177)	.057 (.537)	.285 **(.002)**	.409 **(<.001)**	-

Notes:
Bold: P<0.05

4.8 Linear Regression Analysis

Linear regressions were carried out between social cognition outcomes and symptom, AP usage, and other illness-related variables in patient participants only, to identify any significant relationships (**Table 18**).

Table 18.
Linear Regressions Between Social Cognition Outcomes, AP Usage Variables, PANSS Variables, and Potential Predictor Variables.

	AIHQ Blame		**AIHQ Aggression**		**AIHQ Hostility**		**BLERT**		**Hinting Task**		**SAT-MC**		**EQ-CEF**		**EQ-SSF**		**TEIQue**	
	β	p value	β	p value	β	p value	β	p value	β	p value	β	p value	β	p value	β	p value	β	p value
Gender: Male	.230	.388	.250	.109	.430	.087	1.83	.107	.706	.415	-.004	.997	.773	.595	.464	.609	.210	.358
Ethnicity: White	-.359	.143	.156	.281	-.160	.495	.793	.453	.320	.690	2.77	**.011**	.168	.900	1.14	. 173	.048	.822
Age	.008	.481	-.003	.606	.022	**.027**	-.155	**<.001**	-.016	.653	-.223	**<.001**	.046	.442	-.058	.113	-.026	**.004**
Education: Educated Up to 18yrs	-.391	.093	.090	.512	-.173	.438	1.66	.097	1.39	.065	2.08	**.047**	.392	.759	1.32	.096	-.048	.813
Digit Span	-.031	.219	-.008	.603	-.027	.257	.332	**.002**	.031	.709	.101	.378	-.317	**.019**	.035	.684	.029	.176
MARS5	-.008	.857	-.013	.603	-.005	.902	.007	.969	-.202	.145	-.323	.094	-.189	.418	.025	.863	-.042	.257
AP dose	.413	.320	-.088	.720	.295	.456	-3.67	**.037**	-.362	.789	-4.59	**.013**	.936	.680	-1.14	.420	-.389	.275
AP duration	-.148	.480	-.067	.590	-.050	.801	-1.64	.065	-.926	.172	-2.12	**.023**	.688	.547	.223	.755	.094	.600
PANSS Positive	.026	.260	-.013	.321	.020	.352	-.115	.239	-.002	.983	-.032	.759	-.025	.841	-.140	.070	.026	.184
PANSS Negative	.033	.166	-.028	**.048**	.010	.655	-.259	**.010**	-.103	.184	.010	.925	-.052	.693	-.110	.176	-.008	.682
PANSS General	.034	**.045**	-.010	.327	.018	.252	-.127	.078	-.030	.591	.071	.353	-.148	.106	-.098	.089	.016	.276

Notes:
β = Standardised Beta
Bold: P<0.05

Only two outcomes showed a significant relationship with an antipsychotic usage variable. SAT-MC had a significant negative relationship with AP dose and AP duration (p = .013), meaning participants performed better at social perception when their antipsychotic medication dose was lower, and they had been taking it for a shorter period. There was also a significant negative relationship between SAT-MC and age (p = <.001), a significant positive relationship between SAT-MC and ethnicity (p = .011), and a significant positive relationship between education level and SAT-MC (p = .047). This showed an association between stronger social perception performance and white participants compared to non-white participants, more educated participants compared to less educated participants, and younger compared to older participants.

BLERT also had a significant negative relationship (p = .037) with AP dose, showing a relationship between poorer emotion recognition and higher antipsychotic dose. There was also a negative relationship between BLERT and age (p = <.001), and a significant positive relationship between BLERT and Digit Span (p = .002), meaning participants were more likely to have better emotion recognition if they were younger and had higher cognition scores.

EQ-SSF, and the Hinting Task showed no significant relationships with symptom score, AP usage, or other predictor variables.

A significant positive relationship was identified between AIHQ Blame and PANSS General symptom scores (p = .045), where a stronger blame bias was associated with patients being more symptomatic. For AIHQ Aggression, a significant negative relationship was identified with PANSS Negative scores (p = .048), with an association between more prominent negative symptoms and lower aggression bias. AIHQ Hostility had a significant positive relationship with age (p = .027), showing a stronger hostility bias related to older age in participants. For TEIQue, a significant negative relationship was identified with age (p = .004), where older age was related to a lower EI, and for EQ-CEF a significant negative relationship was seen with Digit Span (p = .019), where a poorer neurocognitive ability was associated with better cognitive empathy.

For the BLERT and SAT-MC, where social cognition outcomes had a significant relationship with an AP-related variable as well as an additional predictor variable, multiple linear regressions were conducted to identify the impact of these predictors on the relationship. These analyses are outlined in the next section.

4.8.1 Multiple Linear Regressions

4.8.1.1 BLERT

Both AP dose and Digit Span variables were identified as significant predictors of TEI scores and were therefore included in multiple linear regression models.

Table 19.1
Table Showing R^2 of BLERT X AP Dose X Digit Span X PANSS Negative Regression Models.

Model Nº	Included Variables	R^2	R^2 change
1	AP dose	.047	-
2	AP dose Digit Span	.146	.099
3	AP dose Digit Span Age	.185	.039
4	AP dose Digit Span Age PANSS Negative	.229	.044

Table 19.2
Table Showing ANOVA Results for BLERT X AP Dose X Digit Span Models.

Model	df regression, df residual	Model Significance (p value)
1	1, 71	**.037**
2	2, 72	**.001**
3	3, 69	**<.001**
4	4, 68	**<.001**

Notes:
Bold: P<0.05

Table 19.3
Table Showing ANOVA Results for BLERT X AP Dose X Digit Span Regression Models

Model	Ivs	β	p value
1	AP dose	-.245	**.037**
2	AP dose	-.196	.079
	Digit Span	.335	**.003**
3	AP dose	-.116	.316
	Digit Span	.244	**.039**
	Age	-.256	**.042**
4	AP dose	-.054	.638
	Digit Span	.191	.103
	Age	-.294	**.018**
	PANSS Negative	-.243	**.029**

Notes:
Bold: P<0.05

A multiple regression was carried out to investigate whether AP dose, Digit Span, age, and PANSS Negative variables could significantly predict participants' BLERT scores. The results of the regression indicated that the final model explained 22.9% of the variance and that the model was a significant predictor of BLERT (df (4,68), p = <.001). age and PANSS Negative contributed significantly to the final model. For

age there was a .294 standard deviation decrease for every standard deviation increase in BLERT, and for PANSS Negative there was a .243 standard deviation decrease for every standard deviation increase in BLERT. AP dose (p = .638) and Digit Span (p = .103) did not contribute significantly to the final model.

4.8.1.2 SAT-MC

AP dose, age, and ethnicity variables were identified as significant predictors of SAT-MC scores and were therefore included in multiple linear regression models.

Table 20.1
Table Showing R^2 of SAT-MC X AP Dose X AP Duration X Age X Education Level X Ethnicity Regression Models.

Model Nº	Included Variables	R^2	R^2 change
1	AP dose	.047	-
2	AP dose AP duration	.068	.021
3	AP dose AP duration Age	.143	.075
4	AP dose AP duration Age Education level	.139	-.004
5	AP dose AP duration Age Education level Ethnicity	.139	0

Table 20.2
Table Showing ANOVA Results for SAT-MC X AP Dose X AP Duration X Age X Education Level X Ethnicity Regression Models.

Model	df regression, df residual	Model Significance (p value)
1	1, 71	**.037**
2	2, 72	**.031**
3	3, 69	**.003**
4	4, 68	**.007**
5	5, 67	**.010**

Notes:
Bold: P<0.05

Table 20.3
Table Showing SAT-MC X AP Dose X AP Duration Age X Education Level X Ethnicity Regression Models.

Model	Ivs	β	p value
1	AP dose	-.245	**.037**
2	AP dose	-.219	.061

	AP duration	-.187	.108
3	AP dose	-.111	.346
	AP duration	-.104	.366
	Age	-.324	**.010**
4	AP dose	-.114	.336
	AP duration	-.078	.512
	Age	-.310	**.014**
	Education level	-.097	.407
5	AP dose	-.117	.326
	AP duration	-.063	.600
	Age	-.365	**.009**
	Education level	.122	.308
	Ethnicity	-.128	.310

Notes:
Bold: P<0.05

A multiple regression was carried out to investigate whether AP dose, AP duration, age, education level, and ethnicity variables could significantly predict participants' SAT-MC scores. The results of the regression indicated that the fourth model and the final model explained 13.9% of the variance and that the model was a significant predictor of SAT-MC (df (5,67), p = .010). Only age contributed significantly to the final model. For age there was a .365 standard deviation decrease for every standard deviation increase in SAT-MC. AP dose (p = .326), AP duration (p = .600), education level (p = .308), and ethnicity (p = .310) did not contribute significantly to the final model.

4.9 Summary

A summarised version of the cross-sectional study findings determining the effects of antipsychotic dose and duration, as well as symptoms on social cognition outcomes, were as follows:

- Higher AP dose and AP duration were found to significantly predict poorer social perception (SAT-MC) performance. However, this relationship failed to remain significant after accounting for age, education level and ethnicity in a multiple regression model.

- Higher AP dose was also found to significantly predict poorer emotion recognition (BLERT) performance. However, this relationship also failed to remain significant after accounting for digit span, age and PANSS Negative in a multiple regression model.

- Of the PANSS variables, a higher PANSS Negative score (e.g., more negative symptoms) was a statistically significant predictor of lower AIHQ Aggression and BLERT scores, and higher PANSS General scores (e.g., more general symptoms) were a statistically significant predictor of higher AIHQ Blame bias scores.

- Digit Span was identified as a significant predictor of EQ-CEF and BLERT, with poorer neurocognitive ability predicting lower cognitive empathy, and poorer emotion recognition. In the BLERT, this relationship remained statistically significant in a multiple regressions model after controlling for AP dose and age, but not when the model also included the PANSS Negative variable.

- Education was identified as a significant predictor of SAT-MC, with those who had been in education to tertiary level performing better than those who had been in education to primary or secondary level. However, this relationship failed to remain significant after accounting for other predictor variables in a multiple regression model.

- Ethnicity was found to be a significant predictor of SAT-MC, with White ethnicity participants outperforming Non-White ethnicity participants. However, this relationship failed to remain significant after accounting for other predictor variables in a multiple regression model.

- Age was a significant predictor of BLERT, TEIQue, AIHQ Hostility, and SAT-MC. AIHQ Hostility had a positive relationship with age, where an older age predicted a stronger hostility bias in participants. All other social cognition domains had a negative relationship with age, where an older age predicted poorer performance. In SAT-MC and BLERT this relationship remained significant after accounting for other predictor variables in a multiple regression model.

- EQ-SFF and Hinting Task showed no significant relationships with any tested variables.

4.10 Social Functioning

Linear regressions were carried out between SFS scores and social cognition outcomes (**Table 21.1**). To identify relationships with other potential predictor variables additional linear regressions were conducted between SFS scores and PANSS variables, AP usage variables and other illness-related variables to identify any significant relationships (**Table 21.2**).

Table 21.1
Linear Regressions Between SFS Scores and Social Cognition Outcomes.

Variable	β	p value
AIHQ Blame	-.202	.087
AIHQ Aggression	.164	.166

AIHQ Hostility	-.323	**.005**
BLERT	-.013	.916
Hinting	.023	.846
SAT-MC	.174	.141
TEIQue	.004	.976
EQ-CEF	.095	.426
EQ-SSF	.277	**.018**

Notes:
Bold: P<0.05

Table 21.2
Linear Regressions Between SFS Scores and PANSS Variables, AP Usage Variables, and Other Potential Predictor Variables, in Patient Participants

Variable	β	p value
Gender	.067	.571
Ethnicity	.152	.199
Age	-.251	**.032**
Education	.314	**.007**
Digit Span	-.027	.822
MARS5	.079	.508
AP dose	-.324	**.005**
AP duration	.059	.621
PANSS Positive	-.235	**.046**
PANSS Negative	-.270	**.021**
PANSS General	-.163	.168

Notes:
Bold: P<0.05

A significant negative relationship was identified between SFS and AIHQ Hostility (p = .005), meaning higher hostility bias was associated with poorer social functioning scores. A statistically significant positive relationship was identified between SFS and EQ-SSF (p = .018). Additional predictor variables identified to have a statistically significant negative relationship with SFS score were AP dose (p = .005), PANSS Positive (p = .046), PANSS Negative (p = .021), and age (p=.032), and education level (p = .007) was found to have a significant positive relationship with SFS score. No other statistically significant relationships between social functioning and social cognition variables were identified.

4.10.1 Multiple Linear Regressions – SFS

AIHQ Hostility and EQ-SSF were identified as significant predictors of SFS scores, alongside education level, age, PANSS positive and PANSS negative scores, and were therefore included in a multiple linear regression.

Table 22.1
Table Showing R^2 of SFS X AIHQ Hostility X EQ-SSF X AP Dose X Education Level X PANSS Negative X Age X PANSS Positive Regression Models.

Model Nº	Included Variables	R^2	R^2 change
1	AIHQ Hostility EQ-SSF	.134	-
2	AIHQ Hostility EQ-SSF AP dose	.215	.081
3	AIHQ Hostility EQ-SSF AP dose Education level	.233	.018
4	AIHQ Hostility EQ-SSF AP dose Education level PANSS Negative	.256	.023
5	AIHQ Hostility EQ-SSF AP dose Education level PANSS Negative Age	.246	-.010
6	AIHQ Hostility EQ-SSF AP dose Education level PANSS Negative Age PANSS Positive	.236	-.010

Table 22.2
Table Showing ANOVA Results for SFS X AIHQ Hostility X EQ-SSF X AP Dose X Education Level X PANSS Negative X Age X PANSS Positive Models.

Model	df regression, df residual	Model Significance (p value)
1	2, 70	**.007**
2	3, 69	**<.001**
3	4, 68	**<.001**
4	5, 67	**<.001**
5	6, 66	**<.001**
6	7, 65	**<.001**

Notes:
Bold: P<0.05

Table 22.3
Table Showing ANOVA Results for SFS X AIHQ Hostility X EQ-SSF X AP Dose X Education Level X PANSS Negative X Age X PANSS Positive Regression Models

Model	Ivs	Standardised Beta	p value
1	AIHQ Hostility	-.256	**.035**
	EQ-SSF	.183	.129
2	AIHQ Hostility	-.239	**.041**
	EQ-SSF	.162	.161
	AP dose	-.287	**.009**
3	AIHQ Hostility	-.233	**.039**
	EQ-SSF	.116	.307
	AP dose	-.276	**.010**
	Education level	.252	**.020**
4	AIHQ Hostility	-.237	**.034**
	EQ-SSF	.088	.436
	AP dose	-.236	**.028**
	Education level	.257	**.016**
	PANSS Negative	-.186	.083
5	AIHQ Hostility	-.230	**.044**
	EQ-SSF	.086	.451
	AP dose	-.224	.052
	Education level	.251	**.021**
	PANSS Negative	-.188	.082
	Age	-.033	.774
6	AIHQ Hostility	-.227	**.049**
	EQ-SSF	.080	.489
	AP dose	-.213	.075
	Education level	.249	**.024**
	PANSS Negative	-.173	.140
	Age	-.042	.726
	PANSS Positive	-.043	.727

Notes:
Bold: P<0.05

A multiple regression was carried out to investigate whether AIHQ Hostility, EQ-SSF, AP dose, education level, PANSS Negative, PANSS Positive, and age variables could significantly predict participants' SFS scores. The results of the regression

indicated that the fourth model explained the most variance in SFS with 25.6% variance, and that the model was a significant predictor of SFS (df (5,67), p = <.001). AIHQ Hostility, AP dose, and education level contributed significantly to the final model. For AIHQ Hostility there was a .237 standard deviation decrease for every standard deviation increase in SFS, for AP dose there was a .236 standard deviation decrease for every standard deviation increase in SFS, and for education level, standardised beta = .257, showing participants were more likely to have a higher SFS who were educated to a tertiary level, compared to those educated to a secondary level (up to 18 years).

4.11 Discussion – Cross-Sectional Results

The purpose of the present cross-sectional study was to explore differences in social cognitive performance between patients with a schizophrenia-spectrum disorder and healthy volunteers. The study also aimed to identify any relationships between social cognition and symptom presentation, and social cognition and antipsychotic usage variables, in patients with a schizophrenia-spectrum disorder. Finally, the relationship between social functioning and social cognition was also explored in patients with a schizophrenia-spectrum disorder.

4.11.1 Social Cognition in Patients with a Schizophrenia-Spectrum Disorder vs. Healthy Volunteers

Results showed that across all domains, healthy volunteers outperformed patients with a schizophrenia-spectrum disorder. Findings of observable significant differences between healthy volunteers and patients with a schizophrenia-spectrum disorder across all social cognition domains were consistent with previous studies, and add to the evidence that, in patients with schizophrenia social cognition deficits are domain-general, and may be a core feature of the disorder (Kharawala et al., 2022; Pinkham et al., 2018). However, the cross-sectional nature of the study failed to account for the effects of long-term symptom or AP dose changes on potential social cognition performance changes over time, and therefore this needs to be further explored.

The age ranges reported for both the patient group and the healthy volunteer group covered a wide range, representative of the general population and increasing the generalisability of these findings. However, these wide age ranges may have introduced additional confounding factors related to age-related differences in social cognition or more general cognition ability. Future studies may consider employing more narrow age ranges to minimise potential age-related biases to better isolate the effects of schizophrenia-spectrum disorder on social cognition.

It is also important to note that diagnosis of patients in this sub-study relied on hospital administration records that were not subsequently verified using a diagnostic interview in the research study. Therefore, it is possible that a proportion of the patient sample did not fulfil the criteria for a schizophrenia-spectrum diagnosis. This lack of diagnostic specificity has implications for the generalisability of these findings, and it is recommended further research with confirmatory diagnostic evaluation is undertaken before social cognition deficits can be recognised as a core feature of schizophrenia-spectrum diagnoses.

Additionally, around one third of participants in the study had a schizophrenia-spectrum diagnosis other than schizophrenia. The inclusion of participants with diverse diagnoses could potentially contribute to additional heterogeneity, influencing the observed social cognition deficits. However, by including patients with various diagnoses under the schizophrenia-spectrum umbrella the findings allow for a more nuanced understanding of social cognition difficulties experienced by individuals who may experience different diagnostic presentations. Further research should be conducted on homogenous samples with specific diagnostic criteria. This approach would provide a clearer understanding of the extent to which social cognition deficits are widespread across different schizophrenia-spectrum disorders.

Also of note, the mean PANSS score of 48 for patients in this study was low, considering that the lowest possible score on the PANSS is 30. This suggests that the participants in the sub-study had mild symptom severity compared to the full range of symptoms observed in individuals with schizophrenia-spectrum disorders in the general population (Leucht et al., 2005). As a result, the generalisability of the study findings may be limited to individuals with milder symptom profiles.

4.12 Social Cognition, Symptom Scores, and Additional Predictive Variables

The correlations observed amongst the social cognition variables suggest that there were interrelationships between the constructs, indicating potential shared underlying factors. To gain a deeper understanding of these relationships and to explore additional influences on the variables, conducting factor analysis could be beneficial. Factor analysis would help identify constructs that represent related domains within social cognition, allowing for a more comprehensive analysis. However, it is important to note that the current sub-study had a relatively small sample size, which limited the feasibility of conducting factor analysis. Additionally, the focus of this sub-study was primarily on investigating the individual relationships between each social cognition domain and other variables of interest (e.g., symptoms, AP dose and duration). Due to the constraints of the study, each social cognition domain was analysed in separate linear regressions, without incorporating intercorrelations between them. However, it is important to acknowledge that considering the correlations between social cognition domains could have provided additional insights and context to the observed relationships. Future studies or further analyses could explore these correlations and their potential impact on the results to gain a more comprehensive understanding of the complex dynamics within the social 99ositive99n domains.

The linear regressions conducted revealed several significant relationships between social cognitive domains, symptom scores, AP usage, and illness-related variables, which will be explored further below:

4.13 Social Cognitive Domains and Antipsychotic Usage

Higher antipsychotic doses significantly predicted poorer emotion recognition performance. However, after accounting for age and PANSS Negative, the relationship between variables was no longer significant. Similarly, higher antipsychotic dose and duration of use significantly predicted poorer social perception performance. However, after accounting for age, the relationship between

variables was also no longer significant. These findings suggest that additional factors, such as age and PANSS Negative, potentially mediate or moderate the relationship between antipsychotic usage and specific domains of social cognition. To further investigate these complex relationships, future research should explore potential mediators and moderators, such as neurocognition, demographic variables, symptom severity, illness duration, or genetic variations. Robust analysis, such as statistical equation modelling (SEM), should be used to examine these relationships; however, this will require an adequate sample to account for inclusion of multiple variables. Additionally, neuroimaging techniques could be incorporated to identify underlying neural mechanisms or biomarkers associated with social cognition.

Furthermore, no statistically significant relationships were identified between other social cognitive domains (emotional intelligence, attribution bias, theory of mind, and empathy) and antipsychotic usage. There were mixed results from previous studies investigating the relationships between antipsychotic usage and social cognition (Haime et al., 2021; Kucharska-Pietura & Mortimer, 2013), and as relationships in the sub-study were not significant it is important to consider factors which may have influenced the results. Not only were the current sample relatively well (Mean PANSS total score = 48.00, being 'mildly ill' according to Leucht et al (2005) would equal PANSS total score = 58.00), but they also started the study taking a low average daily dose of antipsychotics (Mean = 365.51 CPZ equivalent, with <400mg/day considered a low dose in Dudley et al (2017). This may mean the analysis was not sensitive enough to identify effects of the medication, or that lower doses of antipsychotics are less likely to affect social cognition. Additional potential issues with this study, including social cognition measures, and the study sample are discussed in depth in Chapter 6 of this thesis.

4.14 Attribution Bias

4.14.1 AIHQ Aggression

Results showed that a higher PANSS Negative score predicted a lower AIHQ Aggression Bias. These findings were consistent with other studies, where more prevalent negative psychosis symptoms have been associated with lower aggression (Knezevic et al., 2015; Swanson et al., 2006), which may suggest a protective role for negative symptoms in aggression control. This relationship suggests future research should aim to identify specific negative symptoms which may have protective properties for patients, which this study was unable to conclude. Identifying symptoms which lessen aggressive tendencies may assist treatment strategies for recovery. It will also be important for future research to identify the direction of this relationship and how it evolves over time.

4.14.2 AIHQ Blame

Higher PANSS General scores were found to significantly predict a higher AIHQ Blame score. The PANSS General domain incorporates several symptom factors, including depression, anxiety, active social avoidance (symptoms of paranoia), tension, and unusual thought content. Research on the relationship between paranoia and attribution bias has shown mixed results in the literature, with some studies showing no difference between paranoid vs. non-paranoid patients with

schizophrenia at attribution bias tasks (Kaney & Bentall, 1989; Martin & Penn, 2002), and others showing worse deficits on attribution bias measures by paranoid patients (Janssen et al., 2006; McKay et al., 2005). Additionally, psychiatry research has shown that patients with anxiety, and depression symptoms, are more likely to have higher blame biases (Buck et al., 2020; Lahera et al., 2015). Despite this, as the General PANSS domain includes several quite diverse psychiatric symptoms it is not currently possible for this study to conclude whether specific symptoms have significant relationships with AIHQ Blame. Importantly, it should be considered that the General PANSS measure item 'active social avoidance' and the AIHQ are reporting similar 'paranoia' attributes, and this may have biased the results, as scoring for the PANSS was subjective and completed after AIHQ data was collected.

4.14.3 AIHQ Hostility

A significant positive relationship existed between AIHQ Hostility scores and age, with a higher age predicting higher hostility. Existing attributional bias evidence has shown a stronger personalising bias in older adults compared to younger adults (Horhota, 2014), although other research has shown no significant effects of age on overall AIHQ score (Pinkham et al., 2017). Therefore, further research is needed to explore this specific relationship between hostility and age in patients with schizophrenia.

4.15 Theory of Mind (ToM)

The relationship between ToM and symptom scores was not significant according to the baseline data. This result was unexpected as literature in the field has consistently shown an association between higher negative or disorganised psychosis symptoms and ToM (Kelemen et al., 2005; Mazza et al., 2001; Sarfati et al., 1999). However, the high normative Hinting Task scores amongst our patient sample (mean = 16.11), alongside a low average negative PANSS score (mean = 11.41, as described in Leucht et al (2020) suggest a negative symptom score of ≥24 is necessary to identify patients with moderate-to-severe negative psychosis symptoms), present a relatively 'clinically well' sample that may not be representative of populations with more severe negative symptoms.

4.16 Emotional Processing

Baseline patient data analysis showed a statistically significant negative relationship between emotion processing and negative symptom scores. Previous studies have also evidenced a statistically significant relationship between negative symptoms and emotion recognition in patients with schizophrenia (Andrzejewska et al., 2017; Charernboon, 2020). However, where other studies have consistently found associations between positive/general symptoms of paranoia and emotion recognition, in this sub-study no associations were found between the BLERT measure and either positive or general PANSS scores. Previously, some researchers have claimed paranoia causes improvements to emotion recognition (Huang et al., 2013; Combs et al., 2006; Arguedas et al, 2006) and others have refuted these findings, claiming paranoia causes deficits to emotion processing (Mitrovic et al., 2020; Pinkham et al., 2011). The pooling of items in PANSS domains for this sub-study analysis means that this data was unable to identify specific

relationships between symptoms of paranoia and emotion processing, and that a specific measure of paranoia would have allowed clearer comparisons. Overall, symptom findings indicate that those with higher negative symptoms may have difficulty processing emotional content, and therefore this relationship should be particularly considered in treatment of patients with prominent negative symptoms.

Baseline analysis also revealed a statistically significant negative relationship between emotion processing and age, with a higher age resulting in a poorer BLERT performance. A review by Ruffman et al (2008) found similar results from the n= 28 datasets they analysed, with older adults having difficulties in the recognition of anger, sadness, disgust, surprise, and happiness, with significant deficits in recognition of the negative emotions (anger and sadness). This indicates that declines in emotion recognition may be seen over time and therefore longitudinal studies are a necessity for future social cognition research.

A statistically 102ositivee relationship was also shown between emotion processing and Digit Span, with higher Digit Span scores predicting better BLERT performance. Most previous studies have shown emotion processing deficits to be independent from neurocognitive dysfunction (Sergi et al., 2007; Lee et al., 2013). However, this study suggests a possible interplay between neurocognition and emotion processing, and therefore, further research is needed to explore the nature of this relationship.

Linear regressions also revealed a negative relationship between BLERT and AP dose, with higher antipsychotic doses predicting poorer emotion recognition performance, however this relationship failed to remain significant after accounting for age and PANSS Negative symptoms. A previous review by Hempel et al (2010) showed no substantial improvements in facial affect recognition after antipsychotic treatment, they also showed no relationship between affect recognition and symptom severity. Alike to the conclusions from Hempel et al's (2010) review, recommendations should be made for future research to investigate the impact of psychological and behavioural treatments on emotion recognition, and to further explore the impact of antipsychotics on emotion processing in patients with schizophrenia/psychosis in longitudinal studies.

4.16.1 Emotional Intelligence (EI)

Results showed a significant negative relationship between TEIQue and age. This suggests that older age is a predictor of poorer emotional intelligence. Interestingly, previous findings have shown an inverted-U ability for emotional intelligence measures amongst adults, with middle-aged adults scoring higher than both lower-aged and older-aged adults (Cabello et al., 2016). Some research has also identified university-education as a protective factor in emotional intelligence decline in older adults (Cabello et al., 2014). However, there is a lack of research into emotional intelligence decline in patients with schizophrenia, and the factors that may be affecting this apparent relationship, and therefore further exploration is needed in longitudinal studies.

4.16.2 Empathy (EQ)

Relationships between empathy (cognitive and social/affective) and symptom scores were not significant, replicating findings by Achim et al (2011) and Montag et al (2007). Unlike these previous studies however, the findings from this sub-study also identified no significant relationship between age and empathy domains, nor between antipsychotic dose or duration and EQ scores. However, a significant negative relationship was noted between cognitive empathy and Digit Span, with poorer EQ-CEF scores resulting in better Digit Span performance. This result was unexpected but may be explained by the self-rating aspect of the EQ, which can result in inaccuracies due to participant bias (Konstantakopoulous et al., 2014). Current research in this area is sparse and represented by only a few older papers, and the conflicting findings show the need for more robust studies of empathy and psychosis related factors.

4.17 Social Perception

No significant relationship was found between SAT-MC and symptom domains in this study. Very little previous research exists that has looked at relationships between symptoms of schizophrenia and social perception. One early study showed that patients with paranoid schizophrenia performed better than non-paranoid patients on a social perception task (Seidman, 1983), and another study has shown a negative correlation between the individual symptom of conceptual disorganisation and social perception (Toomey et al., 2002). Generally, research seems to have found little evidence for a relationship between social perception and symptoms in patients with schizophrenia (Toomey et al., 2002; Couture et al., 2006; Ihnen et al., 1998).

A negative relationship was also found between age and social perception, with a higher age predicting poorer SAT-MC scores. A previous study by Pinkham et al (2018) found no relationship between a measure of social perception and age. However, they did find a negative relationship between emotion processing and age on a dynamic task. As the social perception task in this study also included a dynamic presentation, it is important to consider if this additional cognitive processing may have been what caused deficits in older aged participants.

Results showed a significant negative relationship between the predictors AP dose and AP duration, and SAT-MC. Meaning that a higher antipsychotic dosage and number of years taken predicted a poorer SAT-MC performance. However, these relationships failed to remain significant after controlling for statistically significant predictors in a multiple regression. These relationships may have failed to remain significant because the sample size was too small to detect an effect in the relationship, or correlations between ethnicity and age, and ethnicity and education level resulted in affected p values. Previous research has shown both no relationship between AP dose and social perception, and improvements in social perception related to AP dose (Sergi et al., 2007; Roberts et al., 2010; Sumiyoshi et al., 2009). These inconsistent results may be due to different social perception measures used across studies (Script Tasks, IPT-15, and the SCRT). In this study we used the SAT-MC which may also be less sensitive to differences in antipsychotic dose compared

to other measures of social perception (see Chapter 6, section 6.7 for measures discussion).

4.18 Social Functioning and Social Cognitive Domains

The fourth regression model in multivariate linear regression analysis including AIHQ Hostility, EQ-SSF, AP dose, education level, and PANSS Negative as predictor variables of SFS, was able to account for a quarter of the variance in SFS score (25.6%).

AIHQ Hostility (B = .237, p = .038) remained a statistically significant predictor in this model, showing a strong relationship between higher hostility bias and poorer social functioning scores. This was similar to findings in a recent study by Strassnig et al (2020) in patients with schizophrenia. They found hostility to be the only significant predictor of social functioning in regressions including hostility, paranoia, and depression as predictors. They also found healthy volunteers who reported greater hostility reported poorer social functioning.

This model also identified AP dose as a significant predictor of social functioning. The results showed that higher antipsychotic dose was related to lower SFS scores in patients with schizophrenia, replicating other cross-sectional findings from Tandon et al (2020). However, this conflicts with findings from Mohr et al (2013) who found improvements to functioning performance with antipsychotic use. The association found between AP dose and SFS in this sub-study did not exist in analysis of all RADAR participants, which suggests differences may exist between those who took part in the sub-study from the main trial population.

Additionally, education level was found to be a significant predictor of social functioning, where those who attended tertiary level education were likely to have better social functioning outcomes. This replicates previous findings that have established higher education levels as a statistically significant predictor of better social functioning in patients with schizophrenia (Melle et al., 2000).

These relationships between variables may be important to consider when considering social functioning as a recovery target in patients with schizophrenia. Further longitudinal studies will be integral in identifying if changes in antipsychotic dose and social cognition, relate to changes in social functioning.

Chapter 5 – Longitudinal Data – Results and Discussion

The purpose of the present longitudinal study was to evaluate whether group assignment (reduction/discontinuation vs. maintenance), predicted social cognition score changes over time, and whether social cognition score changes were related to symptom, neurocognition, or social functioning changes.

This chapter outlines the results from the longitudinal analysis described in Chapter 3 (section 3.4). Findings are then discussed with reference to existing literature in the field related to social cognition relationships with symptoms, antipsychotics, and social functioning.

The aims of this chapter:

Aim 1: Determine if there are significant differences in social cognitive ability across domains, in patients in the reduction/discontinuation group vs. the maintenance group at baseline.

Aim 2: To evaluate:

- Whether *changes* in social cognition domains between timepoints were significantly different between groups.
- Whether changes in social cognition domains between timepoints were significantly different, *across* groups.
- To test for differences in social cognition change between groups and over time after controlling for potential predictors of social cognition change across groups and any relevant variables that differ between groups.
- Whether changes in social cognition are associated with changes in antipsychotic dose

Aim 3: To determine whether changes in social cognition were related to changes in social functioning performance, and to identify other potential predictors of social functioning change.

