Exploring Social Cognition and Mirror Systems in Schizophrenia and Bipolar Disorder

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Submitted in partial fulfilment of the requirement for the degree of

Doctor of Psychology (Clinical Neuropsychology)

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July, 2013

p 16 para 1, line 5: "Blueler" for "Bleuler"

p 45 para 2, line 3: "Rizzolatti" for "G. Rizzolatti"

p 45 para 2, line 6: "Rizzolatti" for "G. Rizzolatti"

p 61 para 2, line 4: "Kim" for "E. Kim"

ADDENDUM

p 40: Add at the end of para 2:

"The inferior frontal gyrus has also been found to be involved in affective empathy (Shamay-Tsoory et al., 2009)."

p 42: Add at the end of para 3:

"The importance of the mPFC - particularly the ventromedial prefrontal cortex - in both empathy and ToM has been further supported by other recent studies (Shamay-Tsoory, 2007; Shamay-Tsoory et al., 2009)."

p 48: Add at the end of para 2:

"In addition to recognising the intentions of others' actions, suppression of the mu rhythm has also recently been found to be implicated in empathy (Perry et al., 2010a; Perry et al., 2010b)."

p 57 para 1, line 15: After "independent living." insert

"Quality of life measures were developed after recognition that the functional status of the individual does not always reflect the individual's perceived health status or wellbeing (Muldoon et al., 1998). A number of psychosocial factors, in addition to health factors, impact on perceived quality of life (Muldoon et al., 1998). The World Health Organisation defines quality of life as 'an individual's perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns" (Skevington et al., 2004). While originally quality of life was measured as a holistic domain, more recently measures have recognised that quality of life can vary over a number of different domains. The World Health Organisation have published a commonly used and well validated measure of quality of life (WHOQOL-BREF), and this measure captures subjective ratings of quality of life in four domains: general health, psychological function, social relationships, and environment quality (Skevington et al., 2004)."

p 101: Add at end of *2.3 Data Analysis* section:

"To control for multiple correlations, a Bonferroni adjusted alpha of .006 was applied."

p 135 para 3, line 3: After "variables was explored" insert "across all three groups".

p 191, after line 18 insert: "Muldoon, M. F., Barger, S. D., Flory, J. D., & Manuck, S. B. (1998). What are quality of life measurements measuring? *BMJ, 316*, 542-545."

p 193, after line 3 insert "Perry, A., Bentin, S., Bartal, I. B., Lamm, C., & Decety, J. (2010). "Feeling" the pain of those who are different from us: Modulation of EEG in the mu/alpha range. *Cognitive Affective and Behavavioral Neuroscience, 10*(4), 493-504. doi: 10.3758/CABN.10.4.493.

Perry, A., Troje, N. F., & Bentin, S. (2010). Exploring motor system contributions to the perception of social information: Evidence from EEG activity in the mu/alpha frequency range. *Social Neuroscience, 5*(3), 272-284. doi: 10.1080/17470910903395767"

p 197, after line 3 insert "Shamay-Tsoory, S. G. (2007). Impaired empathy following ventromedial prefrontal brain damage. In T. Farrow & P. Woodruff (Eds.), *Empathy in mental illness* (pp. 89-110). New York, NY: Cambridge University Press."

p 197, after line 10 insert "Shamay-Tsoory, S. G., Aharon-Peretz, J., & Perry, D. (2009). Two systems for empathy: a double dissociation between emotional and cognitive empathy in inferior frontal gyrus versus ventromedial prefrontal lesions. *Brain, 132*(Pt 3), 617-627. doi: 10.1093/brain/awn279"

Table of Contents

List of Prepared Manuscripts and Presentations

This thesis includes the following manuscripts submitted for peer-review during candidature:

Andrews, S.C., Enticott, P.E., Hoy, K.E., & Fitzgerald, P.B. (Submitted). Do social cognitive deficits underpin reduced quality of life in schizophrenia?

Andrews, S.C., Enticott, P.E., Hoy, K.E., & Fitzgerald, P.B. (Submitted). Social cognition and quality of life in bipolar disorder.

Andrews, S.C., Enticott, P.E., Hoy, K.E., Thomson, R.H., & Fitzgerald, P.B. (Submitted). Evidence for reduced mirror system activity in euthymic bipolar disorder but not schizophrenia.

Part of this thesis was presented as an oral presentation at a local symposium:

Andrews, S.C., Enticott, P.E., Hoy, K.E., & Fitzgerald, P.B. Mirror systems and social cognition in schizophrenia. College of Clinical Neuropsychologists (CCN) 2012 Postgraduate Student Research Symposium.

Part of this thesis was presented as a poster at a conference:

Andrews, S.C., Hoy, K.E., Enticott, P.E., & Fitzgerald, P.B. Mirror systems and social cognition in schizophrenia. Biological Psychiatry Australia 2012 Annual Conference.