The current study aimed to investigate the effects of antipsychotic reduction/discontinuation on social cognition outcomes over time. To this end, changes in social cognition were evaluated by analysing the mean change scores across groups from baseline (0 months) to 12- months, from 12- to 24- months, and over the entire 24- month period. The primary interest was to determine if there were different patterns of change between the reduction and maintenance groups and to explore the overall change in social cognition outcomes. The investigation of change over different time periods was deemed important to explore potential shorter-term adverse effects of antipsychotic reduction/discontinuation. Hence, a thorough evaluation of patterns of change over time in social cognition was necessary.

5.1 Participant Flow

RADAR assessments at baseline were completed in February 2020 with a total of n= 253 participants recruited across 19 sites in the UK. For the social cognition sub-study, n= 73 baseline assessments were completed. Follow-up assessments for RADAR were conducted at 6, 12, and 24-month time-points, until January 2022. The social cognition follow-ups were conducted at 12, and 24- months, with n= 46, and n= 42 participants completing each time-point, respectively.

5.2 Study Completion

The participant study flow for the social cognition sub-study can be seen in **Figure 6.**

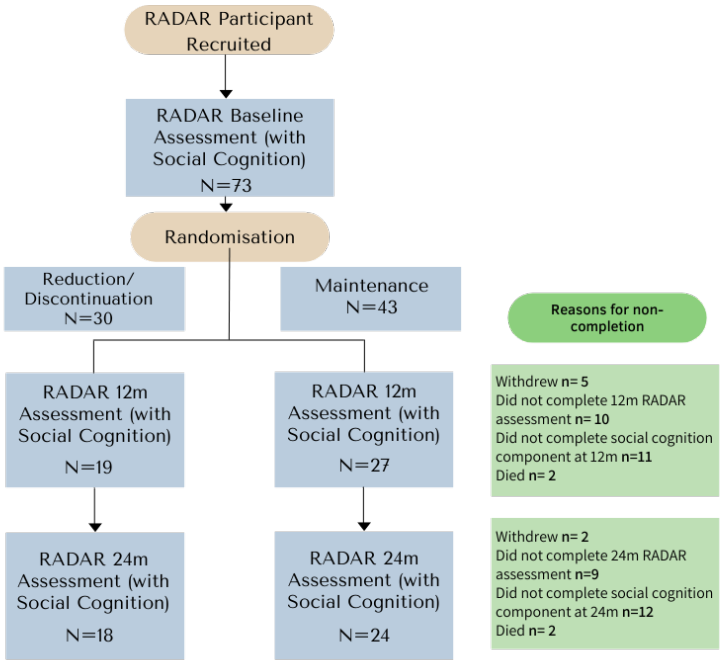

Figure 6. Flow-chart of participation for the social cognition sub-study.

At baseline, 30 participants were randomly assigned to the reduction/discontinuation group, and 43 to the maintenance group. At follow-up, n= 19 (63.3%) of the reduction/discontinuation group and n= 27 (62.8%) of the maintenance group completed the 12m social cognition measures. N=5 participants withdrew from the study by the 12m assessment and n= 2 died before follow-up. Of those who remained in the study but did not complete the 12m time-point n= 10 did not complete any of the RADAR assessment, and n= 10 completed at least one measure in the 12m RADAR assessment but did not complete any of the social cognition component. At 24m, n= 18 (60%) of the reduction/discontinuation group, and n= 24 (55.8%) of the maintenance group completed the social cognition component. N= 2 participants withdrew and n= 2 died between 12-24 months. Of those who remained participants but did not complete the 24m time-point n= 9 did not complete any of the RADAR assessment, and n= 11 completed at least one measure in the 12m RADAR assessment but did not complete any of the social cognition component.

5.3 Missing Data

Missing data for the follow-up measures at 12 and 24- months is visualised in **Table 23**.

Table 23.
Table Showing Data for Measures Missing at 12- Month and 24- Month Timepoints.

Measure	12m Timepoint (n=46)	24m Timepoint (n=42)
Digit Span	0	0
SFS	0	0
MARS-5	0	0
PANSS*	10	2
AIHQ	0	2
BLERT	8	6
Hinting	2	5
EQ-SF	2	4
TEIQue	4	6
SAT-MC/SAT-MC II	12	6

Notes:
*Refers to individual items on measure missing

At the 12- month follow-up, data were missing on the PANSS on single items for 10 participants. For nine of these participants data were missing on G7 'motor retardation'. This item requires the researcher to interpret the body movements of the participant and it is therefore most likely this item was missed due to the start of the COVID-19 pandemic where assessments were transferred to either telephone or internet-based appointments, making observation of participants difficult. Also, at 12m follow-up, full measures were missed by n= 2 participants on the hinting task, n= 8 participants on the BLERT, n= 2 on the EQ, n= 4 participants on the TEIQue, and n=1 2 participants on the SAT-MC II. Again, it is likely that the video-based social cognition measures (BLERT and SAT-MC II) were difficult to administer during the initial COVID-19 pandemic lockdowns (due to technology adjustments), and this may be the reason for their missing data.

At 24- month, follow-up data were missing on the PANSS on 1 item, for n= 2 participants. Data was also missing for n= 2 participants on the AIHQ, n=5 on the Hinting Task, n= 6 on the BLERT, n= 4 on the EQ, n=6 on the TEIQue, and n= 6 on the SAT-MC.

There were no missing data at either follow-up on the SFS, MARS-5 or the Digit Span for participants included in this sub-study.

Baseline data from multiple imputation in Chapter 4 were used in the analyses presented in this chapter. Additionally, multiple imputation was completed on 12-

and 24- month datasets, (see Chapter 3, section 3.9.1 for details), and this was also used for analysis in this chapter.

5.4 Baseline Characteristics of Sub-Study Completers vs. Non-Completers.

Baseline characteristics were compared between those who completed the 24m follow-up assessment, and those who did not, using T-tests and chi-squares to assess for bias in the baseline sample (**Table 24**). No statistically significant differences were shown between groups on variables. This indicates that at baseline, completers and non-completers were similar in demographic characteristics and non social cognition outcomes.

Table 24.
T-Tests and Chi-Squares Between Completers Vs. Non-Completers of The 24m Social Cognition Sub-Study, on Baseline Demographics and Outcome Variables.

Variable	Completed 24m Social Cognition Component (n=42) N (%)	Did Not Complete 24m Social Cognition Component (n=31) N (%)	p-value
Gender			.572
Male	32 (76.2)	22 (71.0)	
Female	10 (23.8)	9 (29.0)	
Ethnicity			.675
Non-White	12 (33.3)	13 (35.5)	
White	30 (66.7)	18 (64.5)	
Education			.183
Up to 18 (Secondary)	17 (45.2)	17 (64.5)	
Tertiary	25 (54.8)	14 (35.5)	
	Mean (SD)	**Mean (SD)**	
CPZ Equivalents*	390.81 (276.33)	331.26 (271.52)	.082
Age*	45.68 (12.19)	48.26 (9.73)	.248
Digit Span	16.14 (4.65)	14.39 (4.54)	.112
SFS	108.19 (9.18)	110.14 (9.01)	.371
PANSS Total*	48.33 (16.11)	47.55 (12.32)	.721

Notes:
*non-parametric t-test
Bold: P<0.05

In addition, 12- and 24- month mean scores for Digit Span, PANSS Positive, PANSS Negative, PANSS General, and the SFS can be seen in **Table A20** and **Table A21** – Appendix F.

5.5 Baseline Comparisons Between Reduction/Discontinuation and Maintenance Group Participants

Aim 1) Determine if there are significant differences in social cognitive ability across domains, in patients in the reduction/discontinuation group vs. the maintenance group at baseline.

To address the first aim of this chapter and in order to ensure the randomised groups were comparable, univariate tests were conducted between groups on baseline demographic characteristics and other illness-related variables, which can be seen in **Table 25**. There was a statistically significant difference in age between the two groups (p = .019), with the reduction/discontinuation group having a higher mean age compared to the maintenance group. Therefore, age was included as a covariate in further multivariate analyses within this chapter. No other statistically significant or clinically relevant differences were observed on demographic variables, CPZ Equivalent medication doses, Digit Span, SFS, or PANSS baseline scores.

Table 25.
T-Tests and Chi-Squares Between Reduction/Discontinuation Vs. Maintenance Groups, on Baseline Demographics and Outcome Variables.

Variable	Reduction/Discontinuation (n=30) N (%)	Maintenance (n=43) N (%)	p-value
Gender			.102
Male	25 (83.3)	29 (67.4)	
Female	5 (16.7)	14 (32.6)	
Ethnicity			.172
Non-White	8 (26.7)	17 (39.5)	
White	22 (73.3)	26 (60.5)	
Education			.672
Up to 18 (Secondary)	16 (53.3)	23 (53.5)	
Tertiary	14 (46.7)	20 (46.5)	
Diagnosis			.474
Schizophrenia	19 (63.3)	29 (67.4)	
Other Psychosis	11 (36.7)	14 (32.6)	
	Mean (SD)	**Mean (SD)**	
CPZ Equivalents*	351.83 (312.62)	375.05 (246.98)	.792
Age	50.70 (10.52)	44.70 (10.48)	**.019**
Digit Span	15.00 (5.54)	15.67 (3.96)	.546

SFS	107.12 (8.79)	110.35 (9.17)	.137
PANSS Negative	11.00 (5.72)	11.65 (4.75)	.319
PANSS Positive	12.10 (4.60)	10.93 (5.09)	.598
PANSS General	24.40 (6.40)	25.76 (7.29)	.411
PANSS Total*	47.50 (14.70)	48.35 (14.58)	.928

Notes:
*non-parametric t-test
Bold: P<0.05

Univariable linear regressions were then conducted between social cognition outcomes and potential demographic and illness-related predictor variables across both groups to identify covariates (**Table 26**). Comparison of means using t-tests and ANCOVAs (where adjustments were made for significant covariates from Table 26) showed no statistically significant differences between reduction/discontinuation and maintenance groups on social cognition domains at baseline, suggesting similar ability across participants in each arm of the RCT (**Table 27)**.

Table 26.
Linear Regressions Between Social Cognition Outcomes and Potential Predictor Variables, Across All Sub-Study Participants (n=73) on Baseline Data.

Variable	AIHQ Blame				AIHQ Aggression				AIHQ Hostility				BLERT			
	β	p-value	95% CI		β	p-value	95% CI		β	p-value	95% CI		β	p-value	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper
Gender: Male	.103	.388	-.298	.758	.189	.109	-.057	.556	.202	.087	-.064	.924	.190	.107	-.406	4.059
Ethnicity: White	-.173	.143	-.843	.124	.128	.281	-.130	.442	-.081	.495	-.625	.305	.089	.453	-1.301	2.888
Age	.084	.481	-.014	.029	-.061	.606	-.016	.009	.258	**.027**	.003	.042	-.396	**<.001**	-.240	-.070
Education: Educated up to 18yrs	-.198	.093	-.849	.066	.078	.512	-.183	.364	-.092	.438	-.614	.269	.196	.097	-.305	3.618
Digit Span	-.146	.219	-.081	.019	-.062	.603	-.037	.022	-.134	.257	-.075	.020	.364	**.002**	.131	.533
PANSS Positive	.134	.253	-.019	.071	-.118	.305	-.040	.013	.111	.356	-.023	.063	-.139	.250	-.308	.078
PANSS Negative	.164	.166	-.014	.080	-.232	**.048**	-.055	.000	.053	.655	-.035	.056	-.299	**.010**	-.455	-.064
PANSS General	.236	**.045**	.001	.067	-.116	.327	-.030	.010	.136	.252	-.013	.050	-.208	.078	-.269	.014

Variable	Hinting Task				SAT-MC				EQ-CEF				EQ-SSF				TeiQue			
	β		95% CI		β	p-value	95% CI		β	p-value	95% CI		β	p-value	95% CI		β	p-value	95% CI	
		p-value	Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper
Gender: Male	.097	.415	-2.408	.002	.002	.997	-1.009	2.421	.023	.850	-2.614	3.163	.097	.415	-1.009	2.421	.109	.358	-.242	.661
Ethnicity: White	.048	.690	.645	.295	.295	**.011**	-1.271	1.911	.058	.626	-2.012	3.322	.048	.690	-1.271	1.911	.027	.822	-.372	.468
Age	-.054	.653	-.305	-.538	-.538	**<.001**	-.086	.054	.074	.535	-.081	-.154	-.054	.653	-.086	.054	**.331**	**.004**	-.043	-.008
Education: Educated up to 18yrs	.217	.065	.028	.233	.233	**.047**	-.088	2.871	-.097	.415	-3.569	1.490	.217	.065	-.088	2.871	-.028	.813	-.447	.352
Digit Span	.044	.709	-.126	.105	.105	.378	-.133	.194	-.058	.627	-.341	.207	.044	.709	-.133	.194	.160	.176	-.013	.072
PANSS Positive	-.003	.970	-.138	-.037	-.037	.716	-.150	.146	.046	.701	-.201	.297	-.005	.970	-.152	.146	.157	.210	-.013	.065
PANSS Negative	-.157	.184	-.206	.011	.011	.925	-.257	.050	.195	.098	-.041	.471	-.157	.184	-.257	.050	-.049	.682	-.049	.033
PANSS General	-.064	.591	-.081	.110	.110	.353	-.139	.080	.136	.250	-.076	.289	-.064	.591	-.139	.080	.129	.276	-.013	.045

Notes:
β: Standardised Beta
95% CI: 95% Confidence Interval (CI) For β
Bold: P<0.05

Table 27.
Baseline T-Tests and ANCOVAs on Baseline Social Cognition Domains in Reduction/Discontinuation Vs. Maintenance Group Participants.

Social Cognition Measure	Reduction Mean (SD)	Maintenance Mean (SD)	p value	Mean Difference	95% CI	
					Lower CI	Upper CI
AIHQ Blame[a]	2.43 (1.07)	2.30 (.939)	.444	.179	-.285	.643
AIHQ Aggression[b]	1.67 (.661)	1.65 (.529)	.725	.048	-.226	.323
AIHQ Hostility[c]	1.93 (1.01)	1.95 (.899)	.464	-.167	-.621	.286
EQ CEF	11.90 (5.30)	11.81 (5.52)	.919	-.128	-2.631	2.375
EQ SSF	4.23 (2.64)	5.49 (3.74)	.118	-1.255	-2.84	.327
TEIQue[d]	4.21 (.802)	4.50 (.870)	.489	-.139	-.539	.260
BLERT[e]	12.03 (4.33)	12.72 (4.22)	.615	.470	-1.387	2.326
Hinting	16.10 (3.18)	16.12 (3.28)	.983	-.016	-1.55	1.52
SAT-MC[f]	9.77 (4.66)	11.42 (4.29)	.672	-.406	-2.308	1.497

Notes:
Mean Difference: Where calculation has been adjusted for multiple comparisons: Least Significant Difference (equivalent to no adjustments).
95% CI: 95% Confidence Interval for Mean Difference
[a] adjusted for PANSS General
[b] adjusted for PANSS Negative
[c] adjusted for Age
[d] adjusted for Age
[e] adjusted for Age, Digit Span, and PANSS Negative
[f] adjusted for Ethnicity (binary), Age, and Education (binary)
Bold: P<0.05

5.6 Longitudinal Analysis of Reduction/Discontinuation vs. Maintenance Antipsychotic Treatment Groups

In this section, results for each social cognition domain will be reported in turn, answering Aim 2: AIHQ Blame, AIHQ Hostility, AIHQ Aggression, BLERT, Hinting Task, SAT-MC, EQ-CEF, EQ-SSF, TEIQue. Results for social functioning, answering Aim 3, will then be presented, and a discussion of the findings will follow.

Aim 2:
To evaluate:

- Whether *changes* in social cognition domains between timepoints were significantly different between groups.
- Whether changes in social cognition domains between timepoints were significantly different, *across* groups.
- To test for differences in social cognition change between groups and over time after controlling for potential predictors of social cognition change across groups and any relevant variables that differ between groups.

- Whether changes in social cognition are associated with changes in antipsychotic dose

To address these aims, the following analyses were performed for each social cognition domain:

- T-tests were conducted on mean change scores from baseline to 12- months, baseline to 24- months, and 12- to -24 months, between and across groups.
- Linear regressions were undertaken to identify predictors of mean change score in social cognition variables, using potential predictor variables including the PANSS symptom, Digit Span, and relevant demographic variables.
- Where significant relationships were identified between group mean change scores, or mean change scores across timepoints, repeated measure linear mixed models (RLMM) were used for further analysis. Any significant variables identified in linear regressions were added as random effects or covariates. Fixed effects were time (baseline=1, 12m=2, 24m=3), and group (randomisation variable), with time x group interaction. To account for baseline differences across individuals in social cognition scores, a random intercept for subject was included in the model. The model used significant predictor variables identified as covariates. When accounting for baseline differences in predictor variables (e.g., PANSS scores) they were included in the model as by-subject random slopes.
- Additional linear regressions were conducted between social cognition change scores and antipsychotic dose change scores at 24- months.

Aim 3)
To determine whether changes in social cognition were related to changes in social functioning performance, and to identify other potential predictors of social functioning change.

To address this aim, the following analyses were performed:

- Spearman correlations were conducted between social functioning mean change scores and social cognition domain mean change scores.
- Linear regressions were performed at 12- and 24- months to identify potential predictors of change in SF including symptom-related and demographic variables.
- Where significant correlations were identified between social functioning mean change scores and social cognition mean change scores at 12- or 24- months, repeated measure linear mixed models (RLMM) were used for further analysis. Any significant variables identified in linear regressions were added as random effects or covariates.

6.1.2 Attribution Bias – AIHQ Blame

A higher AIHQ Blame score indicates a greater likelihood of blame bias towards an ambiguous social scenario. Descriptive statistics (**Table 28.1**) are visualised in Figure 7. Results showed the reduction/discontinuation group mean blame bias increased from baseline to 12- months but reduced at 24- months to below baseline level. The maintenance group showed a decrease of blame bias over time.

Table 28.1
Group (Reduction/Discontinuation vs. Maintenance) Means on the AIHQ Blame at Baseline, 12-Months and 24- Months.

AIHQ Blame Time point	Reduction/Discontinuation Group Mean (SD)	Maintenance Group Mean (SD)
Baseline	2.43 (1.07)	2.30 (.939)
12- months	2.58 (1.26)	2.15 (.818)
24- months	2.22 (1.22)	2.04 (1.08)

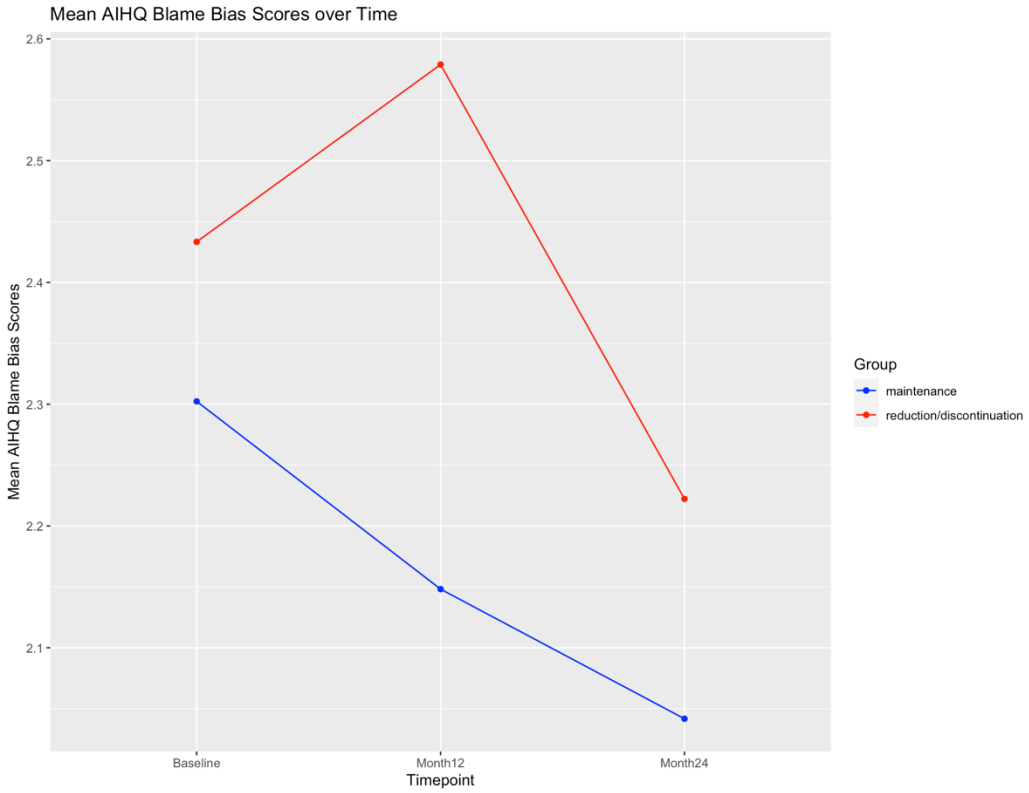

Figure 7 Interaction Plot of Mean AIHQ Blame Scores Over Time for Reduction/Discontinuation vs. Maintenance Group Participants

There were no significant differences between groups (reduction/discontinuation vs. maintenance) in mean change scores, between baseline and 12 months, baseline and 24 months, and 12- and 24- months on AIHQ Blame **(Table 28.2).** Across the whole study population, there was a statistically significant reduction in the AIHQ Blame mean change score from zero, between baseline to 12 months (mean change score = -.239, p = .047) **(Table 28.3).**

Table 28.2

T-tests for Group (Reduction/Discontinuation vs. Maintenance) Differences on AIHQ Blame Mean Change Scores Between Time Points.

Between Time points	Reduction/Discontinuation Mean Change Score (SD)	Maintenance Mean Change Score (SD)	p value	Hedges g	Point Estimate of Mean Difference	Lower CI	Upper CI
12m Change	-.263 (.653)	-.222 (.892)	.868	-.051	-.041	-.525	.443
12m to 24m Change	-.308(.855)	.059 (.556)	.194	-.524	-.367	-.089	.162
24m Change	-.389 (.778)	.000 (.834)	.128	-.480	-.389	-1.08	.122

Notes:

Bold: P<0.05

Table 28.3
One Sample T-tests of Mean Change Score Difference from Zero on the AIHQ Blame.

Between Time points	Mean Change Score Difference	p value	Cohen's d
Baseline to 12- months	-.239	**.047**	-.301
12- to 24- months	-.100	.448	-.140
Baseline to 24- months	-.167	.197	-.202

Notes:
Bold: P<0.05

To identify any predictors of Attribution Blame bias mean change score, univariable linear regressions were conducted between AIHQ Blame mean change score and symptom-related mean change scores, and demographic variables at 12- and 24-months (**Table 29.1-29.4**).

At 24- months ethnicity was found to be a significant predictor of AIHQ Blame mean change score (β = .153, p = .049). Findings represented higher increases in blame bias in White ethnicity participants compared to Non-White ethnicity participants, between baseline and 24-month time-points, showing greater increases in their tendency to assign blame during the study period. No other demographic variables were found to significantly predict AIHQ Blame mean change score at 12- or 24-months.

Table 29.1
Linear Regressions Between AIHQ Blame 12- Month Mean Change Score, and PANSS and Digit Span Mean Change Scores, and Age Across Groups (N=46)

Mean Change Score Variable	Standardised Beta	p value	95% CI for B	
			Lower	Upper
PANSS Positive	-.023	.279	-.066	.019
PANSS Negative	-.032	.146	-.076	.012
PANSS General	-.016	.211	-.042	.011
Digit Span	.018	.379	-.023	.060
Age	.011	.927	-.023	.026

Notes:
Bold: P<0.05

Table 29.2
Linear Regressions between AIHQ Blame 12- month Mean Change Score and Demographic Variables Across Groups (N=46)

Mean Change Score Variable	Unstandardised Beta	p value	95% CI for B	
			Lower	Upper
Ethnicity: White	-.080	.282	-.229	.068
Education level: Up to 18yrs	-.023	.767	-.179	.133
Gender: Male	.011	.869	-.129	.152

Notes:
Bold: P<0.05

Table 29.3
Linear Regressions between AIHQ Blame 24- month Mean Change Score, and PANSS and Digit Span Mean Change Scores, and Age Across Groups (N=42).

		p value	95% CI for B

Mean Change Score Variable	Standardised Beta		Lower	Upper
PANSS Positive	-.007	.981	-.063	.061
PANSS Negative	.019	.530	-.044	.084
PANSS General	.014	.470	-.025	.053
Digit Span	.031	**.**260	-.024	.085
Age	-.006	.619	-.032	.020

Notes:
Bold: P<0.05

Table 29.4
Linear Regressions between AIHQ Blame 24- month Mean Change Score and Demographic Variables Across Groups (N=42).

Mean Change Score Variable	Unstandardised Beta	p value	95% CI for B	
			Lower	Upper
Ethnicity: White	.153	**.049**	.003	.306
Education level: Up to 18yrs	.066	.430	-.102	.235
Gender: Male	.021	.775	-.124	.166

Notes:
Bold: P<0.05

Repeated Measure Linear Mixed Model (RLMM) Analysis of AIHQ Blame scores were analysed with group, time, and group x time as fixed factors, subject as a random effect, and ethnicity and age as covariates. The RLMM showed main effects of time, group, and time x group interactions were not significant **(Table 30)**.

Table 30
Main Effects Model of Time, Group and Time x Group Interactions on AIHQ Blame

	Estimate	Std. Error	p value
Time[1]	-.075	.159	.638
Group[2]	-.133	.278	.632
Time x Group[3]	-.015	.096	.876

Notes:
[1] *Main effect of time*: the difference in social cognition measure scores over timepoints averaged across groups.

6 *Main effect of group*: the difference between antipsychotic reduction/discontinuation vs. maintenance groups on the social cognition measure averaged across timepoints.

6 *Group-by-time interaction effect: the extent to which the difference between groups (antipsychotic reduction/discontinuation vs, maintenance) is different over timepoints.*

Bold: P<0.05

5.6.2 Attribution Bias – AIHQ Hostility

A higher AIHQ Hostility score indicates a greater likelihood of hostility bias towards an ambiguous social scenario. Descriptive statistics (**Table 31.1**) are visualised in Figure 8. Results showed that mean hostility bias scores increased from baseline to 12- months in the reduction group and increased to a lesser extent in the maintenance group. In both groups the mean hostility bias scores then reduced between 12- and 24- months.

Table 31.1
Group (Reduction/Discontinuation vs. Maintenance) Means on the AIHQ Hostility at Baseline, 12-Months and 24- Months.

AIHQ Hostility Timepoint	Reduction/Discontinuation Group Mean (SD)	Maintenance Group Mean (SD)
Baseline	1.93 (1.01)	1.95 (.899)
12- months	2.21 (1.13)	2.03 (1.06)
24- months	2.11 (1.13)	1.88 (1.12)

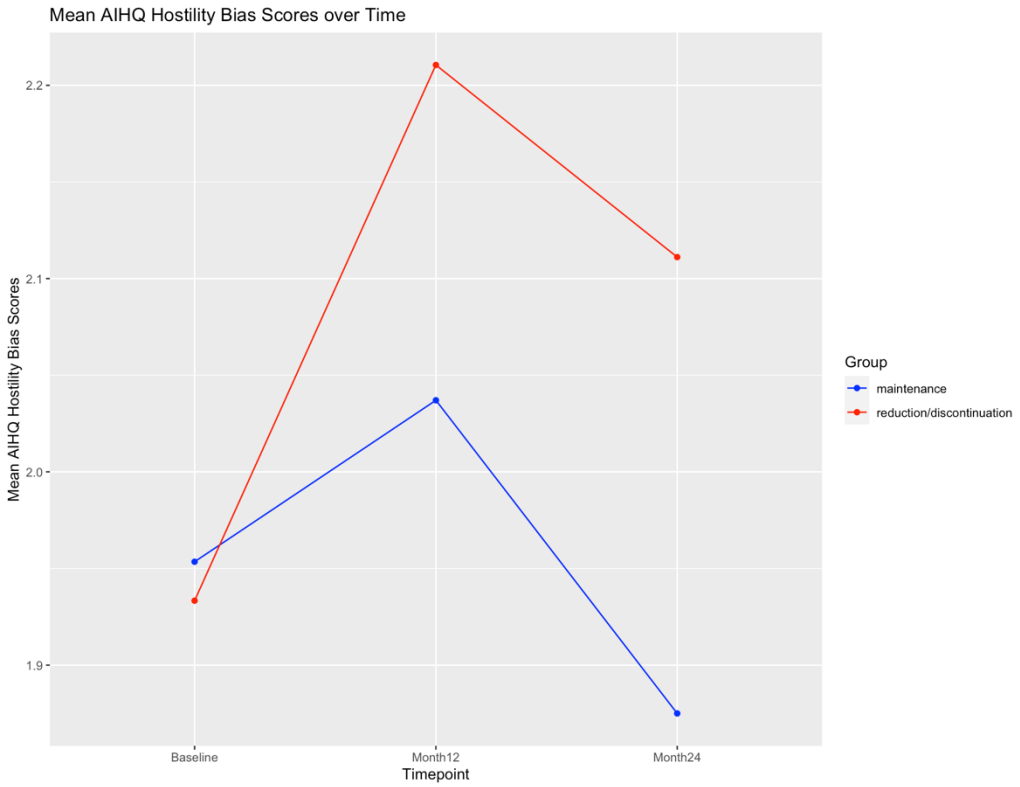

Figure 8 Interaction Plot of Mean AIHQ Hostility Scores Over Time for Reduction/Discontinuation vs. Maintenance Group Participants

There were no significant differences between groups (reduction/discontinuation vs. maintenance) mean change scores, between baseline and 12 months, baseline and 24 months, or 12- and 24- months on AIHQ Hostility (**Table 31.2**). Across the whole study population, there was no significant difference on AIHQ Hostility mean change scores from zero, between baseline to 12 months, baseline to 24 months, or 12- to 24- months (**Table 31.3**).

Table 31.2
T-tests for Group (Reduction/Discontinuation vs. Maintenance) Differences on AIHQ Hostility Mean Change Scores Between Time Points.

Between Timepoints	Reduction/Discontinuation Mean Change Score (SD)	Maintenance Mean Change Score (SD)	p value	Hedges g	Point Estimate of Mean Difference	Lower CI	Higher CI
12m Change	.105 (.737)	-.074 (.781)	.891	.041	.031	-.431	.492

12m to 24m Change	.143 (1.51)	-.059 (.556)	.642	.184	.202	-.605	1.009
24m Change	.222 (1.35)	-.042 (.955)	.486	.231	.264	-.455	.983

Notes:
Bold: P<0.05

Table 31.3
One Sample T-tests of Mean Change Score Difference from Zero on the AIHQ Hostility.

Between Timepoints	Mean Change Score Difference	p value	Cohen's d
Baseline to 12- months	.087	.439	.115
12- to 24- months	.032	.869	.030
Baseline to 24- months	.071	.685	.063

Notes:
Bold: P<0.05

5.6.3 Attribution Bias – AIHQ Aggression

A higher AIHQ Aggression score indicates a greater likelihood of aggression bias towards an ambiguous social scenario. Descriptive statistics (**Table 32.1**) are visualised in Figure 9. Results showed the reduction/discontinuation group mean aggression bias score increased from baseline to 12- months, however at 24-months the mean score reduced to below baseline. In the maintenance group aggression bias reduced across time points.

Table 32.1
Group (Reduction/Discontinuation vs. Maintenance) Means on the AIHQ Aggression at Baseline, 12-Months and 24- Months.

AIHQ Aggression Time point	Reduction/Discontinuation Group Mean (SD)	Maintenance Group Mean (SD)
Baseline	1.67 (.661)	1.65 (.529)
12- months	1.79 (.631)	1.56 (.506)
24- months	1.50 (.618)	1.46 (.509)

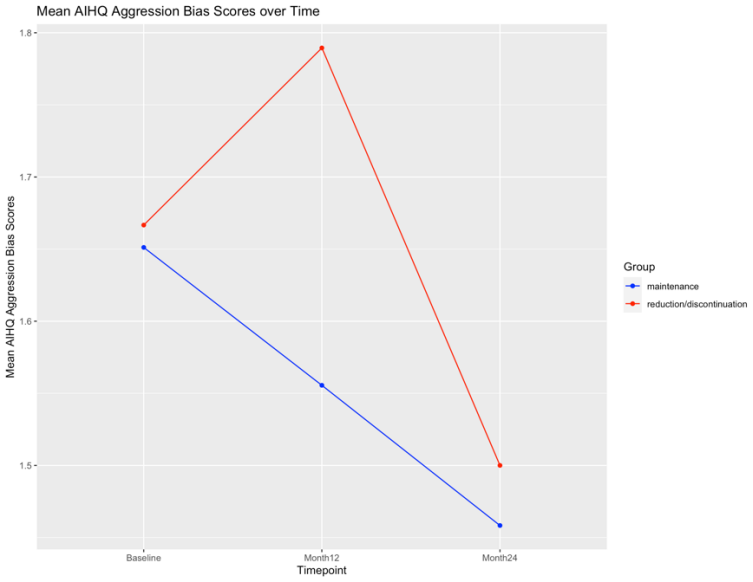

Figure 9 Interaction Plot of Mean AIHQ Aggression Scores Over Time for Reduction/Discontinuation vs. Maintenance Group Participants

There were no significant differences between groups (reduction/discontinuation vs. maintenance) in mean change scores, between baseline and 12 months, baseline and 24 months, or 12- and 24- months on AIHQ Aggression (**Table 32.2**). Across the whole study population, there was no significant difference on AIHQ Aggression mean change scores from zero, between baseline to 12 months, baseline to 24 months, or 12- to 24- months (**Table 32.3)**.

Table 32.2
T-tests for Group (Reduction/Discontinuation vs. Maintenance) Differences on AIHQ Aggression Mean Change Scores Between Time Points.

Between Timepoints	Reduction/Discontinuation Mean Change Score (SD)	Maintenance Mean Change Score (SD)	p value	Hedges g	Point Estimate of Mean Difference	Lower CI	Higher CI
12m Change	.000 (.667)	-.185 (.622)	.347	.289	.185	-.202	.572
12m to 24m Change	-.286 (.611)	-.059 (.556)	.294	-.390	-.227	-.656	.202
24m Change	-.111 (.676)	-.042 (.550)	.724	-.114	-.069	-.452	.313

Notes:
Bold: P<0.05

Table 32.3
One Sample T-tests of Mean Change Score Difference from Zero on the AIHQ Aggression.

Between Timepoints	Mean Change Score Difference	p value	Cohen's d
Baseline to 12- months	-.109	.256	-.169
12- to 24- months	-.161	.134	-.277
Baseline to 24- months	-.071	.445	-.119

Notes:
Bold: P<0.05

5.6.4 Emotion Processing – BLERT

A higher BLERT score indicates better emotional processing performance. Descriptive statistics (**Table 33.1**) are visualised in Figure 10. Results showed the reduction/discontinuation group had increased mean BLERT scores at each time point. The maintenance group showed an increase in mean BLERT scores at 12-months, which declined by 24- months but remained higher than baseline performance.

Table 33.1
Group (Reduction/Discontinuation vs. Maintenance) Means on the BLERT at Baseline, 12- Months and 24- Months.

BLERT Time point	Reduction/Discontinuation Group Mean (SD)	Maintenance Group Mean (SD)
Baseline	12.03 (4.33)	12.72 (4.22)
12- months	12.42 (3.42)	14.93 (3.49)
24- months	12.94 (3.69)	13.29 (4.31)

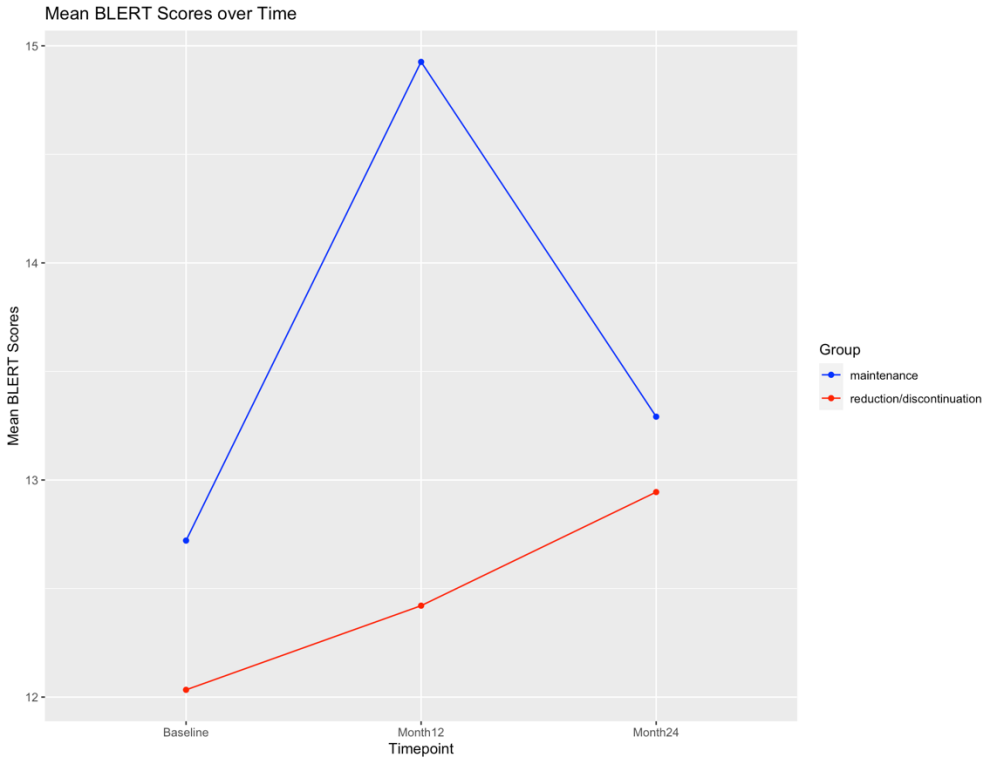

Figure 10 Interaction Plot of Mean BLERT Scores Over Time for Reduction/Discontinuation vs. Maintenance Group Participants

There were no significant differences between groups (reduction/discontinuation vs. maintenance) in mean change scores between baseline and 12 months, baseline and 24 months, or 12- and 24- months on the BLERT (**Table 33.2**). Across the whole study population, there were no significant differences on BLERT mean change scores from zero, between baseline to 12 months, baseline to 24 months, or 12- to 24- months (**Table 33.3**).

Table 33.2
T-tests for Group (Reduction/Discontinuation vs. Maintenance) Differences on BLERT Mean Change Scores Between Time Points.

Between Time points	Reduction/Discontinuation Mean Change Score (SD)	Maintenance Mean Change Score (SD)	p value	Hedges g	Point Estimate of Mean Difference	Lower CI	Higher CI
12m Change	.316 (4.11)	1.26 (4.16)	.450	-.228	-.943	-3.440	1.554
12m to 24m Change	.071 (4.34)	-.471 (2.76)	.691	.152	.542	-2.083	3.168
24m Change	-.278 (3.21)	-.083 (3.20)	.847	-.060	-.194	-2.211	1.822

Notes:
Bold: P<0.05

Table 33.3
One Sample T-tests of Mean Change Score Difference from Zero on the BLERT.

Between Timepoints	Mean Change Score Difference	p value	Cohen's d
Baseline to 12- months	.871	.159	.211

12- to 24- months	-.226	.723	-.064
Baseline to 24- months	-.167	.734	-.053

Notes:
Bold: P<0.05

5.6.5 Theory of Mind (ToM) – Hinting Task

A higher Hinting Task score indicates a better ToM performance. Descriptive statistics (**Table 34.1**) are visualised in Figure 11. Results showed the reduction/discontinuation group mean Hinting Task score decreased from baseline to 12- months, however at 24- months the mean score increased to above baseline. In the maintenance group Hinting Task mean scores slightly increased between baseline and 12- months, however at 24- months the mean scores decreased to below baseline.

Table 34.1
Group (Reduction/Discontinuation vs. Maintenance) Means on the Hinting Task at Baseline, 12-Months and 24- Months.

Hinting Task Timepoint	Reduction/Discontinuation Group Mean (SD)	Maintenance Group Mean (SD)
Baseline	16.10 (3.18)	16.12 (3.28)
12- months	15.42 (3.64)	16.44 (2.82)
24- months	17.78 (2.10)	16.04 (3.13)

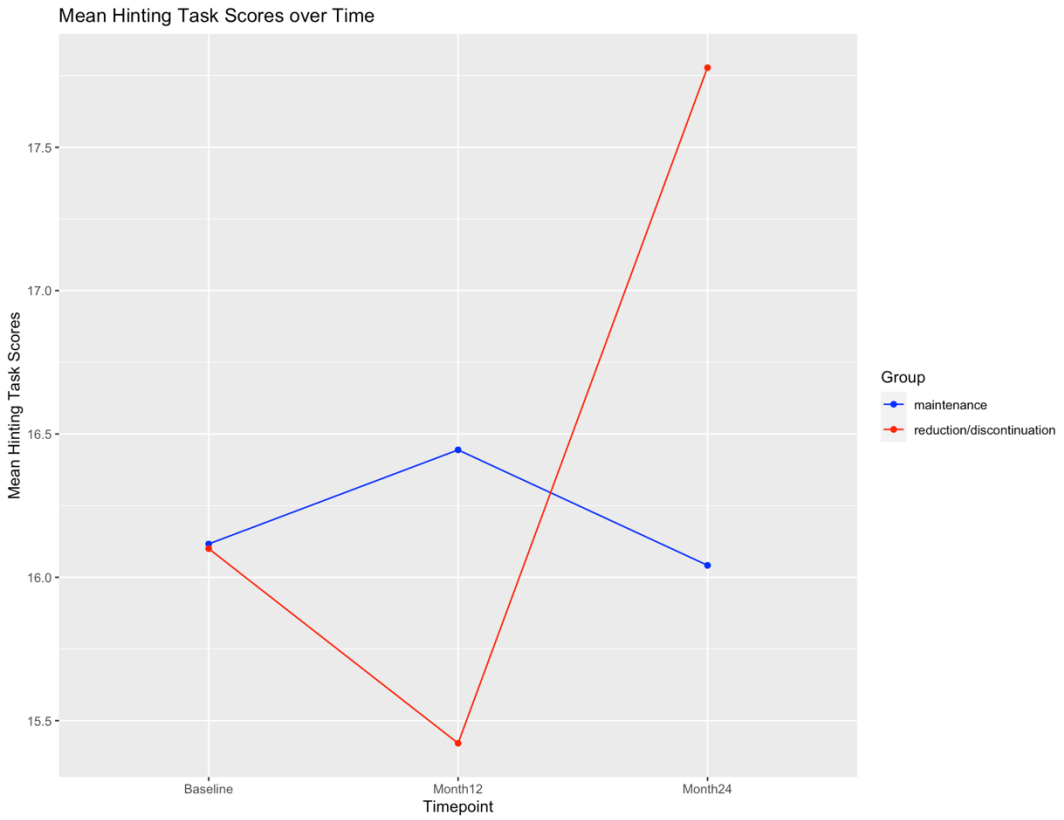

Figure 11 Interaction Plot of Mean Hinting Task Scores Over Time for Reduction/Discontinuation vs. Maintenance Group Participants

There was a significant difference between groups (reduction/discontinuation vs. maintenance) mean change scores (p = .029, Hedges' g = .861), between 12- and 24- months on ToM (**Table 34.2**). There were no significant differences between groups Hinting Task mean change scores from baseline to 12- months, or from baseline to 24- months. Across the whole study population, there were no significant differences on Hinting Task mean change scores from zero, between baseline to 12 months, baseline to 24 months, or 12- to 24- months (**Table 34.3**).

Table 34.2
T-tests for Group (Reduction/Discontinuation vs. Maintenance) Differences on Hinting Task Mean Change Scores Between Time Points.

Between Time points	Reduction/Discontinuation Mean Change Score (SD)	Maintenance Mean Change Score (SD)	p value	Hedges g	Point Estimate of Mean Difference	Lower CI	Higher CI
Baseline to 12- months	-.105 (3.13)	-.500 (4.73)	.732	.095	.395	-2.098	.2.888
12-to 24- months	1.57 (3.01)	-.706 (2.31)	**.029**	.861	2.28	.325	4.230
Baseline to 24- months	1.39 (2.06)	-.261 (3.39)	.062	.572	1.65	-.187	3.486

Notes:
Bold: P<0.05

Table 34.3
One Sample T-tests of Mean Change Score Difference from Zero on the Hinting Task.

Between Timepoints	Mean Change Score Difference	p value	Cohen's d
Baseline to 12- months	-.340	.574	-.082
12- to 24- months	.323	.533	.113
Baseline to 24- months	.463	.323	.156

Notes:
Bold: P<0.05

To identify any predictors of Hinting Task mean change score, univariable linear regressions were conducted between Hinting Task mean change scores and symptom-related mean change scores, and demographic variables at 12- and 24- months (**Table 35.1 – 35.4**). Linear regressions revealed no symptom-related or demographic variables were found to significantly predict Hinting Task mean change score at 12- or 24- months.

Table 35.1
Linear Regressions Between Hinting Task 12- Month Mean Change Score, and PANSS and Digit Span Mean Change Scores, and Age Across Groups (N=46)

Mean Change Score Variable	Standardised Beta	p-value	95% CI for B	
			Lower	Upper
PANSS Positive	.168	.471	-.297	.632
PANSS Negative	.079	.749	-.415	.573
PANSS General	.143	.302	-.139	.437
Digit Span	.244	.280	-.205	.069

Age	.114	.397	-.154	.381

Notes:
Bold: P<0.05

Table 35.2
Linear Regressions Between Hinting Task 12- Month Mean Change Score and Demographic Variables Across Groups (N=46)

Mean Change Score Variable	**Unstandardised Beta**	**p-value**	**95% CI for B**	
			Lower	**Upper**
Ethnicity: White	.-3.496	.288	-10.045	3.052
Education level: Up to 18yrs	-5.185	.103	-11.457	1.086
Gender: Male	-1.117	.751	-8.159	5.925

Notes:
Bold: P<0.05

Table 35.3
Linear Regressions Between Hinting Task 24- Month Mean Change Score, and PANSS and Digit Span Mean Change Scores, and Age Across Groups (N=42).

Mean Change Score Variable	**Standardised Beta**	**p-value**	**95% CI for B**	
			Lower	**Upper**
PANSS Positive	-.014	.954	-.515	.486
PANSS Negative	.126	.623	-.388	.640
PANSS General	.096	.540	-.217	.409
Digit Span	-.075	.734	-.518	.368
Age	.031	.774	-.184	.246

Notes:
Bold: P<0.05

Table 35.4
Linear Regressions Between Hinting Task 24- Month Mean Change Score and Demographic Variables Across Groups (N=42).

Mean Change Score Variable	**Unstandardised Beta**	**p-value**	**95% CI for B**	
			Lower	**Upper**
Ethnicity: White	-1.619	.526	-6.740	3.502
Education level: Up to 18yrs	-2.471	.309	-7.324	2.382
Gender: Male	-2.220	.430	-7.861	3.416

Notes:
Bold: P<0.05

Repeated Measure Linear Mixed Model Analysis of Hinting Task scores were analysed with group, time, and group x time as fixed factors, subject as a random factor, and age as a co-variate (**Table 36.1**). The interaction term time x group was shown to be significant (p = .011), indicating that the effect of group allocation on performance depended on the assessment timepoint. From the interaction plot in Figure 7. We can see that, at baseline, scores on the Hinting Task were similar between groups. At 12- months, reduction/discontinuation group performance began to decline, and maintenance performance slightly improved. By 24- months, these performances reversed, with the reduction/discontinuation group performance improving, and maintenance group performance declining back to near baseline level.

Table 36.1
Main Effects Model of Time, Group and Time x Group Interactions on AIHQ Blame

	Estimate	Std. Error	p value
Time[1]	1.37	.818	.647
Group[2]	1.05	.901	.248
Time x Group[3]	-.749	.289	**.011**

Notes:
[1] *Main effect of time*: the difference in social cognition measure scores over timepoints averaged across groups.

6 *Main effect of group*: the difference between antipsychotic reduction/discontinuation vs. maintenance groups on the social cognition measure averaged across timepoints.

6 *Group-by-time interaction effect: the extent to which the difference between groups (antipsychotics reduction/discontinuation vs. maintenance) is different over timepoints.*

Bold: P<0.05

Based on the significant interaction effect (p = .011), a simple effects analysis was conducted to examine the specific effects of time within each group. The simple effects analysis allowed testing slopes of the regression lines separately for each group and whether if they significantly differed (**Table 36.2).**

Table 36.2
Simple Effects Analysis Results for Reduction/Discontinuation vs. Maintenance Group Hinting Task Changes over Time

Time	Group	Group	Mean Difference	Std. Error	p-value	95% Confidence Interval	
						Lower	Upper
1	Reduction-Discontinuation	Maintenance	-0.016	.738	.982	-1.473	1.441
2	Reduction-Discontinuation	Maintenance	-1.023	.929	.060	-2.858	0.811
3	Reduction-Discontinuation	Maintenance	1.736	.967	**.044**	-0.174	3.646

Notes:
Bold: P<0.05

At time point 1, there was no significant difference in the Hinting Task score between the reduction/discontinuation and maintenance groups. At time point 2, there was no significant difference, however results showed the reduction/discontinuation group had a lower Hinting Task score compared to the Maintenance group. At time point 3, a significant difference emerged, indicating that the reduction/discontinuation group had a higher Hinting Task score compared to the maintenance group (Mean Difference = 1.736, p = .044).

These findings suggest that the effect of time on the Hinting Task score varied depending on the group. While no significant differences were observed at time point 1 or 2, the reduction/discontinuation group showed lower scores compared to the maintenance group, and then significantly higher scores at time point 3. These results indicated that the two groups responded differently within the passage of

time, highlighting the importance of considering the group factor in understanding the changes in ToM over time.

5.6.6 Social Perception – SAT-MC

A higher SAT-MC score indicates better social perception performance. Descriptive statistics (**Table 37.1**) are visualised in Figure 12. Results showed the reduction/discontinuation group had higher mean SAT-MC scores at each time point. The maintenance group showed a slight decrease in mean SAT-MC scores at 12-months, which increased by 24- months but remained below baseline performance.

Table 37.1
Group (Reduction/Discontinuation vs. Maintenance) Means on the SAT-MC at Baseline, 12- Months and 24- Months.

SAT-MC Time point	Reduction/Discontinuation Group Mean (SD)	Maintenance Group Mean (SD)
Baseline	9.77 (4.66)	11.42 (4.29)
12- months	9.95 (4.99)	9.96 (3.70)
24- months	10.83 (4.27)	11.21 (4.33)

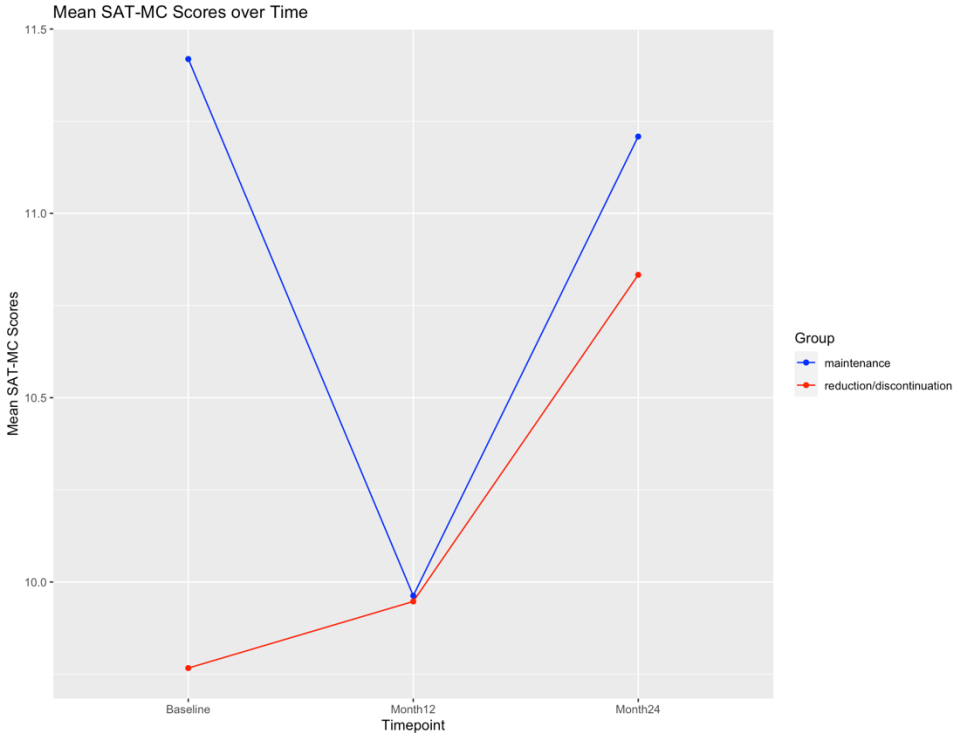

Figure 12 Interaction Plot of Mean SAT-MC Scores Over Time for Reduction/Discontinuation vs. Maintenance Group Participants

There was no significant difference between groups (reduction/discontinuation vs. maintenance) in mean change scores, between baseline and 12 months, baseline and 24 months, or 12- and 24- months on social perception (**Table 37.2**). Across the whole study population, there was a significant difference between 12- and 24-months mean change score and zero ($p = .024$), with a positive mean change score improvement of 1.71 (**Table 37.3**). There was no significant difference in the mean change scores from zero, between baseline and 12 months, or baseline and 24 months on social perception ability of all participants.

Table 37.2
T-tests for Group (Reduction/Discontinuation vs. Maintenance) Differences on SAT-MC Mean Change Scores Between Time Points.

Between Timepoints	Reduction/Discontinuation Mean Change Score (SD)	Maintenance Mean Change Score (SD)	p value	Hedges g	Point Estimate of Mean Difference	Lower CI	Higher CI
Baseline to 12- months	-.421 (3.39)	-.631 (3.80)	.846	.057	.209	-1.988	2.405
12-to 24-months	1.50 (5.11)	1.88 (2.96)	.807	-.094	-.382	-.3.383	2.618
Baseline to 24- months	1.17 (4.72)	-.125 (3.52)	.337	.317	1.292	-1.274	3.858

Notes:
Bold: P<0.05

Table 37.3
One Sample T-tests of Mean Change Score Difference from Zero on the SAT-MC.

Between Timepoints	Mean Change Score Difference	p value	Cohen's d
Baseline to 12- months	-.543	.311	-.151
12- to 24- months	1.71	**.024**	.427
Baseline to 24- months	.429	.499	.105

Notes:
Bold: P<0.05

To identify any predictors of social perception mean change score, univariable linear regressions were conducted between SAT-MC mean change scores and symptom-related mean change scores, and demographic variables at 12- and 24- months (**Table 38.1 – 38.4**). There were no significant relationships between any potential predictor variables and SAT-MC mean change scores, across groups.

Table 38.1
Linear Regressions Between SAT-MC 12- Month Mean Change Score, and PANSS and Digit Span Mean Change Scores, and Age Across Groups (N=46)

Mean Change Score Variable	Standardised Beta	p value	95% CI for B	
			Lower	Upper
PANSS Positive	-.014	.937	-.371	.343
PANSS Negative	-.113	.543	-.483	.258
PANSS General	-.021	.844	-.240	.197
Digit Span	.218	.207	-.125	.561
Age	-.035	.728	-.237	.167

Notes:
Bold: P<0.05

Table 38.2
Linear Regressions Between SAT-MC 12- Month Mean Change Score and Demographic Variables Across Groups (N=46)

Mean Change Score Variable	Unstandardised Beta	p value	95% CI for B	
			Lower	Upper
Ethnicity: White	-.491	.846	-5.552	4.571

Education level: Up to 18yrs	-.265	.914	-5.157	4.626
Gender: Male	-.476	.861	-5.901	4.949

Notes:
Bold: P<0.05

Table. 38.3
Linear Regressions Between SAT-MC 24- Month Mean Change Score, and PANSS and Digit Span Mean Change Scores, and Age Across Groups (N=42).

Mean Change Score Variable	Standardised Beta	p value	95% CI for B	
			Lower	Upper
PANSS Positive	.086	.467	-.151	.321
PANSS Negative	-.137	.256	-.377	.103
PANSS General	.005	.946	-.144	.154
Digit Span	-.089	.392	-.297	.119
Age	-.005	.927	-.107	.097

Notes:
Bold: P<0.05

Table 38.4
Linear Regressions Between SAT-MC 24- Month Mean Change Score and Demographic Variables Across Groups (N=42).

Mean Change Score Variable	Unstandardised Beta	p value	95% CI for B	
			Lower	Upper
Ethnicity: White	-.071	.554	-3.131	1.702
Education level: Up to 18yrs	-.380	.740	-2.676	1.916
Gender: Male	.294	.826	-2.391	2.979

Notes:
Bold: P<0.05

Repeated Measure Linear Mixed Model Analysis of SAT-MC scores were analysed with group, time, and group x time as fixed factors, subject as a random factor, and age as a co-variate. Models showed main effects of time, group, and time x group interactions were not significant **(Table 39)**.

Table 39
Main Effects Model of Time, Group and Time x Group Interactions on SAT-MC

	Estimate	Std. Error	p value
Time[1]	1.072	.950	.262
Group[2]	2.385	1.359	.081
Time x Group[3]	-.599	.574	.299

Note:
[1] *Main effect of time*: the difference in social cognition measure scores over timepoints averaged across groups.

6 *Main effect of group*: the difference between antipsychotic reduction/discontinuation vs. maintenance groups on the social cognition measure averaged across timepoints.

6 Group-by-time interaction effect: the extent to which the difference between groups (antipsychotic reduction/discontinuation vs. maintenance) is different over timepoints.

Bold: P<0.05

5.6.7 Empathy – EQ-CEF

A higher EQ-CEF score indicates better cognitive empathy. Descriptive statistics (**Table 40.1**) are visualised in Figure 13. Results showed the reduction/discontinuation group mean EQ-CEF score decreased from baseline to 12-months, and between 12- and 24- months the mean score increased. In the maintenance group EQ-CEF mean scores increased between baseline and 12-months, and between 12- and 24- months the mean score decreased to below baseline.

Table 40.1
Group (Reduction/Discontinuation vs. Maintenance) Means on the EQ-CEF at Baseline, 12- Months and 24- Months.

EQ-CEF Time point	Reduction/Discontinuation Group Mean (SD)	Maintenance Group Mean (SD)
Baseline	11.90 (5.30)	11.81 (5.52)
12- months	10.26 (4.41)	12.19 (4.46)
24- months	11.18 (6.41)	11.24 (5.17)

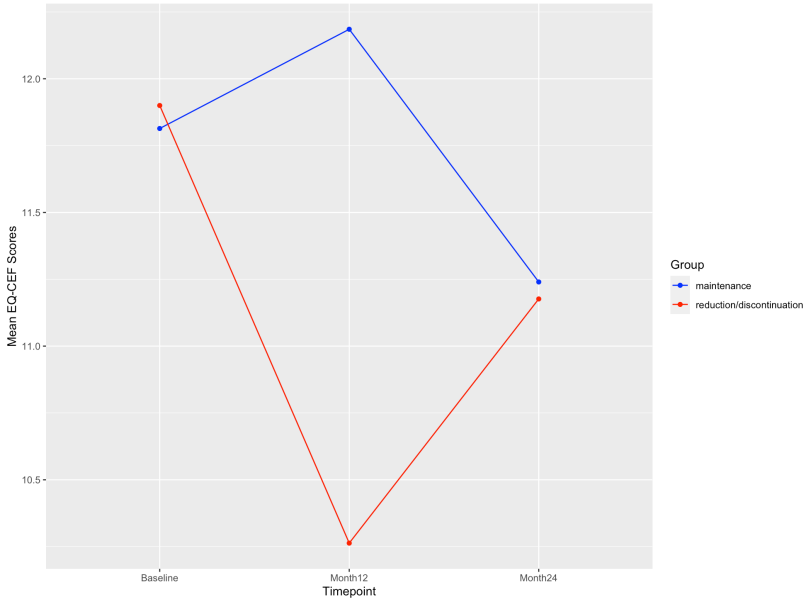

Figure 13 Interaction Plot of Mean EQ-CEF Scores Over Time for Reduction/Discontinuation vs. Maintenance Group Participants

There was no significant difference between groups (reduction/discontinuation vs. maintenance) in mean change scores, between baseline and 12 months, baseline and 24 months, or 12- and 24- months on cognitive empathy ability (**Table 40.2**).. Across the whole study population, there were no significant differences in the mean change scores from zero, between baseline and 12 months, and baseline and 24 months, or 12- to 24-months on cognitive empathy ability of all participants (**Table 40.3**).

Table 40.2
T-tests for group (reduction/discontinuation vs. maintenance) differences on EQ-CEF mean change scores between timepoints.

Between Timepoints	Reduction/Discontinuation	Maintenance Mean Change Score (SD)	p value	Hedges g	Point Estimate	Lower CI	Higher CI

	Mean Change Score (SD)				of Mean Difference		
Baseline to 12- months	-.632 (4.18)	-.370 (3.33)	.815	-.071	-.026	-2.44	1.91
12-to 24- months	2.45 (8.28)	0.00 (7.97)	.471	.303	2.45	-4.42	9.32
Baseline to 24- months	.053 (3.83)	-1.040 (3.67)	.055	.203	1.57	-3.33	6.47

Notes:
Bold: P<0.05

Table 40.3
One Sample T-tests of Mean Change Score Difference from Zero on the EQ-CEF.

Between Timepoints	Mean Change Score Difference	p value	Cohen's d
Baseline to 12- months	-.482	.367	-.133
12- to 24- months	1.12	.511	.140
Baseline to 24- months	-.405	.734	-.053

Notes:
Bold: P<0.05

5.6.8 Empathy – EQ-SSF

A higher EQ-SSF score indicates better social empathy. Descriptive statistics (**Table 41.1**) are visualised in Figure 14. Results showed the reduction/discontinuation group mean EQ-SSF scores were declined from baseline to 12- months, and between 12- and 24- months the mean score increased to above baseline. In the maintenance group EQ-SSF mean scores were slightly increased between baseline and 12- months and decreased between 12- and 24- months near baseline.

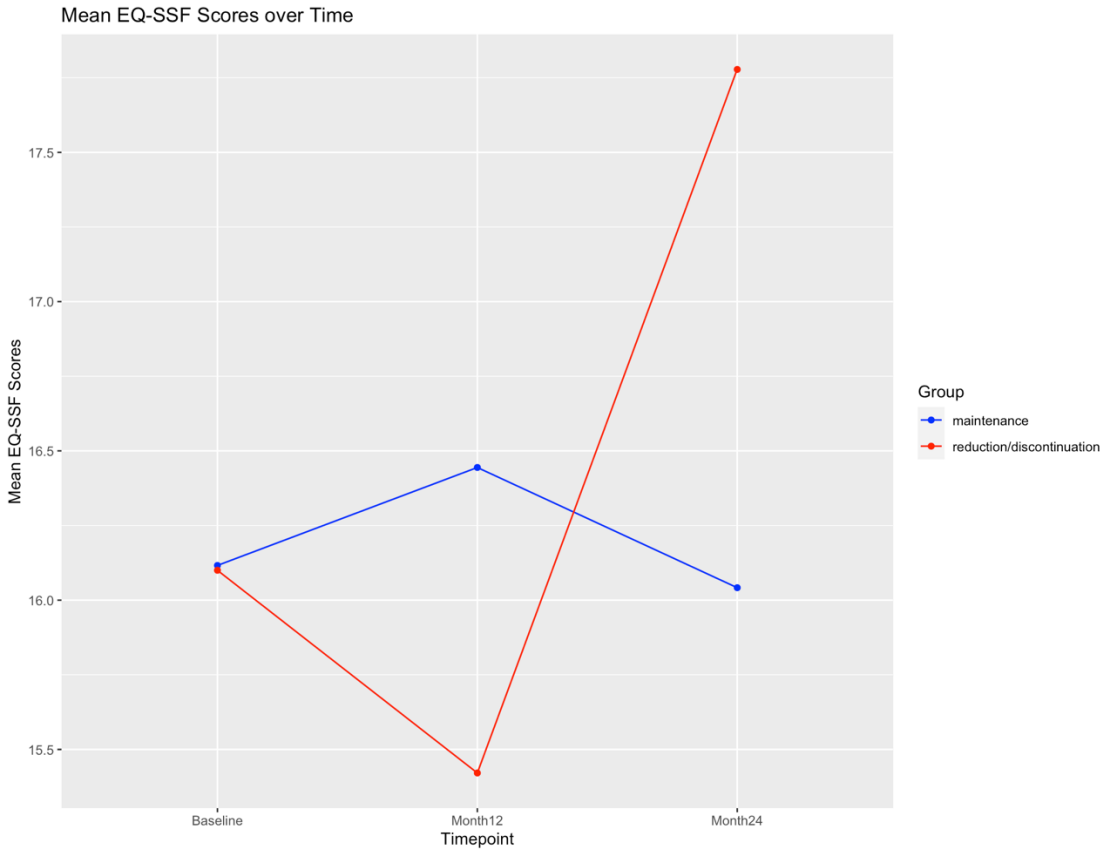

Figure 14 Interaction Plot of Mean EQ-SSF Scores Over Time for Reduction/Discontinuation vs. Maintenance Group Participants

Table 41.1
Group (reduction/discontinuation vs. maintenance) Means on the EQ-SSF at baseline, 12- months and 24- months.