Monash University

Declaration for thesis based or partially based on conjointly published or unpublished work

General Declaration

In accordance with Monash University Doctorate Regulation 17.2 Doctor of Philosophy and Research Master's regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.
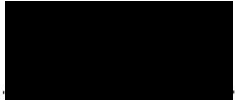
This thesis includes three original papers submitted for publication in peer reviewed journals. The core theme of the thesis is social cognition and mirror systems in schizophrenia and bipolar disorder. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the School of Psychology and Psychiatry under the supervision of Professor Paul Fitzgerald.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters 6, 7, and 8, my contribution to the work involved the following:

Thesis chapter	Publication title	Publication status*	Nature and extent of candidate's contribution
6	Do social cognitive deficits underpin reduced quality of life in schizophrenia?	Submitted	Project design and creation of protocol; hypothesis formulation; ethics applications; recruitment and data collection; data analysis; manuscript writing and preparation
7	Social cognition and quality of life in bipolar disorder	Submitted	As above
8	Evidence for reduced mirror system activity in euthymic bipolar disorder but not schizophrenia	Submitted	As above

I have renumbered sections of submitted papers in order to generate a consistent presentation within the thesis.

Signed: ....

Date: .... 1/7/13 ....

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Abbreviations and Symbols

α	Alpha
ACC	Anterior Cingulate Cortex
ANOVA	Analysis of variance
CT	Computerised Tomography
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders IV
DLPFC	Dorsolateral Prefrontal Cortex
EEG	Electroencephalogram
EMG	Electromyogram
F	F-test
FDI	First Dorsal Interosseous Muscle
fMRI	Functional Magnetic Resonance Imaging
HAM-D	The Hamilton Rating Scale for Depression
IRI	Interpersonal Reactivity Index
MEP	Motor Evoked Potential
MINI	MINI International Neuropsychiatric Interview for DSM-IV
mPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
n	Number
OFC	Orbitofrontal Cortex
p	p-value (significance)
PANSS	Positive and Negative Symptom Scale
PET	Positron Emission Tomography

PMC	Primary Motor Cortex
PrMC	Premotor Cortex
QoL	Quality of life
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
SD	Standard Deviation
ST	Simulation Theory
STS	Superior Temporal Sulcus
t	t-test
TMS	Trancranial Magnetic Stimulation
ToM	Theory of Mind
TT	Theory Theory
WHOQOL-Bref	World Health Organisation Quality of Life scale – Abbreviated
YMRS	Young Mania Rating Scale

Abstract

Schizophrenia and bipolar disorder show some overlap in genetics, epidemiology and clinical features. Individuals with these disorders often have poor social and vocational functional outcomes and reduced quality of life, even during times of symptom remission. Social cognition comprises a number of processes including emotion recognition, empathy and theory of mind (ToM), and recent research has indicated that these skills may be reduced in schizophrenia and bipolar disorder, and contribute to their reduced function. Despite this, the exact nature of these social cognitive deficits, their impact on quality of life, and possible underlying neural substrates, have not yet been established in these disorders. One brain network implicated in social cognition is the mirror system, however, research into this system in schizophrenia or bipolar disorder has been very limited to date. The goal of this thesis was to better understand the nature and impact of social cognitive deficits in schizophrenia and euthymic bipolar disorder, and comprehensively assess mirror system function as a possible contributor to these deficits. In this thesis, I first assessed a number of aspects of social cognition (emotion recognition, empathy and ToM), as well as cognitive, clinical, and quality of life variables in a schizophrenia, euthymic bipolar disorder, and healthy control group. The three groups were then compared using two putative measures of mirror system function (EEG and TMS). I found a significant reduction in cognitive ToM in both disorders, with

the addition of a deficit in the recognition of anger in the schizophrenia sample, indicating some likely shared underlying brain pathology but also disorder-specific differences. Quality of life was not related to these social cognitive deficits in this sample, possibly due to other mediating factors. There was some evidence for underactive mirror systems in euthymic bipolar disorder but not schizophrenia, however, mirror system function was not strongly related to any of the social cognitive measures utilised in this study. The findings of this thesis make a valuable contribution to the understanding of social cognition in schizophrenia and bipolar disorder, and challenge the proposed importance of mirror systems for social cognition. Our findings indicate that social cognitive deficits should be considered in assessment and treatment planning in schizophrenia and bipolar disorder. In addition, this thesis highlights the need for further research aimed at understanding the neurobiology and true impact of social cognitive deficits. It is hoped that this knowledge will lead to better treatments targeting these deficits at both neurophysiological and behavioural levels, and ultimately improve patient outcomes and wellbeing.

Chapter 1: General Introduction and Thesis Overview

Schizophrenia and bipolar disorder are relatively common and often devastating mental illnesses. Most commonly first appearing in the late teens or early twenties, a period when individuals are beginning to establish themselves in the world, these disorders have a significant impact on lives. For reasons that are not well understood, even when the core symptoms of these disorders are in remission, social and vocational functioning, as well as quality of life, often remains poor. Studies have shown these persisting functional deficits are related to cognitive dysfunction. Recently, deficits in aspects of social cognition have also been identified. While social cognitive deficits have also been associated with poor functional outcomes in these disorders, their relationship with quality of life has not been thoroughly explored.