EQ-SSF Timepoint	Reduction/Discontinuation Group Mean (SD)	Maintenance Group Mean (SD)
Baseline	16.10 (3.18)	16.12 (3.28)
12- months	15.42 (3.64)	16.44 (2.82)
24- months	17.78 (2.12)	16.04 (3.13)

There were no significant differences between groups (reduction/discontinuation vs. maintenance) mean change scores, between baseline and 12 months. However, there were significant differences between baseline and 24 months (p = .029), and between 12- and 24- months (p = .046) on social empathy (**Table 41.2**). Across the whole study population, there were no significant difference in the mean change scores from zero, between baseline and 12 months, and baseline and 24 months, and 12- to 24-months or social empathy of all participants (**Table 41.3**).

Table 41.2
T-tests for Group (Reduction/Discontinuation vs. Maintenance) Differences on EQ-SSF Mean Change Scores Between Time Points.

Between Timepoints	Reduction/Discontinuation Mean Change Score (SD)	Maintenance Mean Change Score (SD)	p value	Hedges g	Point Estimate	Lower CI	Higher CI

					of Mean Difference		
Baseline to 12-months	-.105 (3.13)	.111 (3.52)	.828	-.064	-.216	-2.248	1.815
12-to 24- months	1.571 (3.01)	-.706 (2.31)	**.029**	.861	.325	4.230	6.505
Baseline to 24-months	1.389 (2.06)	-.333 (3.33)	**.046**	.602	-.081	3.526	1.640

Notes:
Bold: P<0.05

Table 41.3
One Sample T-tests of Mean Change Score Difference from Zero on the EQ-SSF.

Between Timepoints	Mean Change Score Difference	p value	Cohen's d
Baseline to 12- months	.022	.965	.007
12- to 24- months	.323	.533	,113
Baseline to 24- months	.405	.381	.137

Notes:
Bold: P<0.05

To identify any predictors of social empathy mean change score, univariable linear regressions were conducted between EQ-SSF mean change scores and symptom-related mean change scores, and demographic variables at 12- and 24- months (**Table 42.1 – 42.4**). There were no significant relationships between any potential predictor variables and EQ-SSF mean change scores, across groups.

Table 42.1
Linear Regressions Between EQ-SSF 12- Month Mean Change Score, and PANSS and Digit Span Mean Change Scores, and Age Across Groups (N=46)

Mean Change Score Variable	Standardised Beta	p value	95% CI for B	
			Lower	Upper
PANSS Positive	-.075	.612	-.369	.220
PANSS Negative	.021	.898	-.289	.328
PANSS General	-.129	.148	-.306	.048
Digit Span	.118	.414	-.170	.405
Age	-.093	.264	-.258	.072

Notes:
Bold: P<0.05

Table 42.2
Linear Regressions Between EQ-SSF 12- Month Mean Change Score and Demographic Variables Across Groups (N=46)

Mean Change Score Variable	Unstandardised Beta	p value	95% CI for B	
			Lower	Upper
Ethnicity: White	2.669	.198	-1.449	6.787
Education level: Up to 18yrs	3.261	.102	-.671	7.194
Gender: Male	1.860	.406	-2.604	6.324

Notes:
Bold: P<0.05

Table 42.3

Linear Regressions Between EQ-SSF 24- Month Mean Change Score, and PANSS and Digit Span Mean Change Scores, and Age Across Groups (N=42).

Mean Change Score Variable	Standardised Beta	p value	95% CI for B	
			Lower	Upper
PANSS Positive	.326	.295	-.295	.946
PANSS Negative	.390	.223	-.246	1.025
PANSS General	.130	.496	-.252	.511
Digit Span	.400	.161	-.165	.966
Age	-.049	.719	-.323	.225

Notes:
Bold: P<0.05

Table 42.4
Linear Regressions Between EQ-SSF 24- Month Mean Change Score and Demographic Variables Across Groups (N=42).

Mean Change Score Variable	Unstandardised Beta	p value	95% CI for B	
			Lower	Upper
Ethnicity: White	7.719	.066	1.490	13.940
Education level: Up to 18yrs	3.369	.274	-2.765	9.502
Gender: Male	6.312	.082	-.839	13.463

Notes:
Bold: P<0.05

Repeated Measure Linear Mixed Model Analysis of EQ-SSF scores were analysed with group, time, and group x time as fixed factors, subject as a random factor, and age as a co-variate. Models showed main effects of time, group, and time x group interactions were not significant **(Table 43)**.

Table 43
Main Effects Model of Time, Group and Time x Group Interactions on EQSSF

	Estimate	Std. Error	p value
Time[1]	-.400	.658	.545
Group[2]	-.147	.981	.881
Time x Group[3]	.248	.396	.532

Note:
[1] *Main effect of time*: the difference in social cognition measure scores over timepoints averaged across groups.

6 *Main effect of group*: the difference between antipsychotic reduction/discontinuation vs. maintenance groups on the social cognition measure averaged across timepoints.

6 Group-by-time interaction effect: the extent to which the difference between groups (antipsychotics reduction/discontinuation) is different over timepoints.

Bold: P<0.05

5.6.10 Emotional Intelligence – TEIQue

A higher TEIQue score indicates better emotional intelligence. Descriptive statistics (**Table 44.1**) are visualised in Figure 15. Results showed both groups mean TEIQue score had minimal changes between baseline to 24- months.

Table 44.1
Group (Reduction/Discontinuation vs. Maintenance) Means on the TEIQue at Baseline, 12- Months and 24- Months.

TEIQue Timepoint	Reduction/Discontinuation Group Mean (SD)	Maintenance Group Mean (SD)
Baseline	4.21 (.802)	4.50 (.870)
12- months	4.25 (.897)	4.57 (.735)
24- months	4.22 (1.15)	4.57 (1.29)

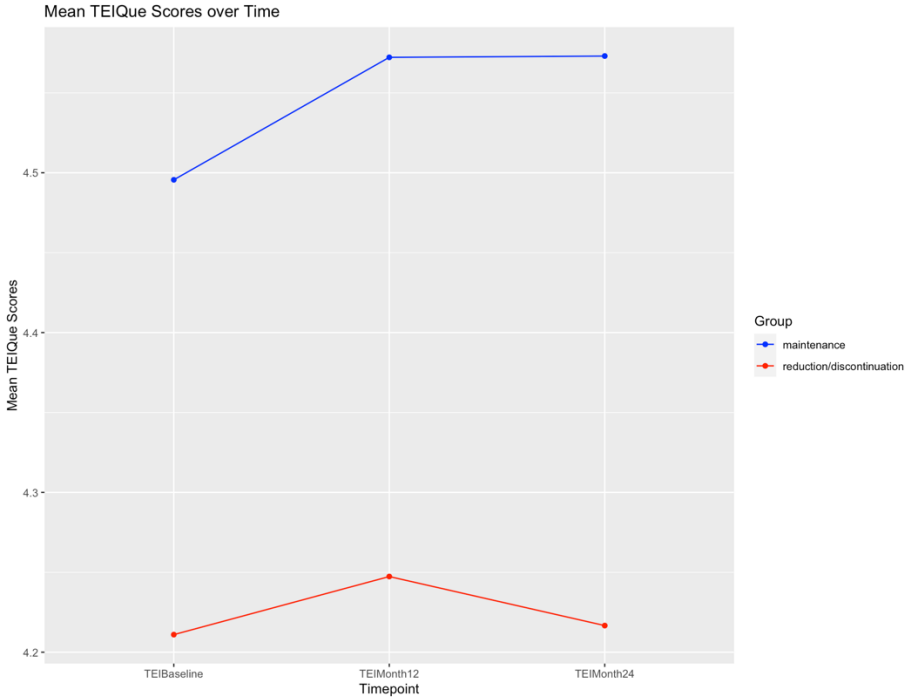

Figure 15 Interaction Plot of Mean TEIQue Scores Over Time for Reduction/Discontinuation vs. Maintenance Group Participants

There was no significant differences between group (reduction/discontinuation vs. maintenance) mean change scores, between baseline and 12 months, baseline and 24 months, or 12- and 24- months on emotional intelligence (**Table 44.2**). Across the whole study population, there was no significant difference in the mean change scores from zero, between baseline and 12 months, and baseline and 24 months, or 12- to 24-months on emotional intelligence of all participants (**Table 44.3**).

Table 44.2
T-tests for Group (Reduction/Discontinuation vs. Maintenance) Differences on TEIQue Mean Change Scores Between Time Points.

Between Timepoints	Reduction/Discontinuation Mean Change Score (SD)	Maintenance Mean Change Score (SD)	p value	Hedges g	Point Estimate of Mean Difference	Lower CI	Higher CI
Baseline to 12-months	-.015 (1.10)	.112 (1.14)	.705	-.114	-.127	-.805	.550
12-to 24-months	-.069 (.746)	-.158 (.621)	.728	.130	.089	-.422	.600

Baseline to 24-months	-.171 (1.38)	.146 (2.02)	.556	-.179	-.316	-1.441	.809

Notes:
Bold: P<0.05

Table 44.3
One Sample T-tests of Mean Change Score Difference from Zero on the TEIQue.

Between Timepoints	Mean Change Score Difference	p value	Cohen's d
Baseline to 12- months	.061	.718	.054
12- to 24- months	-.116	.352	-.173
Baseline to 24- months	.007	.980	.004

Notes:
Bold: P<0.05

6.1 Antipsychotic Dose (AP dose) Change and Social Cognition Change

Spearman's correlations were used to study the relationship between change in AP dose (calculated as chlorpromazine equivalents) and change in social cognition performance between baseline and 24- month time-points (**Table 45**). The results revealed no significant correlations between CPZ Equivalent dose change scores and social cognition change scores.

Table 45.
Spearman's Correlations between Social Cognition Domain Mean Change Scores, and CPZ Equivalent Change Scores Across Groups at 24- month Timepoint.

Social Cognition Variable	r	p value
AIHQ Blame	-.062	.698
AIHQ Hostility	.148	.348
AIHQ Aggression	-.098	.536
BLERT	.179	.258
Hinting Task	.164	.305
SAT-MC	-.423	.101
EQ-CEF	.195	.215
EQ-SSF	.019	.899
TEIQue	-.149	.352

Notes:
Bold: P<0.05

6.1 Summary

Briefly, a summation of the results is as follows:

5.8.1 Changes in Social Cognition

- Observation of interaction plots from baseline to 12-months, showed declines in performance (or increases in attribution biases) for the domains of AIHQ Blame, AIHQ Hostility, AIHQ Aggression, ToM, EQ-CEF, and EQ-SSF in reduction/discontinuation group participants. From 12- to 24- months, mean scores reflected performance improvements (or declines in attribution biases) for the same measures in these participants. However, there was no evidence

of significant differences in mean change scores between groups, or time-points (across groups) after repeated measure linear mixed model analysis in any domain other than ToM (Hinting Task).

- A significant difference in AIHQ Blame mean change scores from baseline to 12- months was identified across groups, with blame bias reducing over time. However, a repeated measure linear mixed model including main effects of time, group, and time x group interactions, as well as random factors and co-variates was not significant

- A significant difference in SAT-MC mean change scores from 12- to 24-months was identified across groups, with improvements in social perception scores between timepoints. However, a repeated measure linear mixed model including main effects of time, group, and time x group interactions, as well as random factors and co-variates was not significant.

- A significant difference in EQ-SSF mean change scores from baseline to 24-months and 12- to 24- months was identified between groups, with improvements in the social empathy score of reduction/discontinuation group members by 24- months, and similar scores to baseline in maintenance group members. However, a repeated measure linear mixed model including main effects of time, group, and time x group interactions, as well as random factors and co-variates was not significant.

- A significant difference between groups in Hinting Task change score was identified from 12- to 24- months with reduction/discontinuation participants performance improving, and maintenance participants performance worsening. In a repeated measure linear mixed model, the group x time interaction was significant, indicating a cross-over interaction.

- No significant differences in AIHQ Hostility, AIHQ Aggression, BLERT, EQ-CEF, or TEIQue were identified between group mean change scores, or in group mean change scores from zero.

5.8.2 Predictors of Change in Social Cognition

- At 12- and 24- month follow-up, ethnicity was identified as a significant predictor of AIHQ Blame mean change score, with White ethnicity participants having higher increases in blame bias scores. At 24- months, Digit Span mean change score was also identified as a significant predictor of AIHQ Blame mean change score, with improved neurocognition scores predicting decreases in blame bias.

- There were no significant predictor variables identified for SAT-MC, EQ-SSF or Hinting Task mean change scores.

5.9 Social Functioning Change – SFS

A higher SFS score indicates better social functioning. Descriptive statistics (**Table 46.1**) are visualised in Figure 16. Results showed maintenance groups mean SFS

score had minimal changes between baseline to 24- months, whereas reduction/discontinuation participants experienced a dip in SFS score between baseline and 12- months, that recovered by endpoint.

Table 46.1
Group (Reduction/Discontinuation vs. maintenance) Means on the SFS at Baseline, 12- Months and 24- Months.

TEIQue Timepoint	Reduction/Discontinuation Group Mean (SD)	Maintenance Group Mean (SD)
Baseline	107.12 (8.79)	110.35 (9.17)
12- months	105.51 (7.78)	110.98 (8.53)
24- months	107.08 (9.49)	110.96 (10.02)

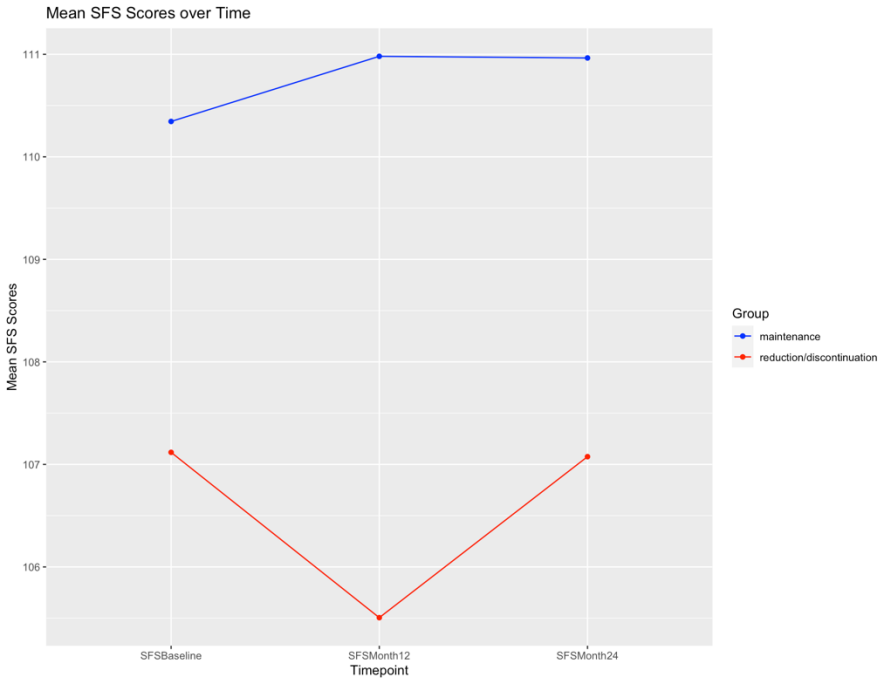

Figure 16 Interaction Plot of Mean SFS Scores Over Time for Reduction/Discontinuation vs. Maintenance Group Participants

Correlations were conducted between SFS mean change scores and social cognition domain mean change scores (**Table 46.2 and 46.3**). Significant weak-moderate negative correlations were identified at 12- months between SFS mean change score and AIHQ Blame mean change score (r = -.326, p = .027), and SFS mean change score and SAT-MC mean change score (r = -.391, p = .007). At 24 months, no significant correlations were identified between SFS mean change scores and social cognition domains mean change scores.

Table 46.2
Spearman's Correlations Between SFS Mean Change Score and Social Cognition Domain Mean Change Scores at 12-Months.

Social Cognition Variable	r	p value
AIHQ Blame	-.326	**.027**
AIHQ Hostility	-.174	.248

AIHQ Aggression	-.114	.452
BLERT	-.116	.443
Hinting Task	-.099	.510
SAT-MC	-.391	**.007**
EQ-CEF	-.093	.651
EQ-SSF	-.059	.694
TEIQue	-.111	.464

Notes:
Bold: P<0.05

Table 46.3
Spearman's Correlations Between SFS Mean Change Score and Social Cognition Domain Mean Change Scores at 24-Months.

Social Cognition Variable	**r**	**p value**
AIHQ Blame	-.064	.687
AIHQ Hostility	-.006	.970
AIHQ Aggression	.045	.776
BLERT	.111	.483
Hinting Task	.082	.611
SAT-MC	-.043	.787
EQ-CEF	.123	.437
EQ-SSF	-.133	.401
TEIQue	-.105	.516

Notes:
Bold: P<0.05

To identify additional potential predictors of social functioning mean change score, univariable linear regressions were conducted between SFS mean change scores and symptom-related mean change scores, and SFS mean change scores and demographic variables at 12- and 24- months (**Table 47.1 – 47.4**). There were no significant predictors of social functioning mean change scores identified at 12- or 24-month timepoints in this sample.

Table 47.1
Linear Regressions between SFS Mean Change Score, and PANSS, Digit Span and Age Variables Across Groups at 12- month Timepoint.

Mean Change Score Variable	**Standardised Beta**	**p-value**	**95% CI for B**	
			Lower	**Upper**
PANSS Positive	.198	.199	-.108	.504
PANSS Negative	-.058	.720	-.383	.266
PANSS General	.076	.421	-.113	.266
Digit Span	-.101	.503	-.406	.202
Age	.009	.915	-.167	.186

Notes:
Bold: P<0.05

Table 47.2
Linear Regressions between SFS Mean Change Score and Demographic Variables Across Groups at 12- month Timepoint.

Mean Change Score Variable	**Unstandardised Beta**	**p-value**	**95% CI for B**	
			Lower	**Upper**

Ethnicity: White	-.802	.716	-5.219	3.613
Education level: Up to 18yrs	-3.552	.091	-7.686	.585
Gender: Male	-.824	.728	-5.560	3.909

Notes:
Bold: P<0.05

Table 47.3
Linear Regressions between SFS Mean Change Score, and PANSS, Digit Span and Age Variables Across Groups at 24- month Timepoint.

Social Cognition Variable	**Standardised Beta**	**p-value**	**95% CI for B**	
			Lower	**Upper**
PANSS Positive	.324	.164	-.138	.786
PANSS Negative	-.014	.953	-.501	.472
PANSS General	-.076	.607	-.373	.220
Digit Span	-.236	.354	-.647	.176
Age	-.187	.058	-.382	.007

Notes:
Bold: P<0.05

Table 47.4
Linear Regressions between SFS Mean Change Score and Demographic Variables Across Groups at 24- month Timepoint.

Mean Change Score Variable	**Unstandardised Beta**	**p-value**	**95% CI for B**	
			Lower	**Upper**
Ethnicity: White	-.623	.796	-5.460	4.214
Education level: Up to 18yrs	-1.209	.596	-5.778	3.359
Gender: Male	-.605	.821	-5.959	4.750

Notes:
Bold: P<0.05

Repeated Measure Linear Mixed Model Analysis of SFS scores were analysed with AIHQ Blame, and SAT-MC, Time, Group and Time x Group as fixed factors, subject as a random factor, and age as a co-variate. Models showed no main effects or interactions were significant **(Table 48)**.

Table 48.
Main Effects Model of Social Cognition, Time, and Group Interactions on SFS scores.

	Estimate	**Std. Error**	**P-Value**
SAT-MC[1]	.065	.279	.817
AIHQ Blame[1]	-1.574	1.056	.141
Time[2]	-1.645	3.064	.592
Group[3]	2.304	2.209	.301
Time x Group[4]	1.528	.821	.413

Note:
[1] *Main effect of social cognition (AIHQ Blame, SAT-MC)*: the extent to which the social cognition measure score effects social functioning score over timepoints averaged across groups.

6 *Main effect of time*: the difference in social functioning measure scores over timepoints averaged across groups.

6 *Main effect of group*: the difference between antipsychotic reduction/discontinuation vs. maintenance groups on the social functioning measure averaged across timepoints.

[4]Time-by-Group interaction effect; the extent to which the change in social functioning relates over time, relates to group.

Bold: P<0.05

5.9.1 Correlations and Predictors of Social Functioning Change

- Observation of interaction plots from baseline to 12-months, showed declines in performance for the SFS measure in reduction/discontinuation group participants. From 12- to 24- months, SFS mean scores reflected performance improvements in these participants. Maintenance participant SFS mean scores slightly improved between baseline and 12- months and then remained roughly similar by 24- months.

- Statistically significant weak negative correlations were identified between SFS mean change scores and AIHQ Blame mean change scores and SAT-MC mean change scores at 12- months.

- No significant additional predictor variables of social functioning change were identified, across time-points.

- A repeated measure linear mixed model including main and interaction effects of group, time, group x time, and social cognition domains, as well as co-variates was not significant.

5.10 Discussion – Longitudinal Results

The purpose of the present longitudinal study was to evaluate whether reduction/discontinuation of antipsychotics vs. maintenance treatment, predicted social cognition score changes over time, whether social cognition score changes were related to other potential predictors such as symptom changes; whether antipsychotic dose was associated with social cognition changes, and whether social cognition changes were associated with changes in social functioning.

5.10.1 Study Completion

Overall dropout in this sub-study was high, with 37% of all participants failing to complete the 12- month assessment, and 42.5% failing to complete the 24- month assessment. Breaking these dropout figures down by group, 33.7% of the reduction group and 37.3% of the maintenance group did not complete the 12- month assessment, and 30% the reduction/discontinuation group and 44.2% of the maintenance group did not complete the 24- month assessment. These rates of dropout were higher than initially predicted (see the sample size calculation in Chapter 3, section 3.4.3.2) and resulted in an inadequate sample for a sufficiently powered analysis, requiring findings from this analysis to be interpreted with caution.

T-tests between sub-study completers (those who completed at least one social cognition measure at 24- months) vs. non-completers were conducted on baseline

characteristics and no significant differences were identified. Therefore, there was no evidence that those who dropped out were different from those who remained in the study.

Assessment burden has been a recognised concern regarding participant retention in clinical trials of patients with severe mental illnesses (Bellack et al., 2007). Dropout rates in this sub-study may therefore be related to the completion of the social cognition measures in addition to the RADAR assessment, which required not only more time from participants, but further cognitive burden. Additionally, in this sub-study maintenance group members showed a higher likelihood of dropout compared to reduction/discontinuation participants. In longitudinal research it is important to incorporate strategies to limit non-contact between assessments (de Leeuw, 2005). In RADAR, attempts to maintain contact with all participants were made through quarterly newsletters, reminder postcards, and phone call catch ups with researchers at 18- months. However, the reduction/discontinuation group members had more regular contact with clinicians to ensure intervention fidelity (usually every two months), and therefore it may have been this increase in clinical time that improved their engagement with the study. Also, it is important to consider that maintenance group members were requested to keep their antipsychotic dose the same during their two years of participation (if they did not experience serious side effects), and that participant attitudes towards this requirement may have changed over their time in the study. This emphasises the need to incorporate frequent participant engagements with all participants throughout longitudinal research studies, and the potential impact clinical contact may have in studies regarding antipsychotics. Additionally, the effect of the COVID-19 pandemic has been shown to effect participant retention in clinical trials over the lockdown period, and this may have affected dropouts in this sub-study (Hooton et al., 2020).

5.11 Social Cognition in Patients with a Schizophrenia-Spectrum Disorder (Reduction/Discontinuation vs. Maintenance)

Longitudinal results showed limited change or variation across social cognition domains in this study, and the analysis of significant changes in social cognition scores over time-points often lost significance after controlling for additional variables. This may reflect social cognition deficits as a stable trait in patients with schizophrenia, replicating evidence from neurocognition studies (Fett et al., 2022). It is also important to acknowledge the impact of attrition rates (see Chapter 6, section 6.4.2), multiple comparisons (see Chapter 6, section 6.4.4), and measurement limitations (see Chapter 6, section 6.6 and 6.7) when attempting to understand the results of this study. These and other study design and procedure considerations will be discussed further in the general discussion (Chapter 6). The interpretations of longitudinal study results will be discussed below:

5.11.1 Baseline Group Differences

5.11.1.1 Age

Due to significant differences in the baseline ages between the sub-study groups, age was considered a crucial factor and was thus integrated into all multivariate analyses conducted within this section to account for its potential impact.

5.12 12- Month Dips in Social Cognition Performance

The descriptive statistics showed similar trends in results for the reduction/discontinuation participants AIHQ Blame, AIHQ Hostility, AIHQ Aggression, ToM, EQ-CEF, and EQ-SSF performance. This pattern showed declines in performance (or an increase in attribution biases) between baseline and 12-month follow-up, followed by improved performance (or decreases in attribution biases) thereafter. Despite no significant differences between the groups in terms of changes from baseline to 12- months, the findings suggest that reducing or discontinuing antipsychotics may lead to a deterioration of social cognition, possibly due to withdrawal effects, destabilisation, or relapse (Brandt et al., 2020). However, this could not be measured within this sub-study as analysis did not include relapse events, nor a measure of withdrawal symptoms. Additionally, there were no significant relationships between symptom changes and social cognition changes, suggesting social cognition performance declines were unrelated to a potential re-emergence of symptoms of psychosis after antipsychotic reduction.

Improvements in performance observed between 12- and 24- months (a change that was identified as significantly different between groups for ToM and EQ-SSF), highlighted possible long-term benefits of being in the antipsychotic reduction/discontinuation group, within these study conditions. However, the lack of significant correlations between antipsychotic dose changes and social cognition change, suggested this was most likely due to factors other than antipsychotic dose reduction, such as increased contact time with clinicians.

As these findings occurred across various social cognition domains it suggests that the pattern did not happen by chance, however due to the lack of significance it is important to exercise caution when interpreting the results. For instance, the dips in performance at 12- months could also relate to changes in assessment format associated with COVID-19 restrictions, and eventual improvements in performance may be due to re-test effects, bias due to participant unblinding, or a regression to the mean. Therefore, further replication studies are needed to clarify the hypothesis that antipsychotic reduction/discontinuation may have short-term adverse effects prior to improved social cognition outcomes in some domains.

5.13 Changes in Social Cognition Over Time

5.13.1 Theory of Mind

Theory of Mind (ToM) refers to the understanding and interpretation people have of others' beliefs, thoughts, and actions.

Through RLMM analysis on the Hinting Task, after controlling for random effects, main effects for group and time were not significant, however there was a significant time x group interaction identified ($p = .011$). This suggests a crossover interaction was evident on the ToM measure, where the group with the larger mean switched over, over time. Findings showed mean scores in the antipsychotic reduction group were lower than the maintenance group at baseline, but at 24- month follow-up these results were reversed, with the significant difference between groups mean change scores between 12- and 24- months having a large effect size (Hedges $g = .861$). This suggests that the antipsychotic reduction group allocation may have led to improvements in patients' ToM, and maintenance group allocation may have led to declines in ToM, over time. However, as maintenance group scores at baseline and 24- months showed only slight differences, mean changes between 12- and 24-

months may show a regression to the mean. A previous cross-sectional study investigating the effects of antipsychotic drugs on ToM found poorer performance compared to healthy volunteers in patients with schizophrenia taking risperidone and typical antipsychotics, but also a similar performance between healthy volunteers and patients taking olanzapine and clozapine (Savina et al., 2007). Another study found improvements during the first two weeks of an antipsychotic treatment compared to baseline, however there was a ceiling effect at 4 and 6 weeks, and one other study found no effect of antipsychotics on ToM (Mizrahi et al., 2007; Kucharska-Pietura & Mortimer, 2013). However, these studies were non-randomised, with short or non-existent follow-ups, and some of the patients were already taking antipsychotics.

Antipsychotic dose change from baseline to endpoint was not significantly correlated with ToM change, which may indicate that other aspects of the RADAR intervention alongside medication reduction, such as increased appointments with the psychiatrist, were beneficial in improving ToM over time. Alternatively, the dose analysis may have been underpowered and thereby missed a real but small effect. It is also important to consider other factors that may have contributed to ToM changes and were not accounted for in this analysis, such as the specific type of antipsychotic medication participants in each group were taking, or what diagnosis the participant had under the schizophrenia-spectrum umbrella.

These results indicated that participants in the guided reduction of antipsychotic group experienced improved ToM performance over a long-term period, although this was not related to changes in their antipsychotic dose. This is a noteworthy consideration, which may support further study into the effects of additional factors, such as clinical contact time on ToM in patients with schizophrenia.

5.13.2 AIHQ Blame

Attribution bias refers to the process of assigning cause to a social event.

The AIHQ Blame measure included in the AIHQ has been evidenced as the most consistent and reliable domain for measuring attribution bias to ambiguous scenarios, in patients with schizophrenia (Pinkham et al., 2016; Buck et al., 2017). Findings from this study, showed that there was a significant difference across participants in AIHQ Blame mean change score from baseline to 12- months, with increases in the reduction/discontinuation group mean, showing increased likelihood of blame bias responses to events, and decreased likelihood in the maintenance group.

RLMM results showed, after controlling for random effects, main effects for group, time and group x time interactions were not significant, despite showing a similar pattern of effect to several other domains, one of which (ToM) did show significant effects. One conclusion of this result may be that there is no effect of antipsychotic reduction/discontinuation on blame bias in patients with schizophrenia, which supports previous study findings by Mizrahi et al (2008). However, despite the lack of significance in the RLMM results, the pattern of change across AIHQ Blame is consistent with the pattern of change across several other domains of social cognition. This may suggest that the findings instead reflect the large drop-out rate of the study and underpowered sample at follow-up (see Chapter 6, section 6.3.2), and

therefore further studies with larger sample sizes are needed to confirm these findings.

5.13.3 Social Perception

Social perception refers to the process of making inferences about social situations based on cues.

The results from the analysis of the SAT-MC/SAT-MC II showed a significant difference between the mean change score across groups from 12- to 24- months. Both groups showed an increase in their mean scores during this time period. This result may be due to the use of two different versions of the test, the SAT-MC II at 12- months, and the SAT-MC at baseline and 24 months. Additionally, the reduction/discontinuation group scored relatively low on the baseline SAT-MC, which may explain the lack of difference in mean between baseline and 12- months. Despite using the SAT-MC II to prevent potential practice effects, the validity of the test has come under scrutiny, and results from this study may indicate further limitations with the test-retest reliability of the measures.

Results of the RLMM showed main effects for group, time, and group x time interactions were also not significant. These findings may suggest that there is no effect of antipsychotic reduction/discontinuation on social perception in patients with schizophrenia. However, it is important to consider alternative explanations of this result, including a lack of adequate sample size for follow-up analysis (Brookes et al., 2004) and issues with the internal validity of the SAT-MC/SAT-MC II measures (see measures discussion in Chapter 6, section 6.7). Additionally, there have been an absence of previous studies into the effects of antipsychotic medication on social perception, meaning there are limits to the overall understanding of this relationship, which is inadequate for evidence-based patient treatment. Therefore, these findings emphasise the need for new social perception measure development, and for further adequately powered RCT antipsychotic reduction studies to explore this social cognition domain.

5.13.4 AIHQ Aggression and AIHQ Hostility

Attribution bias refers to the process of assigning cause to a social event.

Mean change score differences from zero across all participants, and mean change score group differences were not significant for AIHQ Aggression and AIHQ Hostility. Only one previous study has investigated the relationship between attribution style and antipsychotic use, and findings showed no effect of 6 weeks of treatment on social cognition (Mizrahi et al., 2008). Findings from this sub-study may support the result that antipsychotic medication has no apparent effect on AIHQ Hostility, or AIHQ Aggression. It is however important to consider the limitations present with the AIHQ measure when considering this outcome. Pinkham et al. (2016) showed that the hostility and aggression biases specifically showed weak test-retest reliability, under the SCOPE project work. Although a more recent study by Buck et al (2017) supports the inclusion of the AIHQ as a measure of attribution bias, they found mixed evidence for rater-scored hostility and aggression biases, and suggested improvements to the scale were necessary. In this study, we showed significant correlations between the AIHQ domains of Blame, Hostility, and Aggression at baseline. Results could also reflect the possibility that differences in antipsychotic

dose were not sufficient to produce differences in this domain. Overall, these findings support the need for further development of reliable and valid measures of attribution bias in patients with schizophrenia-spectrum disorders.

5.13.5 Empathy

As a reminder empathy refers to the process of understanding, sharing, and responding to others' emotional states.

There was no evidence of any statistically significant change in the EQ-CEF, representing cognitive empathy from baseline to follow-up within or across both groups.

For social empathy, findings showed significant differences between groups on mean change scores between baseline and 24- months, and between 12- and 24-months. Observation of the data showed an initial dip in social empathy scores at 12-months, followed by an increase above the baseline at endpoint in the reduction/discontinuation group, that may have represented some early adverse effects associated with allocation to the group. In the maintenance group there was a slight improvement in social empathy at 12- months, followed by a decrease that may represent a regression to the mean.

RLMM results showed, after controlling for random effects, main effects for group, time, and group x time interactions were not significant. This may be because there was no effect of antipsychotic reduction/discontinuation on social empathy in patients with schizophrenia, replicating the findings of the only previous study to also investigate the effects of antipsychotic medication on empathy (Kucharska-Pietura et al., 2012b). However, it is also integral to consider how participant drop-out through the study may have underpowered the analysis of this data, and that further studies with larger samples may indicate more robust findings.

5.12.6 Emotion Processing and Emotional Intelligence

As a reminder emotion processing refers to the process of recognising and interpreting emotions of others, and emotional intelligence refers to the process of understanding our own and others' emotions in an adaptive way.

There was no evidence of any statistically significant change in the BLERT or TEIQue from baseline to follow-up within or across both groups.

Most of the previous research in the field has been conducted on the domain of emotion processing. However, the findings from these studies have been inconsistent with some research showing impairments to emotion recognition associated with antipsychotic use (Lawrence et al., 2002; Gultekin et al., 2017), some finding no effects (Rock et al., 2016; Lewis et al., 1995; Wölwer et al., 1996; Herbener et al., 2005; Kucharska-Pietura et al., 2012a; Harvey et al., 2006; Sergi et al., 2007; Maat et al., 2014; Koshikawa et al., 2016), and some showing improvements (Behere et al., 2009; Gaebel et al., 1992; Zhou et al., 2017; Kee et al., 1998; Penn et al., 2002; Fakra et al., 2009). This sub-study adds to the evidence that antipsychotic use has no effect on emotion processing, including the results from correlations between AP dose change and BLERT score change. However, the small study sample size (Chapter 6, section 6.3.2), and potential BLERT measure

limitations (see measures discussion Chapter 6, section 6.7), should be considered in the interpretation of these findings.

Studies investigating the effects of antipsychotic medication on emotional intelligence are limited. Two studies have investigated the effects of antipsychotics on emotional intelligence, one found significant improvements at a 6- month follow-up in first-episode psychosis patients after commencing (or switching to) Flupenthixol Decanoate at baseline, however no further improvements were seen in social cognition at 12- months, suggesting stability of emotional intelligence over time (Olivier et al., 2015). The other study found no effect on emotional intelligence at 6-months of commencing (or switching to) paliperidone at baseline, in patients with schizophrenia (Shi et al., 2016).

Despite the lack of available studies of antipsychotic effects, emotional intelligence has been found to be consistently impaired in patients with schizophrenia compared to controls (Martins et al., 2019; Green et al., 2015). Therefore, longer-term follow-up studies (see Chapter 6, section 6.4.3), with validated measures (see Chapter 6, section 6.6 and 6.7), controlling for factors such as symptoms and neurocognition in patients with schizophrenia, are needed to establish the evidence of the effects of antipsychotics on emotional intelligence.

5.14 Predictors of Social Cognition Change

Linear regressions between Hinting Task mean change scores and symptom mean change scores revealed no symptom-related significant predictor variables. These findings are different to that found in the review by Mitchell and Young (2016), who showed that severity of positive symptoms predicted ToM performance regardless of diagnosis, with stronger positive symptoms associated with poorer ToM performance. Additionally, previous literature has focused on a relationship between negative symptoms and ToM (Healey et al., 2016; Ventura et al., 2013), and authors of one study suggest this relationship may be seen consistently due to the prevalence of negative symptoms experienced in patients with schizophrenia spectrum disorders (van Neerven et al., 2021). As patients at all timepoints in this sub-study were only considered ‘mildly ill’ by Leucht at al (2005) symptom severity criteria, it resulted in small mean change scores across PANSS domains, and resultingly may have made significant relationships with social cognition measure change scores difficult to detect. Regressions between potential predictor variables (demographics, and neurocognition and symptom change scores) and social perception and social empathy mean change scores, also identified no significant relationships. Again, these findings may reflect the relatively well sample (with low symptom severity) or limitations in measures, resulting in difficult to detect relationships between variables (see Chapter 6, section 6.7).

Ethnicity was identified as a significant predictor of AIHQ Blame change scores from baseline to 12- months, with White participants more likely to have higher blame bias responses. This finding could show implicit biases evident in White people, who due to systemic factors that encourage privilege, may be more likely to blame others for negative situations (Cooley et al., 2019).

It is also important to consider why the relationship between ethnicity and AIHQ Blame were not evident at baseline. It is possible that the relationship between AIHQ Blame and PANSS General symptom scores was more influential in determining

blame bias scores at baseline, obscuring other relationships. Additionally, it may suggest that changes over time strengthened the associations between ethnicity and blame bias.

5.15 Antipsychotic Dose Change and Social Cognition Changes

Change in dose of antipsychotics was not correlated with change in social cognition test performance, across any social cognition domains. Absence of significant correlations between these variables indicated that there were no strong or consistent relationships between variables. From the studies identified in the systematic review presented in this thesis (Haime et al., 2021), only one showed a potential dose-dependent relationship between antipsychotics and facial recognition of sad and neutral faces (Daros et al., 2014). However, the current study only evaluated overall emotion recognition scores, and therefore more in-depth further analysis of positive and negative emotion recognition domains separately, may provide more insightful results.

Notably, there was no significant difference between groups antipsychotic dose reduction at the 24- month endpoint ($p = .701$). Both groups demonstrated a reduction in mean dose, with the reduction/discontinuation arm showing a slightly higher reduction (9.26%) compared to the maintenance arm (5.52%). These findings suggest participants in both groups lowered their antipsychotic dose during the study. Various factors, such as the study's active monitoring of antipsychotic use increasing awareness of dose reduction to patients and clinicians may have contributed to these outcomes. Smaller differences in mean dose reduction at endpoint may also represent dose increases that happened during the study due to adverse responses to reductions, or relapses. Therefore, it is crucial to acknowledge that the current analysis did not account for fluctuations in dose, and this should be explored more thoroughly in future research.

It may also be that the small sample size, inability to account for different antipsychotic types, and inadequate measures, obscured any potential significant correlations between variables. Further research is needed to better understand the relationships between antipsychotic dose and social cognition in this population.

Additionally, when interpreting the results of this study, finding no correlation between antipsychotic dose change and social cognition change highlights the importance of acknowledging the potential role of non-pharmacological factors on social cognition in future research studies.

5.16 Social Functioning Change

From baseline scores it was evident participants in this sub-study scored relatively well for patients with schizophrenia (mean = 109.02, S.D. = 9.11), but still below healthy sample thresholds in the SFS measure (healthy range: 116-135), as established by Birchwood et al (1990). This implied that participants in the sub-study were likely to have some impairments in their daily social functioning, and therefore the investigation of potential predictors of social functioning change could provide valuable insights. However, it is important to note that the results from this sub-study may not be generalisable to the entire population of individuals with schizophrenia, as functional impairments can vary greatly between individuals.

In this sub-study, at 12-months, there were significant weak to moderate negative correlations between social functioning mean change scores and AIHQ Blame and SAT-MC mean change scores. These same relationships did not occur between variables at 24- months, which could mean the relationships between AIHQ Blame and SFS mean change scores, and SAT-MC and SFS mean change scores were only temporary and may be associated with the adverse effects of involvement in the reduction/discontinuation group replicated in trends of social cognition domains at 12- months. However, this finding may also reflect the possibility of a chance finding due to conducting multiple comparisons, or because of the variability in sample size between timepoints.

Mixed model results did not establish any significant relationships between social cognition domain changes and social functioning changes, nor for main effects of time, group, or time x group on social functioning. This is contrary to evidence from previous antipsychotic reduction studies which have shown significant improvements in social functioning over long-term follow-up in reduction/discontinuation participants compared to maintenance participants. These previous findings do support the observed direction of social functioning mean scores from 12- months to 24- months in this study, and findings may therefore indicate the study was underpowered or too short to identify any relationships between variables (Omachi & Sumiyoshi, 2018; Wunderink et al., 2013). Flaws with the current sub-study may have also influenced the results in other ways. Specifically, where periods of data collection for the sub-study were during COVID-19.

It is particularly likely social functioning was greatly affected by the lockdown environment, and with the prevention of social events enacted in law many participants may have changed their usual activities (the effects of COVID-19 on the research study and participants are further explored in Chapter 6, section 6.8 and 6.9). Therefore, future studies should continue to examine relationships between social cognition, social functioning, and antipsychotic reduction vs. maintenance over longer term periods, with larger sample sizes, to account for the potential methodological limitations present in this sub-study.

Chapter 6. General Discussion

6.1 Summary of Aims and Findings

This thesis explored the impact of antipsychotic medication on social cognition in schizophrenia-spectrum disorders. It began with a systematic review to summarise existing knowledge on the effects of psychiatric medications on social cognition. Then, a sub-study was conducted as part of the larger RADAR RCT, collecting data at baseline, 12- months, and 24- months. A cross-sectional analysis of data examined the relationship between psychiatric symptoms, medication use, and social cognition, as well as any associations between social cognition and social functioning in patients with schizophrenia. The study also compared social cognition scores of patients to those of healthy volunteers. Finally, a longitudinal analysis was conducted to investigate the effect of being in a reduction/discontinuation group vs maintenance group of antipsychotics on social cognition in patients with schizophrenia, over two years. This chapter summarises findings and discusses the strengths and limitations of the work presented in this thesis, as well as its implications, and recommendations for future research.

6.1.1 The Effect of Psychiatric Medication on Social Cognition – A Systematic Review

As a reminder, the aims for the systematic review were:

- To identify if psychiatric medications affect social cognition in human participants.
- To explore any temporal or spatial brain differences of participants partaking in social cognition tasks after administration of psychiatric medication, using neuroimaging papers.

To summarise the findings of the systematic review:

- The review showed high variability between papers investigating the effect of psychiatric medications on social cognition, with differences in study design, including type and dosage of medication, randomisation procedures, and social cognition measures used, that need to be addressed in future research.

- Several studies in healthy volunteers showed that the administration of the benzodiazepine diazepam impaired emotion recognition.

- Antipsychotic studies in healthy volunteers were minimal, and in studies involving patients, findings on the effects on social cognition were inconclusive and suffered from methodological limitations. Further studies are needed in the healthy volunteer population to establish social cognition changes associated with antipsychotic use in individuals without pre-existing cognitive deficits.

- Neuroimaging findings in both antipsychotic and benzodiazepine studies suggested that changes were evident regarding activation of brain regions associated with the social cognition network, however, few studies conducted

simultaneous behavioural social cognition tasks to identify performance changes related to those neural alterations.

In conclusion, the review evidenced the high variability amongst studies investigating the effects of psychiatric medications on social cognition and, as such, it highlighted the need for standardisation in future research to establish clearer and more reliable findings, similar conclusions to the previous review by Kucharska-Pietura & Mortimer (2013). Several studies demonstrated that administration of diazepam, a medication commonly prescribed for anxiety, impaired emotion recognition in healthy volunteers. This was an expected result, as the primary aim of the sedative is to reduce fearful or anxious responses in individuals, which may be achieved through dampening emotion recognition. However, limited antipsychotic studies in healthy volunteers and inconclusive findings in patients emphasised the need for further research to establish how social cognition is associated with other sedative psychiatric medications, particularly in individuals without pre-existing cognitive deficits. Neuroimaging findings suggested changes were evident in the activation of brain regions associated with the social cognition network after psychiatric medication administration. However, studies were unable to establish relationships between these neural adaptations and changes in social cognition performance. Therefore, future research should focus on behavioural tasks in neuroimaging studies, to establish a clearer understanding of the relationship between social cognition task performance and brain changes after psychiatric medication administration.

6.1.2 The Effect of Antipsychotics on Social Cognition in Patients with Schizophrenia – A Cross-Sectional Exploration

As a reminder, the aims for the cross-sectional study were:

- To determine if there were differences in social cognitive ability across domains, between patients with schizophrenia and healthy volunteers.
- To determine if symptoms of schizophrenia, and antipsychotic usage had a significant impact on social cognition task performance, across domains.
- To determine if social cognitive domain scores predicted social functioning outcomes.

To summarise the cross-sectional study results:

- Patients with schizophrenia had impaired social cognition compared to healthy volunteers, across domains.

In patients:

- One third of patients in this sub-study had been in contact with mental health services for over 20 years (32.9%), and 41.1% had four or more previous inpatient admissions, although according to clinical thresholds of symptom scores the sample were considered below ‘mildly ill’.

- Higher antipsychotic dose significantly predicted poorer emotion processing; however, this relationship did not remain significant after controlling for digit

span, age and PANSS Negative score in a multiple regression model.

- Higher antipsychotic dose and antipsychotic duration predicted poorer social perception; however, this relationship did not remain significant after controlling for age, ethnicity, and education level in a multiple regression model.

- There were no statistically significant relationships between antipsychotic dose, and AIHQ Hostility, SAT-MC, EQ, TEIQue, BLERT, and ToM domains, or antipsychotic duration and AIHQ Hostility, SAT-MC, EQ, TEIQue, BLERT, and ToM domains in patients with schizophrenia at baseline.

- There were no statistically significant relationships between symptoms and AIHQ Hostility, EQ, TEIQue, BLERT, and ToM social cognition domains in patients with schizophrenia.

- Younger age and fewer negative symptoms predicted better performance at the emotion processing task.

- Younger age also predicted better performance at the social perception and emotional intelligence tasks, and a higher likelihood for aggression bias towards others.

- Higher general psychosis symptom scores predicted a stronger likelihood for blame bias towards others, and higher negative symptoms scores predicted less likelihood of aggression bias towards others.

- Stronger hostility biases, higher antipsychotic doses, and being educated to only a primary/secondary level, predicted poorer social functioning, but there was no relationship with performance on other social cognition tasks.

In conclusion, findings showed social cognition was impaired in patients with schizophrenia compared to healthy volunteers, replicating studies by Pinkham et al (2014) and Charernboon and Patumanond (2017). Results also revealed consistency with a previous study by Daros et al (2014), with findings that higher antipsychotic dose significantly predicted poorer emotion processing. However, this relationship was not maintained after controlling for other predictors in multivariate analysis. This finding could show a stronger relationship between emotion processing and other predictors, such as age than AP dose. Alternatively, this result may highlight the low average dose of antipsychotics evident in patient participants at baseline, making relationships difficult to detect.

Symptom relationships with social cognition were also considered in patients with schizophrenia, for example, a positive relationship was identified between general psychosis symptoms and a higher likelihood of blame bias towards others. This replicated results
reported in a previous study by Monfort-Escrig and Pena-Garijo (2020), who found a positive association between severity of general psychosis symptoms and a higher likelihood of attributional bias in patients with schizophrenia. The identification of this

relationship in this sub-study suggested that cognitive bias may relate to underlying symptoms of schizophrenia. The relationship may indicate that symptoms impact on cognitive bias, but it may also reflect the situation whereby cognitive bias and certain psychotic symptoms arise from the same underlying mechanism. This illustrates the importance of longitudinal research in this area.

Along with prior research, these findings have highlighted social cognitive deficits as a common feature of schizophrenia. Additionally, results continue to add to the evidence that relationships between social cognition and antipsychotic dose are complex and require more investigation. The current study's limitations, such as the unequal sample size and use of a cross-sectional design, also suggest the need for caution in generalising the findings to the wider population. Further studies using larger sample sizes and longitudinal designs are needed to establish the causal relationships between antipsychotic use, symptoms, and social cognition in patients with schizophrenia.

6.1.3 The Longitudinal Effect of Antipsychotics on Social Cognition in Patients with Schizophrenia

As a reminder, the aims for the longitudinal study were:

- To determine if there were significant differences in social cognitive ability across domains, in patients in the reduction/discontinuation group vs. the maintenance group at baseline.

- To evaluate:

    - Whether changes in social cognition domains between timepoints were significantly different, between groups.
    - Whether changes in social cognition domains between timepoints were significantly different, across groups.
    - Potential predictors of social cognition change across groups.

- To determine whether changes in social functioning performance were related to changes in social cognition in all participants, and to identify any other potential predictors of social functioning change.

To summarise the longitudinal study results, the following points were considered in the discussion:

- On the Hinting Task, a repeated measure linear mixed model with main effects of time, group, and time x group interactions, found the time x group interaction to be significant, indicating a cross-over interaction.

- Mean change scores were significant between baseline and 12- months for the AIHQ Blame, between baseline and 24- months and 12- and 24- months for the EQ-SSF, and between 12- and 24- months for the SAT-MC. However, in repeated measure linear mixed model's main effects of time, group, and time x group interactions were not significant for these domains.

- Interaction plots showed declines in performance for various social cognition domains and in social functioning from baseline to 12- months in the reduction/discontinuation group, but improvement from 12- to 24- months, although differences were not statistically significant except for those identified above.

- Significant weak negative correlations were identified between SFS mean change scores and AIHQ Blame mean change scores, and SFS mean change scores and SAT-MC mean change scores.

- A repeated measure linear mixed model of predictors of SFS change including main and interaction effects of time, group, time x group, social cognition domains and co-variates, was not significant.

In conclusion, findings from the longitudinal study add to the existing literature on the relationship between antipsychotic medication, social cognition, and social functioning change. Previous research in the field has reported mixed results on the effects of antipsychotic medication on social cognition and functioning in individuals with schizophrenia (Yamada et al., 2022; Haime et al., 2021).

During the longitudinal analysis, a visually observed trend was noted in which participants in the antipsychotic reduction/discontinuation group experienced temporary dips in some social cognition domains and social functioning performance, at 12- months. Although, this relationship was only significant for changes between baseline and 12- months for AIHQ Blame, and between 12- and 24- months in ToM, EQ-SSF, and SAT-MC. Despite this, these observed group trends of declines in social cognition between baseline and 12- months may align with previous research indicating short-term antipsychotic dose reductions are associated with higher rates of relapse, and temporary increases in symptoms of psychosis (Leucht et al., 2012; Wunderink et al., 2007). However, as both groups of participants reduced their dose during this sub-study, and symptom changes were not significantly related to changes in social cognition performance, it suggests that these performance dips were likely due to factors beyond medication changes, such as assessment format alternations (in-person vs. online), or unobserved psychosocial factors.

Additionally, longer-term follow-up studies have reported improvements in social functioning for patients in an antipsychotic dose reduction (Omachi and Sumiyoshi., 2018; Wunderink et al., 2013). This would be consistent with the trend seen in this sub-study from 12- to 24- months, where reduction/discontinuation group members performance in social functioning and some social cognition domains improved. However, it should be noted that no correlations were found between changes in social cognition and antipsychotic dose from baseline to 24- months, and that correlations between social cognition and antipsychotic changes between 12- and 24- months were not measured in this sub-study. Therefore, improvements in the reduction/discontinuation group may have been due to a variety of factors, including fluctuations in cognitive ability over time unrelated to antipsychotic change, changes in psychosocial circumstances, or changes due to expectations as participants were unblinded to their study condition. These findings indicate patterns in social cognition and social functioning outcomes of the reduction/discontinuation group over time,

however, the underlying mechanisms driving these changes continue to remain unclear. Further research exploring the complex longitudinal relationships in this context is needed to gain a deeper understanding of these findings.

Following on from this, a significant crossover interaction was identified between groups on the ToM measure from baseline to 24- months, suggesting potential differences in long-term ToM outcomes, based on intervention arm. Previous research has identified ToM improvements in schizophrenia related to antipsychotic use (Mizrahi et al., 2007). Although, it is important to note that this study was short-term (6 weeks) and non-randomised, resulting in an inability to capture the complex relationship between antipsychotic dose and ToM over a prolonged period. Additionally, another study has identified impaired ToM in patients taking certain types of antipsychotic medication, suggesting differences in performance may be dependent on differences in antipsychotic type (Savina et al., 2007). Further investigation is needed to fully understand the relationship between antipsychotics (dose and type) and ToM performance over time. Nonetheless, current findings suggest a supported gradual antipsychotic reduction in collaboration with a clinician may be an influential factor in ToM performance. On the other hand, the current sub-study did not find any significant relationships between changes in antipsychotic dose and changes in ToM performance over time. This indicates that it was likely factors other than the antipsychotic dose reduction that caused the observed patterns of change in the reduction/discontinuation group, such as increased support and clinical contact, or participant expectations due to group allocation. Alternatively, the discrepancy might indicate the patterns of change on tests of social cognitive were chance findings (false positives), or that there was a lack of power to detect a subtle effect of antipsychotic dose.

6.2 Reflections on Findings from This Thesis

Reflecting on the overall findings, this thesis has highlighted the complexity of social cognition deficits in schizophrenia, which may be influenced by various factors such as age, education, symptom severity, and being in a guided antipsychotic reduction vs. maintenance treatment plan. Overall, the studies contribute to a growing body of research on the role of antipsychotic medication on social cognition and functioning in schizophrenia and underscore the need for treatment approaches that take into account the needs and challenges of each patient, which may change over time. Despite this, the results of the present studies should be interpreted in light of some limitations, such as unequal group sizes, high attrition, and inability to account for different antipsychotic types or neurocognitive measures, which may have obscured potential significant relationships between variables. These limitations will be discussed in more detail within this chapter.

6.3 Methodological Considerations

6.3.1 Sample and Recruitment

The baseline sample of the social cognition sub-study was n= 73 patients with schizophrenia, and n= 37 healthy volunteers. The patient sample for this study were recruited as part of the RADAR study:

6.3.1.1 Advantages of Sampling from the RADAR Study

Recruiting the sample for this sub-study directly from the RADAR trial had several advantages. Firstly, having access to participants recruited as part of RADAR enabled contact with a unique set of patients with schizophrenia, taking part in an RCT of reduction/discontinuation vs. maintenance of antipsychotics. The RADAR study design was robust and allowed for a 2-yr follow-up period. The longest previous studies of antipsychotic reduction and social cognition had a 6-month follow-up and no previous antipsychotic reduction studies had included measures of any social cognitive domains.

A benefit of recruiting from the RADAR study was the utilisation of multiple study sites recruiting across England, resulting in participants in the sub-study coming from eight different study sites, making the sample relatively representative. There were also frequent meetings between teams and the central study site, allowing me to monitor how sites were progressing with social cognition assessments, and address any training needs or additional queries promptly.

Another advantage of recruiting via RADAR meant that researchers had established good relationships with clinical teams, consultant psychiatrists, participants, and in some cases participant carers/families. This helped with both recruitment and retaining participant engagement over follow-ups. Finally, as a member of the RADAR team, I was able to utilise the RADAR steering group, Programme Management Group (PMG), and Lived Experience Advisory Group (LEAP) for advice and guidance on the sub-study throughout its development and interpretation of findings.

6.3.1.2 Disadvantages of Sampling from the RADAR Study

Recruiting from the RADAR study sample also had some disadvantages. This included that the sample was limited to participants already taking part in the RADAR study, and therefore the inclusion/exclusion criteria applied. This meant that potential participants deemed ‘a serious risk of harm to self or others’ as judged by their consultant psychiatrist, and participants who had one episode of psychosis lasting less than a year, were unable to be recruited into the sub-study. This may have resulted in a sample with less prominent symptoms of schizophrenia taking part.

Another disadvantage associated with being a sub-study was that the sample size had already been calculated for the RADAR trial before the sub-study was proposed, and therefore the sample size did not account for subgroup analysis based on social cognition measures. Additionally, the RADAR study had been recruiting since March 2017, and the social cognition measures were only approved as a substantial amendment in May 2018. This meant that 27.7% of the overall sample for RADAR (n= 253) had already been recruited. Additionally, some study sites already recruiting for RADAR did not agree to the inclusion of the additional social cognition measures due to potential researcher and participant burden. This meant the potential study sample was limited from the sub-study commencement.

Additionally, a limitation of recruiting the sample from RADAR was that the primary outcome for the RADAR study was the social functioning scale (SFS), followed by 16 secondary outcome measures, and a demographics questionnaire. This resulted in participants completing the social cognition measures last in the assessment pack and gave them the lowest likelihood of completion due to participant fatigue or time burden. Also, as the measures for the RADAR trial assessment had already been approved for the study before the sub-study had been proposed, secondary measures of interest to social cognition relationships were not included, such as a separate measure of paranoia.

Another disadvantage was that recruiting for a RCT of this nature was complex. RADAR required a 2-year commitment, and for participants to agree to have their antipsychotic medication decisions made for them by a randomised choice. Understandably, many potential participants preferred to make these decisions independently and therefore did not wish to take part. This resulted in a sample of patients who may have been more ambivalent about their antipsychotic medication usage taking part, and the sample may therefore be unrepresentative of all patients with schizophrenia.

The final limitation in recruiting from the RADAR sample was that due to the nature of the RADAR study as an RCT of reduction/discontinuation vs. maintenance antipsychotic treatment, all participants had already commenced medication before participation in the trial. The ideal baseline condition would be patients who are medication free, to understand the immediate impact of antipsychotic medication on social cognition. Studying patients already taking antipsychotics requires the consideration of potential confounding factors such as residual effects of medication or withdrawal effects, and the longer term structural and functional brain changes which may exist due to the medication. However, studying antipsychotic-naïve participants would result in a sample likely be limited to first-episode patients, leaving patients with chronic schizophrenia or those on long-term medication at risk of being understudied.

6.3.2 Sample Size

The overall patient sample recruited at baseline was n= 73, adequate for the target sample of n= 66. However, the group sizes were unequal (reduction/discontinuation arm n= 30, maintenance arm n= 43) meaning that the target of n= 33 per arm was not met (Hey & Kimmelman, 2014). As participant allocation was blinded until study recruitment ended, bias in group allocation for the social cognition sub-study was unable to be addressed, which is a common issue with subgroup analyses in RCTs (Brookes et al., 2001), and therefore conclusions from the studies in this thesis should be interpreted cautiously. However, this baseline sample was considerably larger than the two previous randomised longitudinal studies on antipsychotics and social cognition that did not receive pharmaceutical funding, Koshikawa et al (2016) n= 21, and Fakra et al (2009) n= 25. Although other randomised longitudinal studies of this nature, that received pharmaceutical funding, did usually have bigger sample sizes (range: 48 - 223 participants). Despite this, all of the previous RCTs researching the effects of antipsychotics on social cognition were a maximum of 6 months long and included commencing antipsychotics with participants who were not

antipsychotic-naïve (range: 4 weeks - 6 months) (Haime et al., 2021), showing the current analyses presented in this thesis were able to overcome or control for some previous methodological limitations.

Additionally, it should be acknowledged that the original sample size calculation for this sub-study was completed based on literature around the emotion processing outcome. This was because emotion processing is the most widely studied social cognition domain and there was the most evidence to base calculations on (Green et al., 2008). However, this means that other social cognition domains did not impact the sample size calculation and may mean that the sample size was not substantial enough, or was overpowered, for studying those domains.

6.3.3 Randomisation and Blinding

Participants in the RADAR trial were randomly assigned (1:1) to treatment arms (reduction/discontinuation vs. maintenance). However, not all participants took part in the social cognition sub-study and as such there was a risk that the allocation would be biased. The groups at baseline did emerge as unequal for the social cognition sub-study with reduction/discontinuation arm n= 30 and maintenance arm n= 43, however assumptions for data were checked and met before any analysis was conducted. It is important also to consider that the participants who chose to take part in this sub-study were patients who had already completed an assessment of measures for 1.5-2hrs beforehand, and therefore were likely a group of willing and able patients with schizophrenia, which may not be representative.

A double-blind RCT, where the group allocation of the participant would be masked from participants, clinicians and researchers would be the ideal condition for a study of this nature, to prevent bias affecting participant responses. However, due to ethical considerations around the prescription of antipsychotic medication, as well as the need for cooperation between patients and their treating clinicians in the intervention arm, it was not possible for patients or their clinicians to be blinded in this study. Despite this, researchers conducting assessments with participants were blinded to study group allocation, and where unblinding occurred prior to an assessment another researcher was assigned to complete measures with the patient. This blinding worked to prevent potential researcher bias in measures that were more subjective in their scoring such as the PANSS, and AIHQ. Additionally, it is likely objective measures such as the neurocognition assessment Digit Span, and the social cognitive measures, Hinting Task, BLERT, SAT-MC, and SAT-MC II were less likely to be subject to any bias.

6.3.4 Analysis

The baseline study presented in this thesis was cross-sectional in nature, meaning results could not establish any causal relationships between social cognition and other tested variables, a limitation of conducting this type of study design. A more sophisticated study, which involved a longitudinal design was necessary to determine the effects of antipsychotics on social cognition in patients with schizophrenia, which prompted the longitudinal study component of the thesis.

An intention-to-treat (ITT) analysis was conducted for the longitudinal study in this thesis. Using this approach allowed an unbiased evaluation of the efficacy of a reduction/discontinuation intervention on social cognition in patients with schizophrenia and allowed the reporting of findings according to CONSORT guidelines (Gupta, 2011; Moher et al., 2001). However, the effect of the intervention from this analysis may be limited due to the inclusion of participants who did not adhere to their treatment arm. In this study, this included participants in the reduction/discontinuation arm who did not reduce the dose of their antipsychotic a significant amount during the study, and participants in the maintenance group who increased or decreased their antipsychotic a significant amount during the study. This non-adherence to study protocol may represent a more realistic interpretation of 'real-world' intervention compliance. Therefore, if large proportions of the study participants failed to adhere to their assigned group protocol, a more accurate interpretation of the data may be to conduct further 'per-protocol' analysis in the future (Moncur & Larmer, 2009).

6.4 Patient Sample Considerations

6.4.1 Sample Characteristics

The patient sample in this sub-study (n= 73) showed no significant differences on baseline demographics, apart from age, between groups (Sedgwick, 2014). Patient participants were representative of a large age range (reduction/discontinuation group 29 - 65yrs; maintenance group 26 - 68yrs.), however reduction/discontinuation group members had a higher average age (mean = 51yrs.) compared to maintenance group members (mean = 45yrs.). Further analysis to identify if any demographic variables had associations with social cognition outcomes at baseline were conducted using regressions, across the whole patient sample. Age was found to have a significant relationship with AIHQ Hostility, BLERT, SAT-MC, and TEI measures. Therefore, age was used as a covariate in all multivariate analysis.

The sample were reasonably ethnically diverse, however, due to small numbers in many of the original ethnicity categories, they were combined into 'White' and 'Non-White' categories. Around a third of participants in each group identified as a Non-White Ethnicity (reduction/discontinuation group 33%; maintenance group 34%), which is largely representative of the general population of England and Wales, where 81.7% of the population are White (GOV.UK, 2022). However, these figures may not account for the over-representation of Black and Caribbean people diagnosed with a psychotic disorder in the UK (GOV.UK, 2017; Halvorsrud et al., 2019). Many other studies in patients with schizophrenia fail to achieve diversity in the sample ethnicity (Burkhard et al., 2021; Mak et al., 2007), and difficulties recruiting people from Non-White ethnicities in mental health research in general has been well-documented (Freudenthal et al., 2021). In this study, many participants (n= 56) were recruited from areas of London, where a high proportion of Non-Native English speakers live, and a study requirement was a good level of understanding and speaking of the English language, which may have limited the ethnic diversity of the sample. Considering the higher incidence rates of diagnosis of psychotic disorders in Non-White populations, as well as their increased detention under the Mental Health Act in the UK (Singh et al., 2014), it is integral to increase research engagement of diverse ethnic populations in studies of this nature.

Additionally, this sub-study had a higher proportion of males (reduction/discontinuation group 84% males: maintenance group 67% males) to female patient participants. As the prevalence of a psychosis diagnosis is roughly equally split across genders, this sub-study seems to underrepresent the female population with schizophrenia (McManus et al., 2016). This lack of representation for the female gender in this research may be due to exclusion criteria that participants could not be pregnant or breastfeeding during the trial. Previous research on antipsychotics in schizophrenia have had a similar lack of female representation, which highlights our lack of knowledge of the effects of psychiatric medication on women (Fonseca et al., 2021).

The patients included in this study also had a high average number of inpatient admissions (mean = 3.3 occasions), and generally could be considered to have had a long-term diagnosis of schizophrenia, with around a third (32%) having been in contact with mental health services for 4–10yrs, and around another third (34%) for more than 20yrs. However, they were not acutely unwell at their admission into the study, with symptom scores considered lower than mild (mean PANSS Total = 42.73) (Leucht et al., 2005). Participants were also taking low doses of antipsychotics (Dudley et al., 2017) on entry into the study, and both groups had reduced doses at endpoint. It is unclear why the maintenance group had reduced their antipsychotic dose, but it could include participants experiencing adverse effects, participants requesting medication reductions, or psychiatrists using clinical judgements to treat participants. Therefore, the maintenance arm in this study should likely be considered a 'treatment-as-usual' arm. Mean antipsychotic dose in the reduction/discontinuation arm was reduced by 9.26% and in the maintenance arm 5.52% by endpoint, meaning a non-significant ($p = .701$) difference in antipsychotic reduction between groups. Additionally, only 3 participants completely discontinued from their antipsychotic in the reduction/discontinuation arm. This represented relatively similar decreases in antipsychotic dose by 24- months across both groups. Given the limited number of significant differences observed, and the absence of a control group, the study's ability to determine the effects of antipsychotic reduction is constrained. Moreover, it is important to note participants' doses often fluctuated during the study, with some ending on higher than baseline doses (because they requested medication increases, clinicians recommended increases, or due to relapse). It is likely these fluctuating changes in dose within patient data were not captured within this study analysis.

Additionally, there was no way to accurately measure participant adherence to medication during the study. The MARS-5 was used to assess participant medication adherence by self-report, but the measure has limitations, including the premise that medication use is often a dynamic changing behaviour, and it was only able to capture participant antipsychotic use at the given RADAR time-points (baseline, 6-months, 12- months, and 24- months). Also, the MARS-5 may be susceptible to inaccuracies by patients, with potential overestimation of adherence. To overcome some of these issues participant electronic records were accessed every 2 months to record current medication dose and any noteworthy adaptations to their treatment. However, this did not allow for accurate measures to confirm the (oral) medication was taken.

When comparing the patient group with the healthy volunteer group there were no significant differences in demographics at baseline, however patients did score lower in neurocognition. Deficits in neurocognition amongst people with schizophrenia have been well-documented in the literature and are widely believed to represent a core trait symptom of the diagnosis (McCleery & Nuechterlein, 2019; Wilk et al., 2005). However, it has also been disputed that this connection between schizophrenia and neurocognitive deficits may be over-estimated. Such difficulties with neurocognition may instead be due to confounds during assessments (e.g. psychiatric symptoms), the relationship between physical health disorders and poor neurocognition (e.g. obesity), the effects of defeatist beliefs on neurocognition ability, or the potential impact of antipsychotic medication on neurocognitive functioning (Moritz et al., 2021; Moritz et al., 2020). In the sub-study reported in this thesis, neurocognition was controlled for where univariate analysis revealed it to be a potential confounder using the single measure of Digit Span (forward and backwards). However, other domains of neurocognition, such as speed of processing, which has been shown to be associated with antipsychotic use, were not controlled for in the analysis (Faber et al., 2012).

6.4.2 Attrition

Overall, attrition in this study was high, with substantial loss of participants in the sub-study in both the reduction/discontinuation arm (40.0% dropout) and the maintenance arm (44.2% dropout) at 24- month follow-up. A previous review showed estimates of dropouts in complex trials for schizophrenia to be 14% from (non-pharmacological) intervention groups, and around 20% from overall studies (Szymczynska et al., 2017). The minimum sample needed for the baseline study in this thesis was n= 66, with n= 33 in each arm to allow for 15% dropout (based on Moncrieff et al., 2019), with a target of a minimum n= 58 at follow-up.

At 24m, 73% of the baseline sub-study sample completed the RADAR trial assessment, compared to the 57% who completed both the RADAR study assessment and social cognition sub-study measures. Therefore, it should be acknowledged that the predicted drop-out rate for this sub-study was likely to have been too conservative and should have had greater consideration for the additional burden of these measures on participants. However, it is also integral to consider the impact of COVID-19 during this period. The resultant low sample size for the longitudinal analysis of this sub-study means that findings should not be over-interpreted, and lack of differences should be considered with caution. Results from both the longitudinal studies presented in this thesis should therefore be used for hypothesis-generation for further studies that are adequately powered only.

6.4.3 Follow-up Time and Assessment Format

This was the first antipsychotic reduction study to undertake a two-year follow-up with participants, which was important in understanding long-term effects of medication on outcomes. However, it may be that this time-period was not long enough for differences in social cognitive ability to be detected, and that longer follow-ups at five or more years may show further changes dependent on participant group at baseline. This was shown in the seven-year follow-up study by Wunderink et al (2013) who found participants initially recruited to an antipsychotic

discontinuation/reduction group had better recovery rates than those originally assigned to a maintenance group.

Additionally, it is integral to consider the potential effect of changing assessment format from in-person to online, during the COVID-19 period. This shift may have introduced variations in participant experience, response behaviours, and the overall context of the assessments, which could have influenced the outcomes at different time points. It is important to recognise the impact these format changes likely had when interpreting the study findings, as they may have introduced potential confounding factors. Conducting further sensitivity analysis in the future may help to account for the influence of format changes on outcomes, improving the generalisability of results.

6.4.4 Multiple Comparisons

Throughout both study analyses, multiple comparisons were made for each social cognition variable. As the sample sizes were limited for these studies, multiple comparisons in this context may have increased the risk of inflating the Type I error rate, introducing false positive results. However, a decision was made not to use post-hoc tests in analysis as the sample size was already small, and therefore these tests may have reduced statistical power, and potentially led to increased Type II error rates, or false negatives (Zhang et al., 2019). As results from this thesis suffered from unequal sample sizes, high attrition rates, and limitations with measures, alongside a risk of Type I error, it is emphasised again that results should be used for hypothesis-generation in larger and longer RCTs.

6.4.5 Social Cognition Changes and Additional Variables

Social cognitive impairment in schizophrenia is unlikely to be completely independent of other aspects of the illness, as shown in research showing social cognition as a mediating factor in the relationship between neurocognition and social functioning (Fett et al., 2011; Schmidt et al., 2011). Additionally, previous studies have found social cognition domains to be associated with age, gender, and education level (Othman et al., 2011). The potential impact of demographic, neurocognition, antipsychotic usage, and symptom factors on social cognitive measures are therefore necessary to consider when investigating impairments in schizophrenia. The current analyses presented in this thesis were able to include measures of these factors as potential confounding variables in the analysis of social cognition in patients with schizophrenia. This inclusivity of potential confounding variables was consistent with good methodological practice in this type of research, however, more in-depth analysis into mediating and moderating relationships is needed and was not possible in the current analysis due to the limited sample size.

A critical concern in this study may also be the justification of social cognition as independent of other aspects of cognition, as only one neurocognition measure was included in the analysis (Mesholam- Gately et al., 2009). Whilst it may have been more comprehensive to incorporate the battery of neurocognitive measures collected during RADAR into the analysis, it should be noted that this sub-study would have been underpowered to adequately account for multiple comparisons that would have arisen. Thus, the decision to focus on a single neurocognitive measure was made to

maintain statistical power and reduce potential Type I errors. However, future studies should aim to include more neurocognitive measures to better understand their interplay with different social cognitive domains (Woodberry et al., 2010).

Additionally, the current sample were taking a wide range of antipsychotics meaning no comparisons could be made between medication type and social cognitive performance, a larger sample size would also allow for further examination of this relationship.

6.5 Measurement Considerations

6.5.1 Practice Effects

An additional methodological consideration in this thesis was the influence of practice effects on patient outcomes. Practice effects are improvements made on measures due to repeated exposure and participant learning and memory. Measures are more susceptible to practice effects when the task is unfamiliar (Lezak et al., 2004), however, they are less likely to happen when there is a long interval between test and re-test (McCaffrey & Westervelt,1995).
In this thesis, practice effects were unlikely to affect social cognition performance for a couple of reasons:

- A parallel version of the SAT-MC was used (the SAT-MC II) for the 12- month follow-up.

- Intervals between assessments were 12 months, sufficient to reduce practice effects. However, as practice effects are often dependent on individual factors (e.g., motivation and fatigue; Süss & Schmiedek, 2000) and are more pronounced for complex tasks (Onate et al., 2000), it is possible residual effects remained.

Practice effects of the neurocognitive RADAR measure ‘Digit Span’ should also be considered, as it was included at the additional 6-month assessment. It has been shown that repetitive cognitive testing can make participants susceptible to practice effects, however Digit Span seems to be one of the more robust and resilient against this (Bartels et al., 2010).

6.5.2 Social Desirability

Social desirability refers to a participant response bias, where they tend to present themselves in the most socially acceptable way to gain approval of others (Krumpal, 2013; Nederhof, 1985). In this study, several of the measures were based on self-report from participants and were therefore at risk of social desirability bias, including RADAR measures (SFS, and MARS5), and social cognition measures (EQ-SF, AIHQ, and TEIQue). No measure of social desirability bias was used in this study, and therefore it is difficult to assess whether participants were influenced by this bias, however it is also likely this bias would exist for participants at every assessment stage and therefore should not have a significant impact on score changes (Larson, 2018). There are also advantages to consider when using self-

report measures, including their relative ease for participants to complete, the speed in which they can be done, and their ability to ask people directly what they think.

6.5.3 Poor Performance by Patients

Patients included in this study performed significantly poorer at all social cognition domains compared to healthy volunteers. These findings support previous evidence of impaired social cognition in patients with schizophrenia (Haime et al., 2021). However, it is important to consider other factors which may have affected the performance of patients on these measures, such as poor motivation or lack of co-operation. In this study it is thought that the effects of these factors on performance were minimised through patients being under no pressure or obligation to complete the measures and being given regular breaks in assessments if they were tired or irritated.

6.5.3 Lack of Social Cognition Change Over Time

For most social cognition domains, there were no significant differences across timepoints, between or across groups. This may suggest that social cognition domains assessed in the study exhibited stability over time and were not significantly influenced by the intervention (antipsychotic reduction/discontinuation) or the comparison group (maintenance), alike to neurocognition as a stable factor over time in patients with schizophrenia (Fett et al., 2022). These findings indicate that social cognition, as measured in this sub-study, may represent a trait-like characteristic. However, it is important to note there may be other variables, such as antipsychotic type, or assessment format, that were not captured in this study analysis, that could influence social cognition outcomes.

6.6 General Consideration of RADAR Measures

6.6.1 PANSS

The PANSS as a measure has been shown to have good psychometric properties for use with patients with chronic schizophrenia (Kay et al., 1987), and adequate psychometric properties for use with acute patients with schizophrenia (Peralta & Cuesta, 1994). However, more recently research has suggested that the PANSS should be considered as a five-factor model (van der Gaag et al., 2006). Using a five-factor model in the analysis of this thesis may have allowed more precision in identifying symptom relationships with social cognition domains (Lehoux et al., 2009).

As part of this sub-study there were some additional limitations when using the PANSS. For example, as researchers at external sites were employed on several studies that may have used the PANSS, potential training conflicts may have existed. Additionally, as the PANSS was scored retrospectively after each assessment, scoring may have been influenced by other assessment areas. Finally, items N4 and G16 required ratings to be based on information by a treating clinician or family member/friend who had significant contact with the patient (Opler et al.,

2017), therefore, due to study constraints insufficient information may have been available for accurate scoring of these items.

Despite these limitations, research assistants for the RADAR trial were trained by experts in the use of the PANSS, and refresher training sessions were provided. Additionally, double scoring was used to ensure adequate agreement between researchers before they were able to use the PANSS independently.

6.6.2 SFS

The self-report social functioning scale used in this thesis is vulnerable to the social desirability bias already discussed. However, the SFS does show adequate validity as a measure, and has been used as the primary outcome in many clinical trials of patients with schizophrenia (Long et al., 2022). In this study, adaptations were made to include additional leisure activities that participants may take part in, to ensure the scale was inclusive of more modern activities such as online gaming, and social media use. However, it is likely social functioning was particularly affected by COVID-19 (Chapter 6 section 6.7) and therefore scale answers may be less reliable and valid within this sub-study.

6.6.3 Digit Span

The Digit Span is commonly used as a cognitive measure across research studies as it is quick and simple to administer. The measure is also known to be sensitive to changes in working memory over time, making it an appropriate tool for measuring neurocognition change in this study (Hilbert et al., 2014). However, the Digit Span measure has been criticised for being too easy for some individuals, which can lead to ceiling effects and a lack of score variability at the upper end of the scale (Gignac & Weiss, 2015). Additionally, it is important to note the Digit Span is only able to measure working memory and attention, and therefore, it cannot provide a comprehensive assessment of other domains of neurocognition.

6.7 General Consideration of Social Cognition Measures

Social cognition measures used in this sub-study were considered quick, easy to administer, and were largely validated for use in patients with schizophrenia. However, some limitations were evident with measures during their use in the study, including self-report social desirability biases, potential issues with ceiling effects, and poor ecological validity. Despite this, the measures were either recommended for use in clinical trials of this nature, or there were no alternatives accessible. The below table considers the strengths and weaknesses of the social cognition measures used during the sub-study (**Table 49**), and details recommendations for improving psychometric criteria of each in the future.

Table 49.
Strengths and Weakness of Social Cognition Measures.

Social Cognition Measure	Strengths of the Measure	Weaknesses of the Measure	Recommendations
AIHQ	Good test-retest reliability and adequate internal consistency for 'Blame Scores' (Buck et al., 2020; 2017). There are currently no other reasonable measures to measure attribution bias in patients with schizophrenia (Pinkham et al., 2016). Good interrater reliability was shown for AIHQ items in this sub-study.	Low test-retest reliability on the open-ended response items of the Hostility Bias and Aggression Bias factors (with researcher rated scores) (Pinkham et al., 2016).	Brief AIHQ measure by the SCOPE team, which includes the five ambiguous scenario vignettes, but only scores items for the Blame Score, has now been recommended by Halverson et al (2022).
Hinting Task	SCOPE study supported the use of the Hinting Task in clinical research of patients with schizophrenia, finding limited floor and ceiling effects in their study (Pinkham et al., 2016).	Has been found to demonstrate ceiling effects in patients with schizophrenia spectrum disorders (Lindgren et al., 2018; Marjoram et al., 2006). This sub-study found that over half of the patient participants (54%) scored at 'normative' levels on the measure (a score of 17 or above) at baseline, similar to the 57% of patient participants scoring at this level in the study by Roberts & Penn (2009). This high initial scoring could limit the ability of observing significant changes over time.	The SCOPE study utilised a more stringent scoring system in their study, which has since been shown to improve the psychometric criteria of the measure and is now recommended for future use (Klein et al., 2020).
BLERT	Bell et al (1997) tested the psychometrics of the BLERT on 50 participants with schizophrenia and a	The BLERT has significant practice effects over short-term periods (Pinkham et al., 2016).	Through this sub-study the ecological validity of this measure has been bought into contention. Despite the

	comparison group of healthy volunteers and labelled the measure as 'good' for use in this population. Pinkham et al (2016) described the BLERT as being among the measures with the highest psychometric properties with sensitivity to group differences between patients with schizophrenia and controls, high tolerability, and limited potential for floor/ceiling effects.		dynamic nature of the actor in the video representing real-world facial and body movements related to the nature of the emotion being expressed, the character is played exclusively by a White male-presenting adult actor, with an American accent. This fails to be inclusive of participant experiences in the UK and elsewhere. An ecologically valid measure should aim to be inclusive of different genders, ethnicities, and ages, also including people who may have a visible difference. When exploring emotion processing it seems important that the participant has the opportunity to recognise features that may assist them with this process, and therefore the ecological validity of this measure cross-culturally needs to be further explored.
SAT-MC/SAT-MC II	Bell et al (2010) found that performance on the SAT-MC classified 75% of a large sample of chronic schizophrenia outpatients from healthy volunteers, with high scale reliability. Johannesen et al's (2013) study of healthy student volunteers, findings showed the SAT-MC II had a reliability score, comparable to the SAT-MC. The SAT-MC II performance was also highly associated with the BLERT measure. Johannesen et al (2018) found that, in contrast to the SCOPE study results, the SAT-MC and SAT-MC-II performed favourably in comparison to the TASIT.	Pinkham et al (2016) suggested that the SAT-MC and SAT-MC II were not good enough to be used in clinical trials of patients with schizophrenia, due to their low floor performance ratings	According to findings from Pinkham et al (2018) there is no appropriate measure of social perception in patients with schizophrenia currently available.

TEIQue	The TEIQue-SF in this study was decided firstly due to its free of charge availability for academic research purposes and no required training to administer the questionnaire. This is in contrast to the MSCEIT, where researchers require training and certification at a cost of around £1750 to administer the questionnaire (Psysoft, 2022). The TEIQue-SF can be completed in under 5 minutes, whereas the MSCEIT consists of 141 items and takes 30-45 minutes to complete. The Mayer-Salovey-Caruso Emotional Intelligence Test (Mayer et al., 2002) was recommended for use in clinical trials of people with schizophrenia. This is despite, as Eack et al (2010) pointed out, the measure only being validated in healthy volunteers.	The psychometric properties for the TEIQue have not been investigated in patients with schizophrenia thus far, however it has been shown to be substantially reliable and valid for use in research, from studies in healthy volunteer populations (Siegling et al., 2015),	There is a need for the TEIQue to be validated in patients with schizophrenia for future use.
EQ-SF	A psychometric study into the Empathy Quotient in patients with schizophrenia compared to healthy volunteers (Bora et al., 2008) using the 40-item measure, found a significant deficit in empathetic experience in the patient population (P = <0.001, ES = 0.91) The short form of the EQ was originally introduced to reduce burden to participants	The psychometric properties for the EQ-SF have not been investigated in patients with schizophrenia thus far, although a factor analysis of the 15-item version in healthy volunteers considered it a valid measure of empathy (Muncer & Ling, 2006).	There is a need for the EQ to be validated in patients with schizophrenia for future use.

6.8 Impact of the COVID-19 Pandemic on This Research Study

During the RADAR trial in March 2020, a worldwide pandemic was declared over coronavirus 'COVID-19'. In the timeline of this sub-study, all participants had been recruited and completed their baseline assessments before the start of the pandemic, with some having completed their 12- month assessments also (n= 25). In this sub-study, at the beginning of the pandemic (March 2020), n= 4 had withdrawn, n= 2 did not complete a 12- month RADAR assessment, and n= 4 did not complete the social cognition component of the 12- month RADAR assessment. COVID-19 pandemic restrictions were introduced during the first lockdown in March 2020 and were eased steadily across the country in early summer 2020. However, due to rising infection and mortality rates in the autumn, tiered restrictions were introduced in October 2020 and a nation-wide lockdown began after Christmas. Deployment of a vaccine started in early December 2020, and restrictions began to lift in February 2021, with access to venues limited in some places to those with vaccine passports. The final COVID-19 restrictions in the UK lifted in February 2022 **(COVID-19 event timeline can be viewed in Appendix D)**. This timeline resulted in most of the 12-month and 24- month follow-ups for this sub-study taking place whilst COVID-19 infection and mortality rates were high, and lockdowns or social restrictions were in place. Conducting a clinical trial with complex procedures revealed several unexpected considerations and adaptations during this time (Sohrabi et al., 2021), including:

- Changing procedures and measures – Study-wide procedural changes were made to the RADAR trial due to nationwide lockdowns. All study visits by researchers were moved to be conducted remotely via telephone or through an online video-based communication tool. For this sub-study, this meant that adaptations were made to two social cognition measures, the BLERT and the SAT-MC. The videos associated with the two measures for these domains were previously shown in-person to participants via an electronic device (tablet) which they could view whilst responding with their answers to the researcher. During the pandemic, an amendment was approved that required these two videos to be uploaded to a private YouTube account, where they were able to be viewed only by people who were sent the link. The link was provided to all research sites and during the assessment researchers could either 'share screen' and play the video to the participant or provide the participant with the link so that they could view it on their own device. Researchers continued to collect the answers from participants but entered them onto a 'word document' version of the social cognition questionnaire so that this could be sent (encrypted) via email, for data entry. Alongside other measures in the RADAR assessment, these social cognition measures had not been previously validated for online use, however for the safety of participants and to ensure the continuation of the study, the movement to online data collection was deemed necessary for the circumstances.

- Training of new staff via video-communication – During the pandemic staff turnover at the research sites conducting this sub-study increased, as they were often moved to work on rapidly developing COVID-19 studies. This required staff training procedures to also be moved online. The central research team remained responsible for site initiations and measure training

through this time and were able to transfer materials to online presentation with ease. However, at the beginning of the pandemic it should be noted that there was an unfamiliarity with online meetings, and those attending the training may have had difficulties with technology that interrupted their capacity to engage with the sessions. Additionally, during this period (Dec 2020) I left my position as a research assistant on RADAR. However, I continued to have an honorary contract at NELFT to ensure I was able to access data and assist with any training or researcher liaison where necessary regarding the social cognition sub-study.

- NHS availability – During the pandemic, medically trained personnel were considered essential staff, and many were called upon to take up clinical duties where staff numbers were fewer. This resulted in deployment of secondary mental health care and research psychiatrists to ward-based duties, where staff numbers were reduced due to sickness. Additionally, 'non-essential' community services were paused, and moves were made for many secondary care appointments to be online (Patel et al., 2021). These changes in care resulted in burden and uncertainties around care for both clinical staff and for patients during the time of pandemic (Liberati et al., 2021). For this sub-study it is important to consider the impact this had on participants, as well as those clinicians responsible for their medication, and how this likely affected participant non-compliance with their study arm, non-completion of social cognition measures, and withdrawals from the overall study (Yahya et al., 2020).

6.9 Effects of COVID-19 on Participants

It is important to consider the potential impact COVID-19 and the pandemic lockdowns also had on patient participants in this sub-study. Firstly, although social distancing was considered a high priority in the country for preventing the spread of COVID-19 it may have resulted in greater social isolation. Recent evidence has shown that loneliness in psychosis can affect cognitive and emotional functioning, physical health, and determinants of quality of life in individuals (Badcock et al., 2020). It is not known the extent to which social isolation may have affected these areas of patients' lives over the sub-study period, however, interestingly one piece of research has emerged showing that patients with schizophrenia had stable levels of psychotic symptoms and increased subjective well-being over the pandemic period (Stefano et al., 2021). These results may show that, due to the high prevalence of patients with schizophrenia living in isolated social conditions before the pandemic (Eglit et al., 2018), lockdown legislation had little impact on outcomes of patients with schizophrenia.

Secondly, it is important to consider the effect of COVID-19 on social cognition itself. Research into this area is gradually emerging since the pandemic, with one study showing that healthy volunteers ability to recognise happy faces significantly reduced, and ability to recognise sad faces significantly increased during the most stringent lockdown period (21st April to 10th May 2020) (Bland et al., 2022). These findings were confirmed by another study showing that recognition of sadness significantly increased during COVID-19 confinement (Meléndez et al., 2020). Unfortunately, at the time of writing this thesis there is little published research

investigating the effects of COVID-19 isolation on social cognition and therefore no substantial conclusions can be made about how participants in this sub-study were affected. However, as links between neurocognition and COVID-19 self-isolation are emerging in the literature, it may be likely that social cognition was also impacted during this time (Alle & Berntsen, 2021).

Lastly, it is also integral to consider the impact contracting COVID-19 may have had on participants in this sub-study. Research has shown that patients with schizophrenia were more vulnerable to contracting severe COVID-19 and were at higher risk of mortality from the virus (Ji et al., 2020; Nemani et al., 2021). Participants in this sub-study may have therefore taken more precautions against COVID-19 (e.g., not returning to social situations following lockdowns), they also may have been physically impacted had they been infected with COVID-19. Studies into the impact of COVID-19 infection on functioning are in their infancy, however, research has already emerged showing that COVID-19 can lead to deficits in speech, mobility, attention, memory, and problem solving (Olezene et al., 2021). It will be integral to understand the impact contracting COVID-19 may have longitudinally on social cognition to fully understand the results of the current sub-study.

6.10 Clinical Implications

Work in this thesis established that there is currently little informative research on how psychiatric medications affect the domains of social cognition. This work was able to confirm that patients with schizophrenia perform worse at social cognition compared with healthy volunteers, and that age and symptoms predict some of these deficits, although relationships were not consistent across social cognition domains. Additionally, this thesis presented provisional tentative evidence that guided antipsychotic reductions may worsen performance in some domains of social cognition, and in social functioning in the short-term, followed by longer-term improvements. However, no correlations between antipsychotic dose and social cognitive performance were shown across groups. In these studies, stronger hostility bias also predicted poorer social functioning at baseline, however there were no relationships between changes in social cognition and changes in social functioning longitudinally.

Overall, tentative evidence exists that suggests being in a supported antipsychotic reduction may have some influence on aspects of social cognition over time, although results were largely, not significant. In particular, being in the reduction group was observed to have short-term adverse effects on some social cognition domains, possibly as individuals experienced withdrawal effects, destabilisation, or relapse, as reduction regimes were encouraged to take place between the baseline and 12- month assessments. However, it is important to highlight that this sub-study did not analyse 12-month dose changes, relapse events or measure withdrawal effects, limiting the ability to establish clear relationships in this regard. Furthermore, important factors such as changes in assessment format (in-person vs. online) and potential additional psychosocial influences were not accounted for in the analysis.

Interestingly, social cognition improvements were also seen in these reduction/discontinuation group members between 12- and 24- months. The fact that

social cognition change was not correlated with AP dose change at endpoint suggests that these improvements may be more closely associated with group processes in the study. There were various reasons being in the reduction/discontinuation group may have affected outcomes, including increased clinical contact and socialisation, bias introduced by unblinding participants to their treatment group, or patient empowerment through shared decision-making, This would also align with the fact that both groups (reduction/discontinuation and maintenance) reduced antipsychotic dose by 24- months, and that there was no significant difference between groups in total dose reduction. These potential effects of increased clinical involvement with patients in the reduction group should be considered during significant treatment changes in practice. However, due to limitations of the sub-study, interpretations of these results should remain tentative.

Although this sub-study did not find evidence of an association between social cognition and social functioning, previous research has suggested a strong link between the two (Couture et al., 2006; Hoe et al., 2012; Schmidt et al., 2011; Fett et al, 2011), which is important when considering how to support people to have the best outcomes possible. Social functioning is a priority of patients, in particular (Law & Morrison, 2014). Therefore, through gaining a better understanding of the relationship between social functioning and social cognition, effective treatments can be developed, ultimately improving patient outcomes and quality of life.

Additionally, through a comprehensive systematic review, good evidence has been presented for emotion processing impairments associated with diazepam administration. Other drugs with sedative effects, which include all antipsychotics, may have similar effects either directly on social cognition, or more indirectly via changes in symptoms. For this reason, it is important clinicians continually assess and monitor pharmacological treatment effects on social cognition in their patients.

Overall, findings suggest that an awareness of impairments in social cognition is needed by clinicians to identify the subtle difficulties patients with schizophrenia may have processing and interpreting social signals and behaviours. Clinicians should be encouraged to access and utilise social skills training or psychological interventions for patients with social cognition difficulties. These steps may help to improve social cognition possibly leading to better overall functional outcomes in patients with schizophrenia. However, further research is needed to better understand the relationship between antipsychotic treatment, demographic factors, social functioning, and social cognition.

6.11 Future Directions

The previous section highlighted the importance of considering social cognition in the treatment of patients with schizophrenia-spectrum disorders. This section outlines potential future research directions that may help to advance the understanding and treatment of social cognition deficits in this population.

Firstly, it is essential that valid and reliable social cognition measures are rapidly developed, specifically those designed for use in populations with schizophrenia or symptoms of psychosis, and brief versions for use in clinical trials.

Next, it is also crucial that the relationship between changes in social cognition and changes in social functioning is clarified, and further exploration should be done to establish whether symptoms, antipsychotic usage or other factors effect this relationship. The nature of the relationship between symptoms and social cognition needs further clarification to assess whether they have a causal relationship to each other or whether they are different manifestations of the same basic pathological processes. Additionally, research should consider whether important clinical outcomes such as quality of life, or relapse are associated with social cognition, and what the implications of these findings mean for patients with schizophrenia.

Next, further research is needed to determine the effects of antipsychotics on social cognition, which requires longitudinal studies on healthy volunteers and drug-naïve patients newly starting on antipsychotics, and further RCTs of supported reduction of antipsychotic dose in people with long-term conditions who have been taking antipsychotics long-term. Additionally, studies of other psychiatric drugs should determine their effects on social cognition, especially as many other classes of drugs have sedative and emotion-blunting effects (Thompson et al., 2020; Kucharska-Pietura & Mortimer, 2013).

Further research should also be done to assess how changeable social cognition is in this population utilising psychological interventions, such as social cognitive interaction training, and determining whether any changes are maintained long-term. Finally, studies should also consider utilising qualitative approaches to understand the relevance and impact of social cognition deficits on patients' lives and how they prioritise social cognitive difficulties in their recovery.

6.12 Final Conclusions

In conclusion, this thesis highlights the importance of considering social cognition deficits in the treatment of patients with schizophrenia-spectrum disorders, and the potential impacts of drug treatment. While there is limited current research on how psychiatric medications affect social cognition in patients, findings show that diazepam reduces emotion recognition in healthy volunteers. This emphasises the need for high quality studies investigating similar relationships between social cognition and medications with sedative effects, including antipsychotics, in both patients and healthy volunteers. Additionally, trends in this thesis show performances may deteriorate during initial guided antipsychotic reductions, however further research is needed to confirm what determines this relationship. Additionally, long-term improvements may be associated with reduction group processes, such as increased clinician appointments with patients or involvement in medication decisions, and therefore these interventions should be investigated further. Given the limitations of existing social cognition measures, the development of valid measures is also crucial in this patient population to ensure reliable and robust future study findings. Finally, it is important to acknowledge the limitations associated with these studies and consider the impact the COVID-19 pandemic may have had on participant dropout, and their outcomes in this sub-study.

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APPENDICES

Appendix A: Literature Search Strategy

The following databases were searched:

Database Name	Results Retrieved
MEDLINE	207
Embase	919
PubMed	311
CINAHL	0
LILACS	0
Web of Science	1259
PSYCINFO (+ PsycExtra)	229
SCOPUS	0
Greylit.org	0
OpenGrey.eu	6

The search strategy was to combine searches of:

- "tranquiliser" and "sedative" and "antipsychotic" and "benzodiazepine" and "z-drug" and "barbiturate" and "tricyclic antidepressant" and "Mirtazapine" and "Trazadone" related terms. Where MeSH terms did not include specific medication names, these were listed separately.
- "social cognition" related terms
- "psychosis" and "psychiatric disorder" and "healthy volunteer". Where MeSH terms did not include specific psychiatric diagnosis, these were listed separately.

Example Search:
MEDLINE was searched using the OvidSP interface on 30/12/2019 from inception to present dates.

Step	Search Terms	Results Retrieved
1	(anti-anxiety agents or antipsychotic agents or psychotropic or antipsychotic* or Hypnotics or Sedatives or tranquil* or neuroleptic* or psychiatric medication or depot or Benzo* or benzos or benzod* or non-benzo* or z-drug* or barbiturates* or Tricyclic Anti* or Olanzapine or Ziprasidone or Zopliclone or Zopidem or Zaleplon or Allobarbital or Alphenal or Brallobarbital or Pipotiazine or Zuclopenthixol or Levomepromazine or Amisulpride or Asenapine or Valium or Pericyazine or Clobazam or Clonazepam or ketazolam or Halazepam or loprazolam or Quinalbarb* or luminal or Librax or Butobarbitone or Amylobarbitone or Adinazolam or Mirtazapine or Bretazenil or Brotizaolam or Camazepam or Cinolazepam or Clotiazepam or Cloxazolam or Deslorazepam or Etizolam or	**476066**

	Fludiazepam or Haloxazolam or Oxazolam or Nimetazepam or Nordazepam or Phenazepam or Pinazepam or Tetrazepam or Tofisopam or Quazepam or Lormetazepam or Trazadone or pregabalin).mp,ti,ab	
2	(Mental Disorders or schizophren* or psychosis or psychotic disorders or paranoi* or healthy volunteer* or healthy control* or OCD or PTSD).mp,ti,ab	**669776**
3	(Social Cogniti* or social perception or social knowledge or social competence or emotion recognition or emotion perception or affect recognition or affect perception or attribution bias or theory of mind or mentali* or mindblindness or mind-reading or social judgment or empath* or emotional intelligence or EI or facial recognition or facial affect or facial expression or face perception or FEIT or FERT or interpersonal perception or interpersonal interaction or hinting task or SCRT or MCCB or “sat-mc“ or "reading in the mind’s eye" or AIHQ or BLERT or CANTAB).mp,ab,ti.	**108068**
4	1 AND 2 AND 3	**520**
5	exp anti-anxiety agents/ or exp antipsychotic agents/	**188662**
6	(psychotropic or antipsychotic* or Hypnotic* or Sedative* or tranquil* or neuroleptic“ or "psychiatric medica”ion*" or depot or Benzo* or benzos or benzod* or non-benzo* or z-drug* or barbiturates* or Tricyclic Anti* or Olanzapine or Ziprasidone or Zopliclone or Zopidem or Zaleplon or Allobarbital or Alphenal or Brallobarbital or Pipotiazine or Zuclopenthixol or Levomepromazine or Amisulpride or Asenapine or Valium or Pericyazine or Clobazam or Clonazepam or ketazolam or Halazepam or loprazolam or Quinalbarb* or luminal or Librax or Butobarbitone or Amylobarbitone or Adinazolam or Mirtazapine or Bretazenil or Brotizaolam or Camazepam or Cinolazepam or Clotiazepam or Cloxazolam or Deslorazepam or Etizolam or Fludiazepam or Haloxazolam or Oxazolam or Nimetazepam or Nordazepam or Phenazepam or Pinazepam or Tetrazepam or (Tofisopam or Quazepam or Lormetazepam or Trazadone or pregabalin)).mp,ti,ab	
7	5 OR 6	**572574**
8	exp Mental Disorders/	**1318032**

9	(schizophren* or psychosi* or "psychotic disorder*" or paranoi* or "healthy volunteer*“"healthy control*" or OCD or PTSD).mp,ab,ti.	**499638**
10	8 OR 9	**1594954**
12	("social Cogniti*“ or "social percept*“ or "social knowledge“ or "social competence“ or "emotion recognition“ or "emotion perception“ or "affect recognition“ or "affect percept*“ or "attribution bias“ or "theory of mind" or mentali* or mindblindness or mind-reading or "social judgment" or empathy or "emotional intelligence“ or "facial recognition“ or "facial affect“ or "facial express*“ or "face perception" or FEIT or FERT or "interpersonal percept*“ or "interpersonal interaction“ or "hinting task" or SCRT or MCCB or sat-mc or "reading in the mind’s eye" or AIHQ or BLERT or CANTAB).mp,ab,ti.	**100832**
13	11 OR 12	**100832**
14	7 AND 10 AND 13	**719**
15	14 NOT 4	**214**
16	*filter inception-2019*	**207**

Example Search:
Web of Science was searched on 30/12/2019 from inception to present dates.

1	(TI=(anti-anxiety agents or antipsychotic agents or psychotropic or antipsychotic* or Hypnotics or Sedatives or tranquil* or neuroleptic* or psychiatric medication or depot or Benzo* or benzos or benzod* or non-benzo* or z-drug* or barbiturates* or Tricyclic Anti* or Olanzapine or Ziprasidone or Zopliclone or Zopidem or Zaleplon or Allobarbital or Alphenal or Brallobarbital or Pipotiazine or Zuclopenthixol or Levomepromazine or Amisulpride or Asenapine or Valium or Pericyazine or Clobazam or Clonazepam or ketazolam or Halazepam or loprazolam or Quinalbarb* or luminal or Librax or Butobarbitone or Amylobarbitone or Adinazolam or Mirtazapine or Bretazenil or Brotizaolam or Camazepam or Cinolazepam or Clotiazepam or Cloxazolam or Deslorazepam or Etizolam or Fludiazepam or Haloxazolam or Oxazolam or Nimetazepam or Nordazepam or Phenazepam or Pinazepam or Tetrazepam or Tofisopam or Quazepam or Lormetazepam or Trazadone or pregabalin)) OR AB=(anti-anxiety agents or antipsychotic agents or psychotropic or antipsychotic* or Hypnotics or Sedatives or tranquil* or neuroleptic* or psychiatric medication or depot or Benzo* or benzos or benzod* or non-benzo* or z-drug* or barbiturates* or Tricyclic Anti* or Olanzapine or Ziprasidone or Zopliclone or Zopidem or Zaleplon or Allobarbital or Alphenal or Brallobarbital or Pipotiazine or Zuclopenthixol or Levomepromazine or Amisulpride or Asenapine or Valium or Pericyazine or Clobazam or Clonazepam or ketazolam or Halazepam or loprazolam or Quinalbarb* or luminal or Librax or Butobarbitone or Amylobarbitone or Adinazolam or Mirtazapine or Bretazenil	**465,192**

	or Brotizaolam or Camazepam or Cinolazepam or Clotiazepam or Cloxazolam or Deslorazepam or Etizolam or Fludiazepam or Haloxazolam or Oxazolam or Nimetazepam or Nordazepam or Phenazepam or Pinazepam or Tetrazepam or Tofisopam or Quazepam or Lormetazepam or Trazadone or pregabalin)	
2	((TI= (Mental Disorders or schizophren* or psychosis or psychotic disorders or paranoi* or healthy volunteer* or healthy control* or bipolar or OCD or PTSD)) OR ((AB= (Mental Disorders or schizophren* or psychosis or psychotic disorders or paranoi* or healthy volunteer* or healthy control* or bipolar or OCD or PTSD))	**815,972**
4	((TI=(Social Cogniti* or social perception or social knowledge or social competence or emotion recognition or emotion perception or affect recognition or affect perception or attribution bias or theory of mind or mentali* or mindblindness or mind-reading or social judgment or empath* or emotional intelligence or EI or facial recognition or facial affect or facial expression or face perception or FEIT or FERT or interpersonal perception or interpersonal interaction or hinting task or SCRT or MCCB or sat-m“ or "reading in the mind” eye" or AIHQ or BLERT or CANTAB))) OR ((AB=(Social Cogniti* or social perception or social knowledge or social competence or emotion recognition or emotion perception or affect recognition or affect perception or attribution bias or theory of mind or mentali* or mindblindness or mind-reading or social judgment or empath* or emotional intelligence or EI or facial recognition or facial affect or facial expression or face perception or FEIT or FERT or interpersonal perception or interpersonal interaction or hinting task or SCRT or MCCB or sat-mc“ or "reading in the mind” eye" or AIHQ or BLERT or CANTAB)))	**532,873**
5	((#3) AND #2) AND #1	**1405**
6	*Filter inception-30/12/2019*	**1259**

Appendix B: Systematic Review Extraction Table

Table A1.

Systematic Review Data Extraction Table

Table 1. Data Extraction of All Studies Included in the Narrative Synthesis, with Data Quality Scores.

Author & Date.	Study Design	Sample	Medication Name/s	Dosage	Treatment Pre-Intervention	Placebo	Domain/s	Measure/s	Follow-Ups	Key Findings	Limitations	D&B Checklist Score
Benzodiazepine Studies												
Healthy Volunteers												
Blair and Curran (1999)	Double-blind, independent group design	32 healthy volunteers	Diazepam	15mg	N	Y	Emotion Processing	FERT	N/A	• Diazepam has a selective effect on the recognition of angry expressions. However, it did not affect the recognition of any of the other five expressions investigated.	• Limited sample size • Absence of a control group of psychiatric patients • No follow-up	12
Coupland et al (2003)	Randomised, counterbalanced, double-blind, placebo-controlled, within-subjects comparison	28 healthy volunteers	Diazepam	15mg	N	Y	Emotion Processing	FERT	N/A	• Diazepam produced impairments in emotional recognition accuracy. The processing of surprise and disgust were most affected.	• No follow-up • Limited sample size	18
Murphy et al (2008)	Randomised, between-group, double-blind, placebo-controlled design	24 healthy volunteers	Diazepam	5mg	N	Y	Emotion Processing	FERT	N/A	• No significant effect of Diazepam on accuracy or reaction times.	• Limited sample size • Low dosage of Diazepam	19

Pringle et al (2016)	Double-blind intervention	36 healthy volunteers	Diazepam	15mg	N	Y	Emotion Processing	FERT	6, 7 or 8 days	• Diazepam makes participants significantly slower on emotional face recognition than healthy volunteers.	• Limited sample size	19
Zangara et al (2002)	Double-blind independent group design	45 healthy volunteers	Diazepam Metropolol (selective antagonist of B1 adrenoceptors)	15mg 50mg	N	Y	Emotion Processing	FERT	N/A	• Diazepam impairs the ability to recognise angry and fearful expressions.	• No follow-up • Limited sample size	21
Nilsonne et al (2018)	Double-blind randomised controlled experiment.	Wave 1 = 37 healthy volunteers Wave 2 = 39 healthy volunteers	Oxazepam	25mg	N	Y (Vitamin D3)	Empathy	Empathy for Pain Questionnaire	N/A	• No significant effect of Oxazepam on empathy	• Demographics of patient sample limits generalisability (all-male, largely university educated)	23
Patient Studies												
Zurowska et al (2018)	Intergroup Difference Study	The sample comprised 43 patients with schizophrenia in three groups: (1) during detoxification from benzodiazepines (N = 13), (2) after detoxification (N = 15), (3) a matched control group (N = 15).	Diazepam	concentrations of BZD differed significantly between patients	N	N	Emotion Processing/Empathy	Computerised emotion recognition task/Empathy Quotient	N/A	• Patients with schizophrenia (during detox) addicted to benzodiazepines decreased ability to recognise emotions. Specifically, negative emotions (fear, sadness, and anger) compared to healthy volunteers	• Patients going through detoxification of bzds could be experiencing more severe symptoms than those addicted – may impact general emotional outcomes – no assessment of withdrawal symptoms • Small sample size • Did not control for anxiety and depression	12

Neuroimaging Studies (healthy volunteer and patient studies)												
Paulus et al (2005)	Double-blind, placebo-controlled, randomised dose-response study.	15 healthy volunteers	Lorazepam	0.25 or 1mg	N	Y	Emotion Processing	Emotional Face Assessment – ask - fMRI	N/A	• Lorazepam decreased activation in Amygdala and Insula when viewing emotional faces.	• No follow-up • Limited sample size	20
Olofsson et al (2011)	Double-blind experimental task.	45 healthy volunteers	Oxazepam	20mg	N	Y	Emotion Processing	Affective Processing – ask - EEG	1 week	• Oxazepam does not influence electrocortical indexes of emotional perception	• No patient sample • Only one medication type	14
Del-Ben et al (2012)	Randomised, balanced-order, double-blind, placebo-controlled crossover design	12 healthy volunteers	Diazepam	10mg	N	Y	Emotion Processing	FERT	N/A	• Diazepam impaired the recognition of fear in female faces • Reduced activation in right Amygdala and right OFC • Reduced activation of bilateral ACC to angry faces • Enhanced activation of posterior left Insula	• Limited sample size • Patients may be aware of treatment arm	17

Richter et al (2010)	Double-blind independent group design	6 catatonic patients with schizophrenia (recovered) 16 healthy controls (8 placebo/8 Lorazepam)	Lorazepam	A dose of lorazepam 1–2.5 mg was administrated intravenously 2–4 times (mean: 5.2mg)	N	Y (saline)	Emotion Processing	–APS - fMRI analysis	N/A	• High signal decreases in OFC and MPFC in catatonic patients during negative emotional stimulation after Lorazepam administration	• Limited sample size • Absence of a control group of psychiatric patients • fMRI measurements covered only the frontal lobe – so relationship between amygdala and MPFC regarding emotional processes remains unclear	18
Antipsychotic Studies												
Healthy Volunteers												
Lawrence et al (2002)	2 experimental test conditions (drug vs. placebo) - crossover study design - participants who took Sulpiride in week 1 testing took placebo in week 2 testing, and vice versa	14 healthy volunteers	Sulpiride	400mg	Testing commenced 100 min following tablet (drug or placebo) ingestion in order to maximise drug levels during test administration. In order to provide an adequate washout period, two test sessions were separated by a median interval of 3 weeks. In each of the two testing sessions, participants completed a test of emotion recognition from the face and a control task of unfamiliar face matching (the Benton task).	Y (lactose)	Emotion Processing	FERT	baseline, ~3weeks	• Following Sulpride use, recognition of anger facial expression at follow-up was impaired compared to baseline, other emotions intact	• Limited sample size • Short follow-up time	13

Rock et al (2016)	Between-subject, randomised, double-blind, placebo-controlled design	40 healthy volunteers	Quetiapine	150mg	27 received Quetiapine for 7 days - dropout to n=20 for Emotion Processing task	Y	Emotion Processing	FERT	baseline, one week	• No effect of Quetiapine on emotion processing ability in healthy participants at one week, compared to baseline	• No compliance measure • Healthy volunteers only • One-week duration only • Modest sample size • Dropout in Quetiapine arm (reduction of power) • Authors consultants for pharmaceutical company	22
Patient Vs. Healthy Volunteers												
longitudinal studies												
Behere et al (2009)	Short-term treatment follow-up	55 antipsychotic-naïve patients with schizophrenia 30 healthy volunteers	Risperidone	4mg/daily	25 drug-naïve schizophrenia (DSM-IV) patients	N	Emotion Processing	TRENDS	Not specified (short-term)	• Patients with schizophrenia showed impairments in emotion processing at baseline compared to healthy volunteers • Risperidone use in patients with schizophrenia resulted in improvements in patient scores on the emotion processing task, when comparing	• Non-specified follow-up dura–ion - may be practice effects • Only one antipsychotic type • non-randomised design	16

										their scores at baseline and follow-up		
Gaebel et al (1992)	Experimental task	23 patients with schizophrenia 21 MDD 15 healthy volunteers	13 Perazine 10 Haloperidol (patients with schizophrenia only)	The mean daily/cumulative dosages were 376/10160mg CPZE and 445/16400 mg CPZE respectively.	11/23 patients with schizophrenia weredrug-naïve, remaining 12 were drug-free	N	Emotion Processing	FERT	baseline and 4 weeks	• Patients with schizophrenia showed impairments in emotion processing at baseline compared to healthy volunteers • Both patients with schizophrenia and healthy volunteer groups improved at follow-up, larger improvements in patients with schizophrenia group	• Practice effects due to short follow-up time • Mixture of drug-naïve and drug-free patients	18

Olivier et al, (2015)	Case-control design over 12 months.	92 FEP patients 100 healthy volunteers	Flupenthixol Decanoate (LAI)	10mg	< 4 weeks of treatment (not a statistically significant difference at baseline, but difference is present)	N	Emotional Intelligence	MCCB	6-month, 12 months	• FEP performed significantly worse at baseline in all cognitive domains bar social cognition compared to healthy volunteers • FEP significantly improved in all MCCB domains (including social cognition) between baseline and 6 months. • No further improvements were seen in social cognition at 12 months in the FEP group, suggesting stability of emotional intelligence over time.	• Additional oral Flupenthixol was prescribed at the discretion of the investigator. • Not all patients were tested in their first language • Patients were not necessarily antipsychotic naïve • One antipsychotic type • FEP only	16
Zhou et al (2017)	12-week treatment study	56 schizophrenia inpatients 28 healthy volunteers	haloperidol (n=12), fluphenazine (n=8), chlorpromazine (n=6), or trifluoperazine (n=2). Risperidone (n=28)	The mean chlorpromazine-equivalent dose was 502.0±198.3 mg/d. The mean (±standard deviation) dose of risperidone was 4±1.5 mg/d.	In the risperidone treatment group, 19 patients were drug-naïve and 9 were drug-free (5 for at least 6 months and 4 for at least 1 month). In the typical antipsychotic treatment group, 17 patients were drug-naive and 11 were drug-free (8 for at least 6 months and 5 for at least 1 month).	N	Emotion Processing	FEDT	baseline, 4 weeks, 12 weeks	• Patients with schizophrenia showed impairments in emotion processing at baseline compared to healthy volunteers • Risperidone improved social cognition in patients with schizophrenia	• Mixture of drug-naïve and drug-free patients	18

										after 12 weeks compared to baseline, but not at 4 weeks.		
Lewis et al (1995)	Experimental task	18 psychosis patients 10 healthy volunteers	Haloperidol	5-20mg	Drug-free at baseline (for an unspecified time period)	N	Emotion Processing	FERT	baseline and 2 weeks	• Patients with schizophrenia showed impairments at emotion processing at baseline compared to healthy volunteers • Haloperidol had no effect on patient performance at follow-up compared to baseline scores	• Small sample size • Short follow-up time period - practice effects • Did not subtype psychotic patients • Patients were not antipsychotic naïve	16
Wölwer et al (1996)	Experimental task	32 acute schizophrenia inpatients (S/a) 36 remitted schizophrenic patients (S/r) 21 healthy volunteers	Perazine Haloperidol Chlorpromazine Clozapine **S/r and S/a only**	The S/a were orally treated with either perazine (n = 20) or haloperidol (n = 12). The average daily dosage in chlorpromazine equivalents (CPZE) in the T0-T1 interval did not differ significantly (perazine: 436 + 217 mg CPZE; haloperidol: 531 +	Among S/r 10 patients were treated with clozapine (mean daily dosage = 426 -+ 144 mg CPZE), 21 received typical neuroleptic drugs either orally or as depot (mean daily dosage = 477 + 430 mg CPZE) and 5 patients were drug-free in the T0"-T1" interval. Five S/a, but none of the S/r, received anticholinergic medication.	N	Emotion Processing	FERT	baseline and 4 weeks	• Acute and remitted schizophrenic patients demonstrated a stable deficit in emotion recognition compared to healthy volunteers. • Antipsychotic medication had no effect on	• Non-randomised design • Short follow-up - practice effects • Patients were not antipsychotic naïve	15

				313 mg CPZE). Among S/r 10 patients were treated with clozapine (mean daily dosage = 426 -+ 144 mg CPZE), 21 received typical neuroleptic drugs either orally or as depot (mean daily dosage = 477 + 430 mg CPZE)						patient performance at follow-up compared to baseline scores.		
Herbener et al (2005)	Short-term follow-up study	13 patients with schizophrenia 13 healthy volunteers	Risperidone Ziprasidone Aripiprazole Haloperidol	mean dose R= 3.38mg Z= 140mg A= 30mg H= 4.5mg	< 4 weeks prior antipsychotic treatment in lifetime	N	Emotion Processing	CNB	baseline, average 31.3 days later (where clinically stable)	• Patients with schizophrenia showed impairments at emotion processing at baseline compared to healthy volunteers • Antipsychotic medication had no effect on patient performance at follow-up compared to baseline scores	• Limited sample size • non-randomised design • Short –follow-up time - practice effects	11

Daros et al (2014)	Blocked experimental task	54 Healthy volunteers 29 Patients with schizophrenia 28 Patients with Bipolar Disorder	**Schizophrenia** Risperidone (79.2%) Aripiprazole (12.5%) Haloperidol (8.3%) Ziprasidone (4.2%). **Bipolar Disorder** Risperidone (86.7%) Olanzapine (6.7%)	Drugs in chlorpromazine equivalents was 326.9 mg (SD = 218.9; range: 34.4−907.8 mg) for SCZ patients and 154.4 mg (SD = 125.7; range: 34.4−524.6 mg) for BP patients.	FEP patients. At study entry, some patients with SCZ and BP had previously been exposed to atypical antipsychotics (45.0%), antidepressants (30.0%), typical antipsychotics (15.0%), mood stabilizers/anticonvulsants (12.5%), and stimulants (12.5%), typically for brief periods of time in the months preceding their participation. No patient had taken a dose of any of these medications within three days of assessments, with the exception of BP (6.3%) and SCZ (12.5%) patients who were on maintenance antidepressant treatment started prior to study entry. Up to four weeks of prior cumulative lifetime antipsychotic treatment was allowed.	Y	Emotion Processing	CNB	baseline and an average of 6.8 weeks	• Patients with schizophrenia showed impairments on emotion processing at baseline compared to healthy volunteers • Compared with healthy volunteers, patients with schizophrenia were worse at recognising mildly and moderately sad expressions at follow-up. • At follow-up, patients with schizophrenia and bipolar disorder did not significantly differ from each other on any emotion category.	• Non-randomised design • Authors consult for pharmaceutical company	12
cross-sectional studies												

Kucharska-Pietura et al (2012)	Naturalistic treatment conditions	100 patients with schizophrenia 50 healthy volunteers	Typical Atypical	Not stated	Twenty-eight (13 males) were treated with FGAs (perphenazine, n=14; haloperidol, n=14) and 56 (31 males) were treated with SGAs (olanzapine, n=28; clozapine, n=28). All patients were clinically stable after 3–4 weeks of antipsychotic treatment.	N	Emotion Processing Theory of Mind ' Empathy	FERT 'Reading in the Mind's Eye' test Balanced Emotional Empathy Scale	N/A - cross-sectional	• Patients with schizophrenia showed impairments at emotion processing at baseline compared to healthy volunteers • Antipsychotic medication had no effect on patient performance compared to healthy volunteers	• Non-randomised design • No follow-up evaluation • Antipsychotic medication not specified	15
Patient Only Studies												
longitudinal studies												
Kee et al (1998)	Baseline phase, brief placebo washout, and two double-blind phases 8 weeks double blind	18 Patients with schizophrenia	Haloperidol Risperidone	15mg 6mg	During baseline, patients received 15-30 mg/day of haloperidol for 3 weeks. This phase was followed by a period of 3-7 days of placebo wash-out. Upon entering the subsequent double-blind phases, patients first were randomly assigned to receive either 6 mg/day of risperidone or 15 mg/day of haloperidol for 4 weeks (fixed- dose phase). In the second double-blind phase, which also lasted for 4 weeks, medication doses from the previous phase could be changed according to symptom and	N	Emotion Processing	FEIT	baseline and 8 weeks	• Risperidone improved the ability to perceive emotions compared to Haloperidol at follow-up compared to baseline	• Small sample size • Short follow-up time period - practice effects • Patients were not antipsychotic naïve	19

					side-effect considerations (flexible-dose phase).							
Harvey et al (2006)	8 week, multicentre, double-blind, parallel-designed, randomised, flexible-dose study	166 patients with schizophrenia	Risperidone Quetiapine	2-8mg/daily 200-800mg/daily	Sleep medication and benzodiazepines were allowed as needed but were not allowed within 24 hours of clinical or neuropsychological assessments. Participants were taking antipsychotic medication at the start of the study and there was no titration period.	N	Emotion Processing	CNB	baseline, 8 weeks	• No significant differences associated with antipsychotic treatment at follow-up compared to baseline	• Supported by pharma company • Patients were not antipsychotic naïve • Short follow-up time period - practice effects • High drop-out at follow-up (%) – low generalisability	18
Mizrahi et al (2007)	Cross sectional study and a longitudinal study	17 FEP patients	Clozapine Risperidone Olanzapine Loxapine	Clozapine=300 (n=1) and 225mg (n=1) Risperidone= 4mg (n=4), 3mg (n=1), 3.5mg (n=1), or 1mg (n=1). Olanzapine= 10mg (n=4), 20mg (n=1), 15mg (n=1), or 2.5mg (n=1). Loxapine= 35mg (n=1)	Most subjects were started on atypical antipsychotic medications, except for two patients who were restarted on their previous clozapine dose (300 and 225 mg). The rest were started on risperidone 4 mg (n=4), 3 mg (n=1), 3.5 mg (n=1), 1 mg (n=1) or olanzapine 10 mg (n=4), 20 mg (n=1), 15 mg (n=1), 2.5 mg (n=1), and one patient was restarted on her previous 35 mg of loxapine.	N	ToM	Hinting–Task	baseline - 6 weeks (measured every 2 weeks)	• Greatest improvement in ToM occurred during first 2 weeks of antipsychotic treatment, compared to baseline	• FEP patients only • Mixture of antipsychotic-naïve and drug-free patients • non-randomised design • Short follow-up time period - practice effects	18

Sergi et al (2007)	8, week double blind, randomised study	73 outpatients with schizophrenia-spectrum disorder	Risperidone Olanzapine Haloperidol	4mg 15mg 8mg	Patients were initially enrolled and tested at baseline on their pre-study medication; there was no medication washout period.	N	Emotion Processing/Social Perception	Half-profile of non-verbal sensitivity/IPT-15	baseline, 8 weeks	• No significant changes in social cognition associated with treatment over an 8-week study period.	•Pharmaceutical funding-medications for the study were provided by pharmaceutical companies • Modest group size and two random assignment paths - limited statistical power • Short follow-up time period - practice effects • Patients were not antipsychotic-naïve (no washout period)	21
Mizrahi et al (2008)	Cross sectional study and a longitudinal study	17 FEP patients	Typical Atypical	Not stated	The study was a cohort of consecutively admitted antipsychotic-free patients to the inpatient and outpatient Schizophrenia program who were willing to start antipsychotic medication. Patients had previously untreated psychosis and were antipsychotic-naïve at the beginning of the study, or had started or changed medication to improve symptoms in the previous 48 h.	N	Attribution Style	IPSAQ	baseline, 6 weeks	• Attributional style scores did not change during 6 weeks of antipsychotic treatment	• Small longitudinal cohort – may not have sufficient power • Short follow-up time period - practice effects • FEP patients only • Antipsychotic medication not specified	11
Fakra et al (2009)	Controlled, open, randomised, and prospective design.	25 patients with schizophrenia	Haloperidol Risperidone	Not stated	Followed a wash-out period of at least 1 week for prior antipsychotic treatment. Random assignment to Haloperidol or Risperidone treatment groups. Use of other antipsychotics or long-life benzodiazepines was prohibited.	N	Emotion Processing	FEDT	baseline, 2 weeks, 4 weeks	• Greater beneficial effect of Risperidone than Haloperidol in schizophrenic patients' ability to discriminate facial emotions at follow-up compared to baseline	• Small sample size • Patients were not antipsychotic-naïve • Short follow-up time period - practice effects	17

					Benzodiazepines were not administered for a minimum of eight hours before emotional testing.							
Penn et al (2009)	Random assignment to double-blind intervention	873 patients with schizophrenia	Olanzapine Quetiapine Fumarate Risperidone Ziprasidone Perphenazine	(Zyprexa, Eli Lilly) (7.5 mg), (Seroquel, AstraZeneca) (200 mg) (Risperdal, Janssen Pharmaceuticals) (1.5 mg) (Trilafon, Schering-Plough) (8 mg) (Geodon, Pfizer) (40 mg)	Overlap in the administration of the antipsychotic agents that patients received before study entry was permitted for the first four weeks after randomization to allow a gradual transition to study medication. Concomitant medications were permitted throughout the trial, except for additional antipsychotic agents.	N	Emotion Processing	FEDT	baseline and 2 months	• Patients in all treatment groups (with the exception of Ziprasidone) showed small, non-significant improvements in emotion perception from baseline to two months	• Authors consult for pharma companies • Medications provided by pharma companies • Patients were not antipsychotic-naïve (medication was gradually titrated over 4 weeks following randomisation)	22
Roberts et al (2010)	Randomised, double-blind clinical trial.	223 Schizophrenia-spectrum patients	Olanzapine Quetiapine	olanzapine mean dose = 15.6mg quetiapine mean dose = 455.8mg *Chlorpromazine equivalents* of these doses are 312 mg/day and 607.7 mg/day, respectively.	Participants entered a 2-week titration period during which they were switched from their current medication to Olanzapine or Quetiapine.	N	Social Perception	SCRT	baseline and 6 months	• Olanzapine and Quetiapine significantly improve ¾formance on 3/4 social cue recognition tasks at follow-up compared to baseline	• Patients were not antipsychotic-naïve (medication was titrated over 2 weeks following randomisation) • Pharmaceutical funding	20
Maat et al (2013)	8 weeks, randomised, multicentre, open-label study	48 patients with schizophrenia	Aripiprazole Risperidone	maximum 30mg maximum 6mg	Overlap in the administration of the antipsychotic agents that patients received before study entry was permitted for the first 2 weeks after randomisation to allow for gradual transition. Concomitant medication other than antipsychotics was permitted throughout the trial; the dosage was restricted to a maximum	N	Emotion Processing	FERT	baseline, 8 weeks	• No significant effect of medication-group on endpoint performance on social cognition at follow-up compared to baseline	• High drop-out rate (few follow-ups) • Short follow-up time period - practice effects • Funded by pharma company • Patients were not antipsychotic-naïve	17

					of 30mg diazepam or equivalent, 120mg propranolol, and 12mg biperiden or equivalent.							
Shi et al (2016)	Single-arm, open-label study	95 patients with schizophrenia	Paliperidone	3-12mg/daily	Single antipsychotic usage for at least 4 weeks before study.	N	Emotional Intelligence	MCCB	baseline, 6 months	• Treatment associated with improvements in 5/6 cognitive domains, but not social cognition	• Funding from pharma company • Open-label, single-arm design (efficacy bias)	19
Koshikawa et al (2016)	6-month pilot, open-label, randomised controlled study	21 Schizophrenia-spectrum patients	Paliperidone Palmitate Risperidone (LAI)	PP- doses of the drug were adjusted according to clinical status, upper limit of 50 mg /2 weekly. R(LAI)-The dose was determined depending on patient's clinical status, with an upper limit of 150mg/monthly	Inclusion: Having received risperidone long-acting injection for 2 months or longer. Exclusion: Current treatment with oral risperidone or oral palmitate risperidone. Current treatment with multiple oral antipsychotics.	N	Emotion Processing	SECT	baseline, 6 months	• No significant differences between the two groups in terms of the SECT accuracy at follow-up	• Small sample size • Patients were not antipsychotic-naïve (excluded if they were not currently being treated with antipsychotic medication)	21
Gultekin et al (2017)	Longitudinal naturalistic study	19 Schizophrenia-spectrum patients	Clozapine Risperidone	CPZE equivalent = 600mg/day CPZE equivalent = 800mg/day	being under current antipsychotic treatment included in inclusion criteria	N	Emotion Processing	FERT	baseline, 16-20 weeks	• Ability to recognise disgust faces poorer by a significant amount in the Risperidone group compared to the Clozapine group at baseline and significantly poorer after treatment with Risperidone then with Clozapine at follow-up. • Mean	• Small sample size • Patients were not antipsychotic-naïve	16

										responses to facial emotions significantly shorter after Clozapine and Risperidone than at baseline		
cross-sectional studies												
Savina et al (2007)	Experimental task Naturalistic design	84 schizophrenia-spectrum patients 24 healthy volunteers	clozapine (n= 18) olanzapine (n= 20) risperidone (n= 23) perphenazine (n= 2) fluphenazine (n= 8) flupentixol (n= 6) zuclopenthixol (n= 4) stelazine (n= 1) haloperidol (n= 2)	Not stated	received clozapine (n= 18), olanzapine (n= 20), risperidone (n= 23) or typicals (n= 23), including perphenazine (n= 2), fluphenazine (n= 8), flupentixol (n= 6), zuclopenthixol (n= 4), stelazine (n= 1) and haloperidol (n= 2), for at least 4 months. Most were also receiving mood stabilizers or other medications, but these were not systematically recorded. However, treating physicians were asked not to refer patients who received anticholinergic medication.	N	ToM	First-order Belief Task	N/A - cross-sectional	• Olanzapine and Clozapine groups performed similar to healthy volunteers on ToM task. • Risperidone and typical antipsychotic groups performed worse on ToM task (compared to healthy volunteers)	• Non-randomised design • No follow-up evaluation • Patients were not antipsychotic-naïve	13
Kucharska-Pietura et al (2012)	Naturalistic, pragmatic sample	84 Schizophrenia-spectrum patients	FGAs and SGAs	Not stated	39 patients were treated using conventional antipsychotic drugs (perphenazine, perazine, fluphenazine, haloperidol) and 61 were treated with atypical antipsychotic drugs (olanzapine, risperidone, amisulpride, clozapine and quetiapine).	N	Emotion Processing	FERT	N/A - cross-sectional	• No significant differences in performance between typical and atypical treatment groups.	• Non-randomised • No follow-up evaluation	15

					All patients were clinically stable after 4 weeks of antipsychotic use							
Labuschagne et al (2013)	Experimental task	113 Early HD patients	Neuroleptics Not specified	Not stated	Of those taking neuroleptics (n1⁄429) almost all of the patients were on atypical neuroleptics except for one patient; the most common neuroleptic taken was olanzapine (14 patients). The neuroleptic daily dose range (expressed as the equivalent dose of chlorpromazine) was 50–800 mg. These patients may have been taking additional medications such as SSRI's that were not fully listed. adjusted for stage of disease	N	Emotion Processing	FERT	N/A	• In early HD neuroleptic use was associated with worse facial emotion recognition compared to those not using neuroleptics	• Emotion recognition deficits in HD may be due to facial perception impairments • Time constraints in testing – presenting only 10 stimuli per emotion • Single channel of emotion processing – faces only	13
Neuroimaging Studies (healthy volunteer and patient studies)												
Sumiyoshi et al (2009)	Longitudinal treatment design	20 outpatients with schizophrenia	Perospirone	Dose adjusted to optimise improvement in symptoms. Subjects who had already been treated with antipsychotic drugs, had medication switched stepwise to Perospirone monotherapy during the initial 6 weeks.	7/20 drug-free, 13/20 on antipsychotic medication	N	Social Perception	Script Tasks	baseline, 6 months	• Perospirone was associated with an increase in P300 ERP in the left PFC. • Performance on script tasks (social cognitive task) was improved during treatment, positively correlated with P300 changes.	• Subjects heterogeneous in terms of premedication • Small sample size due to large drop-out rate • Funding from pharmaceutical company	15

Takahashi et al (2005)	Single-blind, randomised, placebo-controlled design study.	13 healthy volunteers	Sultopride Fluoxetine (antidepressant)	25mg 50mg	N	Y (lactose)	Emotion Processing	Affective Processing Task - fMRI	Not specified 3 sessions	• After antipsychotic administration healthy volunteers showed decreased BOLD responses in limbic areas when viewing emotional stimuli	• Pharmacological actions may be on vascular and respiratory systems which in turn effect BOLD • Only healthy volunteers used • Pharmacological changes did not represent the minimal behavioural changes	14
Franken et al (2008)	Randomised, double-blind, placebo-controlled crossover design.	32 healthy volunteers	Bromocriptine (Beta-Blocker) Haloperidol	2.5mg 2mg	All subjects received a single oral dose of placebo (lactose), bromocriptine (2.5 mg), and haloperidol (2 mg) in a counterbalanced order. The medication was provided by the pharmacy of the Erasmus Medical Centre in indistinguishable capsules.	Y (lactose)	Emotion Processing	Affective Processing Task - EEG	weekly (for each condition - 3 weeks total)	• Low dose haloperidol and bromocriptine did not change ERPs towards affective stimuli.	• Substantial dropout in Bromocriptine group – lower generalisability • Low doses–of medication - due to unwanted side effects • Some participants received Domperidone to treat nausea	21

Abbreviations: SMI (serious mental illness), FERT (facial emotion recognition task), fMRI (functional Magnetic Resonance Imaging), EEG (Electroencephalography), IAPS (International Affective Picture System), MPFC (Medial Pre-Frontal Cortex), OFC (Orbitofrontal Cortex), ACC (Anterior Cingulate Cortex), FEIT (facial emotion identification test), CNB (computerised neurocognitive battery), ToM (theory of mind), IPSAQ (internal, personal, and situational attributions questionnaire), FEDT (facial emotional discrimination task), SCRT (social cue recognition test), FGA (first-generation antipsychotic), SGA (second-generation antipsychotic), MCCB (Matrics Consensus Cognitive Battery), SECT (social emotional cognition task), LAI (long-acting injection), CPZE (chlorpromazine equivalent), ERP (event-related potential), TRENDS (tool for recognition of emotions in neuropsychiatric disorders), DSM-IV (diagnostic statistical manual 4th edition), BOLD (blood-oxygen level dependent), D&B (Downs and Black Checklist

Appendix C: Cognition in Healthy Volunteers Study – Recruitment Materials

Consent Form:

Cognition in Human Volunteers – Consent Form
CONSENT FORM FOR ADULT PARTICIPANTS IN RESEARCH STUDIES

Please complete this form after you have read the Information Sheet and/or listened to an explanation about the research.

Title of Study: COGNITION IN HEALTHY HUMAN VOLUNTEERS
Department: DEPARTMENT OF PSYCHIATRY
Name and Contact Details of the Research Supervisor: Dr Joanna Moncrieff j.moncrieff@ucl.ac.uk
Name and Contact Details of the Principal Researcher: ZOE HAIME z.haime@ucl.ac.uk
Name and Contact Details of the UCL Data Protection Officer: data-protection@ucl.ac.uk
This study has been approved by the UCL Research Ethics Committee: Project ID number: _____

Thank you for considering taking part in this research. The person organising the research must explain the project to you before you agree to take part. If you have any questions arising from the Information Sheet or explanation already given to you, please ask the researcher before you decide whether to join in. You will be given a copy of this Consent Form to keep and refer to at any time.

I confirm that I understand that by initialling each box below I am consenting to this element of the study. I understand that it will be assumed that unticked/initialled boxes means that I DO NOT consent to that part of the study. I understand that by not giving consent for any one element that I may be deemed ineligible for the study. Optional statements are marked with an asterisks (*).

		initials
1.	I confirm that I have read and understood the Information Sheet for the above study. I have had an opportunity to consider the information and what will be expected of me. I have also had the opportunity to ask questions which have been answered to my satisfaction and would like to take part in this individual interview.	
2.	I understand that if I withdraw from the study my data will be kept unless I request otherwise.	
3.	I consent to participate in the study. I understand that my personal information regarding demographic data and performance on cognitive tasks will be used for the purposes explained to me. I understand that according to data protection legislation, 'public task' will be the lawful basis for processing.	
4.	**Use of the information for this project only** I understand that all personal information will remain confidential and that all efforts will be made to ensure I cannot be identified I understand that my data gathered in this study will be stored anonymously and securely. It will not be possible to identify me in any publications.	
5.	I understand that my information may be subject to review by responsible individuals from the University College London (UCL) for monitoring and audit purposes.	
6.	I understand that my participation is voluntary and that I am free to withdraw at any time without giving a reason, without the care I receive or my legal rights being affected. I understand that if I decide to withdraw, any personal data I have provided up to that point will be deleted unless I agree otherwise.	
7.	I understand the potential risks of participating and the support that will be available to me should I become distressed during the course of the research.	
8.	I understand the direct/indirect benefits of participating.	
9.	I understand that the data will not be made available to any commercial organisations but is solely the responsibility of the researcher(s) undertaking this study.	
10.	I understand that I will be compensated for the portion of time spent in the study.	
11.	*I agree that my anonymised research data may be used by others for future research. [No one will be able to identify you when this data is shared.]	
12.	I understand that the information I have submitted will be published as a report and I wish to receive a copy of it. Yes/No	

12.	I understand that the information I have submitted will be published as a report and I wish to receive a copy of it. Yes/No	
13.	I hereby confirm that I understand the inclusion criteria as detailed in the Information Sheet and explained to me by the researcher.	
14.	I hereby confirm that I understand the exclusion criteria as detailed in the Information Sheet and explained to me by the researcher; and I do not fall under the exclusion criteria.	
15.	I have informed the researcher of any other research in which I am currently involved or have been involved in during the past 12 months.	
16.	I am aware of who I should contact if I wish to lodge a complaint.	
17.	I voluntarily agree to take part in this study.	
18.	I understand that the data I provide will be archived at University College London. I understand that other authenticated researchers will have access to my anonymised data	

If you would like your contact details to be retained so that you can be contacted in the future by UCL researchers who would like to invite you to participate in follow up studies to this project, or in future studies of a similar nature, please tick the appropriate box below:

	Yes, I would be happy to be contacted in this way Phone: Email:	
	No, I would not like to be contacted	

If you would like to be contacted about the results of this study once it has been completed then please provide your details:

	Yes, I would be happy to be contacted in this way Address: Email:	
	No, I would not like to be contacted	

_____	_____	_____
Name of participant	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Recruitment Poster:

RESEARCH PARTICIPANTS NEEDED.
for study on human cognition.

- for adults 18+
- fluent in English language
- with no personal history, and no family history of a psychiatric condition
- no current use of a psychotropic medication (antipsychotic/antidepressant/anxiolytic/ mood stabilizer)
- with no history of a neurological disorder

The study will take 45-60 minutes and will involve:
Questions about your background and medical history.
Cognitive tasks (attention, memory, social perception, etc)
Self-complete questionnaires

We will reimburse you for your time.

Please Contact Zoë Haime:
Email: z.haime@ucl.ac.uk
Text: [redacted]

UCL

Cognition in Human Volunteers V1 07.01.2019

Screening Form:

Participant ID	

Cognition in Human Volunteers

Inclusion Criteria

Participant is aged 18 years or older.	
Participant has no current psychiatric diagnosis and does not have a history of psychiatric diagnosis.	
Participant has no family history of psychiatric diagnosis.	

Exclusion Criteria

Participant is not fluent in English Language	
Participant has a disability that prevents them from completing the measures included in the study (e.g. visual impairment)	
Participant is currently taking psychiatric medication (including anxiolytics, antipsychotics, antidepressants or mood stabilisers)	
Participant has had a diagnosis of a neurological disorder or has suffered any kind of head injury or systemic disease that might affect the central nervous system	

Information Sheet:

Cognition in Human Volunteers

Participant Information Sheet for Adult Participants

UCL Research Ethics Committee Approval ID Number: _____

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET

Title of Study: Cognition in Human Volunteers
Department: Department of Psychiatry
Name and Contact Details of the Principal Researcher: Zoe Haime (z.haime@ucl.ac.uk)
Name and Contact Details of the Research Supervisor: Dr Joanna Moncrieff (j.moncrieff@ucl.ac.uk)

1. Invitation to this study

You are being invited to take part in a research project looking at cognition in healthy human volunteers. Before you decide to take part it is important for you to understand why the research is being done and what participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part. Thank you for reading this.

2. What is the project's purpose?

The purpose of this project is to collect data on neurocognitive and social cognitive measures in healthy human volunteers. This is to compare with data from part of a larger study looking at the same measures in individuals with non-affective psychoses. We are interested in differences in abilities in these measures between healthy individuals and those suffering from schizophrenia spectrum diagnoses.

3. Why have I been chosen?

We have approached you about the study because we believe you fit the below criteria and are therefore eligible to be a participant in this study, we aim to recruit 74 participants altogether with 37 healthy participants and 37 patients.

Inclusion Criteria

- Participant is aged 18 years or older
- Participant has no current and does not have a history of psychiatric diagnosis
- Participant has no family history of psychiatric diagnosis

Exclusion Criteria

- Participant is not fluent in English Language
- Participant has a disability that prevents them from completing the measures included in the study (e.g. visual impairment)
- Participant is currently taking psychiatric medication (including anxiolytics, antipsychotics, antidepressants, or mood stabilisers)
- Participant has had a diagnosis of a neurological disorder or has suffered any kind of head injury or systemic disease that might affect the central nervous system

4. **Do I have to take part?**

   It is up to you to decide whether to take part in this study. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. You can withdraw at any time without giving a reason and without it affecting you in any way. If you decide to withdraw you will be asked what you wish to happen to the data you have provided up that point, data can be withdrawn up until the point of analysis.

5. **What will happen to me if I take part?**

   Participants will be required to attend one session which will last between 45 and 60 minutes. You will be given £10 for this session for travel expenses and your time.

   During this session, you will be required to answer questions regarding some background information about you, and complete some cognitive tasks looking at neuropsychological and social cognitive measures.

6. **What are the possible disadvantages and risks of taking part?**

   We do not expect there to be any risks or disadvantages to taking part in this research. If there are any unexpected discomforts, disadvantages or risks to the participant the researcher will act to help in any way possible.

7. **What are the possible benefits of taking part?**

   Participants will receive £10 reimbursement for their involvement in the study.
   It is also hoped that this research will assist in improving our understanding of cognitive issues in non-affective psychosis patients compared to healthy individuals, and that this will lead to further research in the potential treatment of cognitive deficits in mental health disorders.

8. **What if something goes wrong?**

   If you wish to raise a complaint about this research study please contact the researcher Zoe Haime (z.haime@ucl.ac.uk). If you feel your complaint has not been handled satisfactorily or you would like to take your complaint to a person not directly involved in the study please contact the Chair of the UCL Research Ethics Committee – ethics@ucl.ac.uk

9. **Will my taking part in this project be kept confidential?**

   All the information that we collect about you during the research will be kept strictly confidential. You will not be able to be identified in any ensuing reports or publications.

10. **Limits to confidentiality**

    Please note that confidentiality will be maintained as far as it is possible, unless during our conversation I hear anything which makes me believe there is a serious risk of harm to yourself or someone else. You will be informed if confidentiality needs to be broken due to a risk of harm to yourself.

11. What will happen to the results of the research project?

At the end of data collection, we aim to publish the results in a scientific journal, you will be sent a copy of the published results if you consent to receive them. All published data will be reported anonymously so you will not be able to be identified.
Data collected during this study may be used for additional subsequent research if you consent to this.

12. Data Protection Privacy Notice

Notice:
The data controller for this project will be University College London (UCL). The UCL Data Protection Office provides oversight of UCL activities involving the processing of personal data, and can be contacted at data-protection@ucl.ac.uk. UCL's Data Protection Officer can also be contacted at data-protection@ucl.ac.uk.

Your personal data will be processed for the purposes outlined in this notice.

The legal basis that would be used to process your personal data will be performance of a task in the public interest.

The legal basis used to process special category personal data will be for scientific and historical research or statistical purposes.

Your personal data will be processed so long as it is required for the research project. If we can anonymise or pseudonymise the personal data you provide we will undertake this, and will endeavour to minimise the processing of personal data wherever possible.

If you are concerned about how your personal data is being processed, please contact UCL in the first instance at data-protection@ucl.ac.uk. If you remain unsatisfied, you may wish to contact the Information Commissioner's Office (ICO). Contact details, and details of data subject rights, are available on the ICO website at: https://ico.org.uk/for-organisations/data-protection-reform/overview-of-the-gdpr/individuals-rights/

13. Who is organising and funding the research?

University College London (UCL) will be the study sponsor.

16. Contact for further information

Please contact researcher Zoë Haime with any questions or information requests:

Email: z.haime@ucl.ac.uk
Phone/Text: [redacted]

You will be given a copy of this information sheet and a signed consent form to keep.

Thank you for reading this information sheet and for considering taking part in this research study.

Appendix D: Evidence for Multiple Imputation of Dataset

Missing vs. Non-Missing Data Analysis.

Significant differences between missing and non-missing group data were measured at each time point using T-tests or chi-squares on the following baseline variables: gender, age, ethnicity, education level, Digit Span, AP dose (Log), AP duration (Log), PANSS Total, and SFS. These analyses provide evidence as to the plausibility of the MAR assumption. Where those with and without missing data differ on more than one observed variable, then it is plausible that they may also differ on unobserved variables. Note that a lack of significant univariate associations does not provide proof that the data are MCAR or MAR but can justify the MI approach when considered alongside Littles Test of MCAR.

Participants with missing data at baseline were more likely to have a lower SFS score, and higher doses of antipsychotics at baseline (Table 1). At 12-month participants who had missing data were more likely to have higher symptom scores at baseline and be male (Table 2). At 24-month participants who had missing data were more likely to have lower symptom scores at baseline and be of a Non-White ethnicity (Table 3).

Table A2.
Baseline variables showing a significant difference between baseline missing vs. non-missing value groups.

	Missing N=14 Mean	**Non-Missing N=59 Mean**	**p value**
AP dose (Log)	2.82	2.62	.014
SFS	104.38	110.12	.033

Table A3.
Baseline variables showing a significant difference between 12-month missing vs. non-missing value groups.

	Missing N=15 Mean	**Non-Missing N=31 Mean**	**p value**
PANSS Total	49.20	43.19	.027
	% (male) missing	**% (male) non-missing**	**X^2**
Gender	66.7	74.2	.044

Table A4.
Baseline variables showing a significant difference between 24-month missing vs. non-missing value groups.

	Missing N=20 Mean	**Non-Missing N=22 Mean**	**p value**
PANSS Total	41.9	54.18	.011
	% (white) missing	**% (white) non-missing**	**X^2**
Ethnicity	40.0	90.9	<.001

Complete Case Analysis

Linear Regression

Complete case analysis was conducted on baseline data, participant data was removed using listwise deletion for any participant with a missing data value at baseline, there were n= 59 remaining participants. Linear regression analysis was repeated between social cognition domains and potential predictor variables, as in the MI analysis (Table 4). PANSS General was no longer a significant predictor of AIHQ Blame. In the BLERT, AP dose was no longer a significant predictor, and PANSS General became a significant predictor. In the SAT-MC, Education level and AP duration were no longer significant predictors. Multiple analysis was completed for the SAT-MC only (Table 5), as this was the only social cognition domain that had a remaining antipsychotic usage variable predictor, alongside other predictors. Results from this replicated the MI analysis, showing only age remained a significant predictor of social perception.

Table A5.
Linear regressions between social cognition domains and potential predictor variables at baseline, after listwise deletion.

Variables	AIHQ Blame		AIHQ Aggression		AIHQ Hostility		BLERT		Hinting Task		SAT-MC		EQ-CEF		EQ-SSF		TEIQue	
	Beta	p value	Beta	p value	Beta	p value	Beta	p value	Beta	p value	Beta	p value	Beta	p value	Beta	p value	Beta	p value
Gender	-.114	.712	.141	.446	.133	.654	1.58	.212	.519	.596	-1.22	.386	2.58	.135	.643	.570	.113	.680
Ethnicity	-.413	.134	.185	.267	-.149	.578	1.65	.146	.167	.850	2.45	.050	.024	.988	1.13	. 264	.122	.620
Age	.011	.340	-.001	.831	.021	.050	-.132	.004	-.011	.762	-.228	<.001	.035	.592	-.067	.110	-.027	.006
Education	-.483	.064	.047	.765	-.154	.544	1.99	.063	1.33	.108	2.04	.087	.620	.676	1.49	.118	-.024	.920
Digit Span	-.024	.397	-.011	.518	-.004	.897	.304	.007	.057	.525	.180	.162	-.363	.020	.064	.536	.029	.251
MARS5	-.003	.942	-.010	.722	.007	.872	.025	.899	-.252	.090	-.242	.262	-.373	.160	.056	.746	-.028	.513
AP dose	.877	.076	-.055	.855	.339	.480	-3.94	.052	1.00	.527	-.003	.027	2.38	.398	-1.59	.384	-.803	.066
AP duration	.002	.994	-.021	.878	-.011	.959	-1.59	.085	-1.31	.065	-.136	.151	.394	.757	.118	.887	.135	.501
PANSS Positive	.054	.077	-.018	.346	.029	.330	-.169	.185	-.038	.703	-.008	.958	.036	.839	-.162	.151	.041	.132
PANSS Negative	.032	.257	-.037	.028	-.010	.704	-.339	.003	-.071	.429	.028	.831	-.007	.965	-.083	.427	-.022	.387
PANSS General	.032	.102	-.017	.152	.015	.425	-.204	.010	-.037	.553	.099	273	-.133	.230	-.090	.213	.011	.548

Table A6.
Table showing R^2 of SAT-MC x AP dose x age x ethnicity regression models after listwise deletion.

Model Nº	**Included Variables**	***R^2***	***R^2* change**
1	AP dose	.165	-
2	AP dose Age	.364	.199
3	AP dose Age Ethnicity	.365	.001

Table A7.
Table showing ANOVA results for SAT-MC x AP dose x age x ethnicity regression models after listwise deletion.

Model	**df regression, df residual**	**Model Significance (p value)**
1	1, 57	.001
2	2, 56	<.001
3	3, 55	<.001

Table A8.
Table showing SAT-MC x AP dose x age x ethnicity regression models after listwise deletion.

Model	IVs	B	P
1	AP dose	-.406	.001
2	AP dose	-.209	.077
	Age	-.487	<.001
3	AP dose	-.213	.076
	Age	-.508	<.001
	Ethnicity	-.045	.719

Complete Case Analysis: Longitudinal Data

Data were deleted on a listwise basis: Firstly, only those who attended all timepoints (baseline, 12m, and 24m) were kept. Secondly, participants who had at least one missing data value from any timepoint were deleted from all timepoints.

Table A9.
Table showing number of participants with data remaining at each timepoint, after listwise deletion.

Timepoint	Maintenance N=	Reduction/Discontinuation N=
T1	9	5
T2	8	4
T3	5	4

Demographics
Complete case analysis shows a much less diverse and a smaller sample size. No female, or non-white participants remain in the reduction/discontinuation group. Additionally, there is no longer a significant difference between groups on age of participants.

Table A10.

T-tests and Chi-Squares on baseline demographic data between groups, after listwise deletion with follow-up data.

Variable	Reduction/Discontinuation (n=5) N (%)	Maintenance (n=9) N (%)	X^2
Gender			.078
Male	5 (100)	5 (55.0)	
Female	0 (0)	4 (45.0)	
Ethnicity			.078
Non-White	0 (0)	4 (45.0)	
White	5 (100)	5 (55.0)	
Education Level			.872
Up to 18 (Secondary)	2 (40.0)	4 (45.0)	
Tertiary	3 (60.0)	5 (55.0)	
	Mean (SD)	**Mean (SD)**	**p value**
CPZ Equivalents	270.83 (67.85)	317.75 (81.47)	.641
Age	***53.20 (13.26)***	***46.00 (11.65)***	***.311***
Digit Span	16.60 (7.02)	15.22 (4.24)	.651
SFS	105.40 (12.20)	114.23 (5.47)	.082
PANSS Total	46.40 (7.57)	39.89 (6.29)	.109

Note**: *Bold and Italic* text** denotes a change in significance (p <.05) from MI analysis

RLMM

Complete case analysis was conducted on a sample of 14 participants who completed all timepoints and had no missing values. This sample size meant analysis was highly underpowered, and as such results should be used for hypothesis building only. Analysis revealed much higher confidence intervals during pairwise comparisons of time for all domains, compared to MI analysis. Additionally, some significant differences are noted between results in MI compared to RLMM. From demographics results we see the complete case analysis results in a highly biased sample, with no female, or non-white participants in the reduction/discontinuation group. Therefore, the MI dataset and analysis provides a more diverse, less biased sample.

5.9.1 AIHQ Aggression

Table A11.

Main Effects Model of Time, Group and Time x Group Interactions on AIHQ Aggression.

	F Statistic	**p value**
Time	2.710	.091
Group	2.378	.152
Time x Group	1.142	.339

Note**: Bold** text denotes a change in significance (p <.05) from MI analysis

5.9.2 AIHQ Hostility

Table A12.

Main Effects Model of Time, Group and Time x Group Interactions on AIHQ Hostility.

	F Statistic	**p value**
Time	.763	.480
Group	.037	.850
Time x Group	.519	.604

Note**: Bold** text denotes a change in significance (p <.05) from MI analysis

5.9.3 AIHQ Blame

Table A13.
Main Effects Model of Time, Group and Time x Group Interactions on AIHQ Blame.

	F Statistic	**p value**
Time	**4.112**	**.034**
Group	1.034	.328
Time x Group	2.322	.128

Note**: Bold** text denotes a change in significance (p <.05) from MI analysis

5.9.4 BLERT

Table A14.
Main Effects Model of Time, Group and Time x Group Interactions on BLERT.

	F Statistic	**p value**
Time	.325	.727
Group	.199	.663
Time x Group	2.376	.122

Note**: Bold** text denotes a change in significance (p <.05) from MI analysis

5.9.5 Hinting Task

Table A15.
Main Effects Model of Time, Group and Time x Group Interactions on the Hinting Task.

	F Statistic	**p value**
Time	.638	.541
Group	.170	.688
Time x Group	**.176**	**.840**

5.9.6 EQ-CEF

Table A16.
Main Effects Model of Time, Group and Time x Group Interactions on EQ-CEF.

	F Statistic	**p value**
Time	.753	.485
Group	.211	.654
Time x Group	.875	.434

Note**: Bold** text denotes a change in significance (p <.05) from MI analysis

5.9.7 EQ-SSF

Table A17.
Main Effects Model of Time, Group and Time x Group Interactions on EQ-SSF.

	F Statistic	**p value**
Time	1.454	.265
Group	.966	.347
Time x Group	**5.589**	**.015**

5.9.8 SAT-MC

Table A18.
Main Effects Model of Time, Group and Time x Group Interactions on SAT-MC.

	F Statistic	**p value**
Time	**10.9**	**<.001**
Group	3.99	.067
Time x Group	1.23	.314

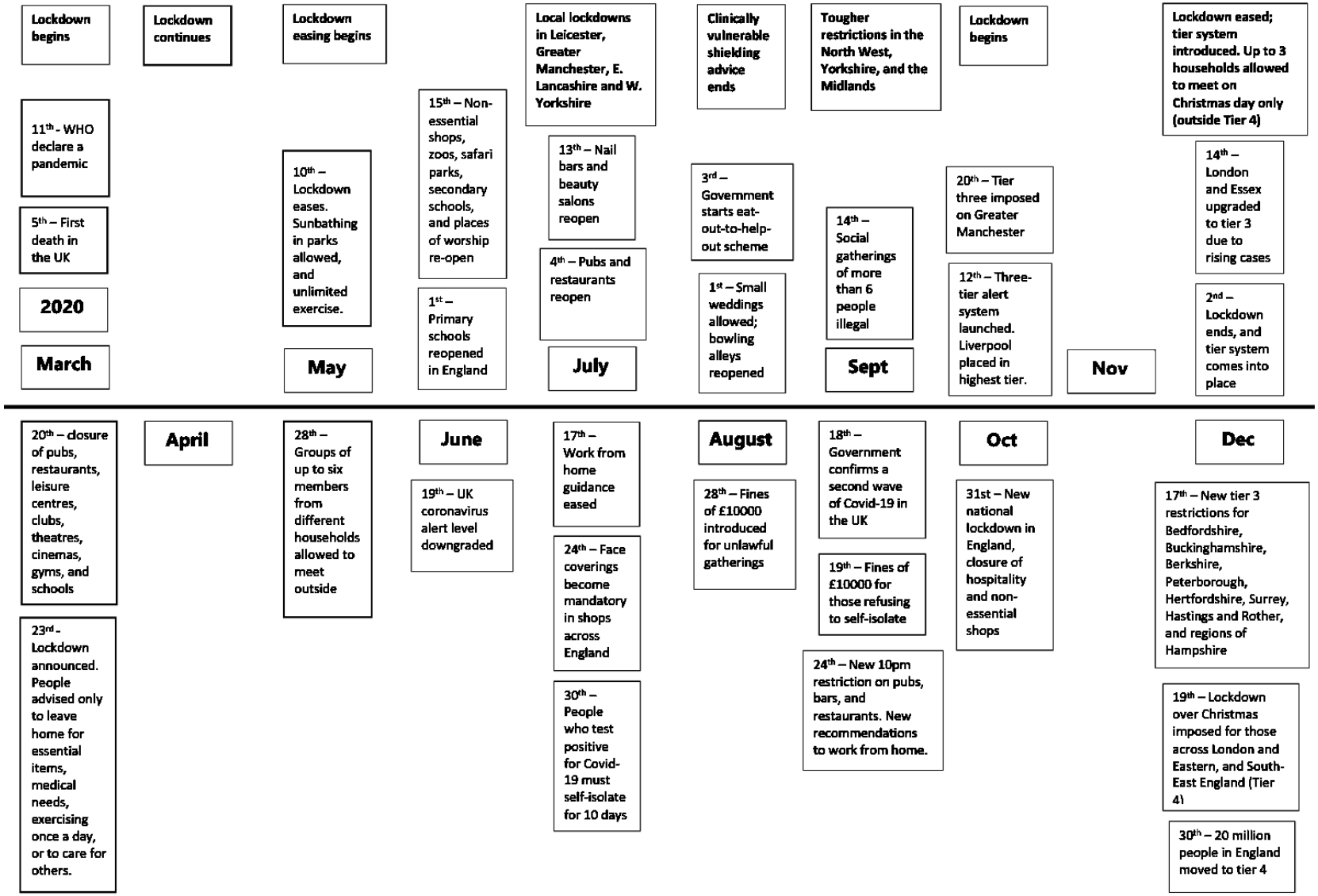
5.9.9 TEIQue

Table A19.
Main Effects Model of Time, Group and Time x Group Interactions on TEIQue.

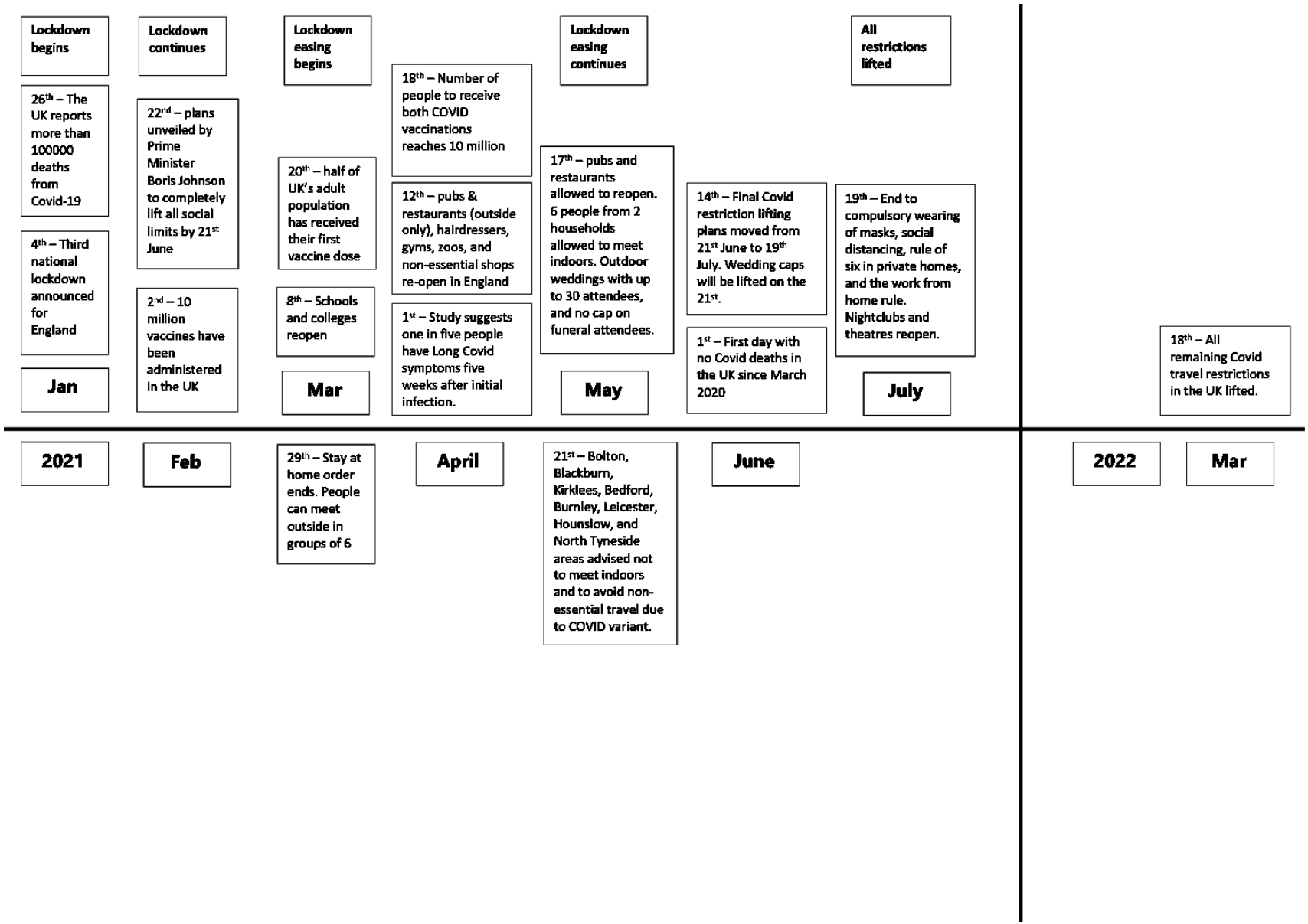
	F Statistic	**p value**
Time	.510	.608
Group	**.552**	**.470**
Time x Group	.018	.982

Note**: Bold** text denotes a change in significance (p <.05) from MI analysis

Appendix E: COVID-19 Lockdown Timeline 2020:



2021/2022:


Lockdown begins
26th – The UK reports more than 100000 deaths from Covid-19
4th – Third national lockdown announced for England
Jan
2021
Lockdown continues
22nd – plans unveiled by Prime Minister Boris Johnson to completely lift all social limits by 21st June
2nd – 10 million vaccines have been administered in the UK
Feb
Lockdown easing begins
20th – half of UK's adult population has received their first vaccine dose
8th – Schools and colleges reopen
Mar
29th – Stay at home order ends. People can meet outside in groups of 6
18th – Number of people to receive both COVID vaccinations reaches 10 million
12th – pubs & restaurants (outside only), hairdressers, gyms, zoos, and non-essential shops re-open in England
1st – Study suggests one in five people have Long Covid symptoms five weeks after initial infection.
April
Lockdown easing continues
17th – pubs and restaurants allowed to reopen. 6 people from 2 households allowed to meet indoors. Outdoor weddings with up to 30 attendees, and no cap on funeral attendees.
May
21st – Bolton, Blackburn, Kirklees, Bedford, Burnley, Leicester, Hounslow, and North Tyneside areas advised not to meet indoors and to avoid non-essential travel due to COVID variant.
14th – Final Covid restriction lifting plans moved from 21st June to 19th July. Wedding caps will be lifted on the 21st.
1st – First day with no Covid deaths in the UK since March 2020
June
All restrictions lifted
19th – End to compulsory wearing of masks, social distancing, rule of six in private homes, and the work from home rule. Nightclubs and theatres reopen.
July
2022
18th – All remaining Covid travel restrictions in the UK lifted.
Mar

Appendix F: Follow-up Mean Scores

Table A20

12- Month Means for Illness-Related Variables by Group (Reduction/Discontinuation vs. Maintenance)

	Reduction/Discontinuation Group Mean (SD)	Maintenance Group Mean (SD)
SFS	105.51 (7.78)	110.98 (8.53)
PANSS Positive	10.79 (6.29)	10.23 (4.10)
PANSS Negative	10.07 (4.32)	10.29 (4.15)
PANSS General	22.88 (8.54)	25.43 (10.57)
Digit Span	16.43 (5.20)	15.26 (4.49)

Table A21

24- Month Means for Illness-Related Variables by Group (Reduction/Discontinuation vs. Maintenance)

	Reduction/Discontinuation Group Mean (SD)	Maintenance Group Mean (SD)
SFS	107.08 (9.49)	110.96 (10.02)
PANSS Positive	10.95 (4.75)	9.32 (5.67)
PANSS Negative	10.55 (3.78)	9.64 (3.66)
PANSS General	25.65 (7.46)	22.61 (6.51)
PANSS Total	47.15 (14.22)	41.57 (13.28)
Digit Span	10.80 (4.07)	11.79 (4.89)