One possible brain network posited to contribute to social cognition is the mirror system, and it is possible that dysfunction in the mirror system might be contributing to social cognitive deficits in schizophrenia and bipolar disorder. To date, however, very little research has explored mirror systems in schizophrenia or bipolar disorder.

This aim of the research presented in this thesis was to therefore investigate the nature and impact of social cognitive deficits in schizophrenia and euthymic bipolar disorder, and comprehensively assess mirror system function as a possible contributor to these deficits.

The following studies were conducted to achieve these aims:

1. A study comparing a schizophrenia sample with a healthy control group on a number of aspects of social cognition, and assessing the relationships between any social cognitive deficits identified, with quality of life, neurocognitive deficits, and clinical variables.

2. A study comparing a euthymic bipolar disorder group with a healthy control group on several aspects of social cognitive function and quality of life, and examining any relationships between social cognitive deficits, quality of life, neurocognition, and clinical variables.

3. An investigation of mirror systems function across a schizophrenia, bipolar disorder and healthy control group using a novel multimodal approach (using EEG and TMS), and examinations of the relationships between mirror system activity and aspects of social cognition.

The thesis will be presented in the following format:

Chapters two to four provide an overview of schizophrenia and bipolar disorder, analyse the literature surrounding theories of social cognition, and examine how mirror systems are implicated. Chapter five synthesises current research into mirror systems and social cognition in schizophrenia and bipolar disorder, and describes the rationale for the current thesis. Chapters six to eight are manuscripts reporting my findings on social

cognition and mirror systems in schizophrenia and bipolar disorder, and chapter nine

reports additional analyses undertaken but not reported in the preceding manuscripts.

Finally, chapter ten contains a general discussion, which integrates the key findings from

the thesis and discusses the broader implications.

Chapter 2: Schizophrenia and Bipolar Disorder

Overview

Schizophrenia and bipolar disorder are two serious mental disorders that have a substantial impact on the individual and those closest to them. The distinction between schizophrenia (dementia praecox) and bipolar disorder (manic depressive insanity) was initially made by Kraepelin in 1896, and was adopted into modern psychiatry (Jablensky, 1999). The presence of overlapping symptoms and a number of common features in these two disorders, however, has led to a rejection by some of the so-called "Kraepelinian dichotomy" in favour of dimensional approach. As such, a growing body of research now includes both clinical groups (Craddock & Owen, 2005, 2010). This chapter provides an overview of each disorder, including its historical context, diagnostic criteria and course, epidemiology, aetiology, and pathophysiology. A summary of the key findings indicating a relationship between the disorders is then provided.

Schizophrenia

Schizophrenia is a complex, heterogeneous illness that affects approximately 1% of the population (Lieberman, Stroup, & Perkins, 2006). Most often diagnosed in early adulthood, the disabling nature of schizophrenia often prevents the normal career and relationship milestones that occur during the twenties. In addition, the recurrent and chronic nature of the illness often leads to ongoing functional impairment, which is distressing for the patient and costly to the healthcare system.

Although references to "madness" and "paranoia" existed two millennia ago, it is difficult to find any descriptions matching that of the modern day concept of schizophrenia before 1800 (Lieberman et al., 2006). While during the 1800's a number of

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different syndromes were characterised that featured aspects of psychosis, including "persecutory delirium" and "catatonia", Kraepelin for the first time examined patterns of symptoms and clinical course, and suggested the term "dementia praecox" to define our modern understanding of schizophrenia. He contrasted this with "manic depression" which had a recurrent, rather than degenerative, course. While Eugen Bleuler agreed with Kraepelin on many points, Blueler disagreed that disorder had a necessarily poor prognosis, noting that patients can remain stable without decline for long periods. As such, Blueler coined the disorder schizophrenia, reflecting the separation of thought from affect. He also recognised the heterogeinty of the disorder, referring to "the group of schizophrenias" (Blueler, 1950). While Kraepelin had focussed on hallucinations and delusions as core symptoms of the disorder, Blueler characterised the fundamental symptoms of schizophrenia as that of association (loosening of associations), affectivity (blunted affect), and autism (detachment from others and the outside world) (Blueler, 1950). These core features allude to disorganised, negative, and social symptoms, while positive symptoms were labelled as "accessory symptoms". For much of the late 20th century, however, research and treatment of the disorder focused on the positive symptoms, due to their distressing and prominent nature, and largely neglected the negative symptoms, as well as the cognitive and social dysfunction common to the disorder. Only during the last two decades has research into the disorder begun to focus on these features as treatment priorities.

Diagnostic Criteria and Clinical Course

Although a fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) has now been released, this was not available for the majority of my

candidature, and so the fourth edition text revision (DSM-IV-TR) will be referred to in the current thesis. The diagnosis of schizophrenia according to the DSM-IV-TR requires the presence of at least two of the following symptoms for at least a month: hallucinations, delusions, disorganised speech, disorganised or catatonic behaviour, or negative symptoms (American Psychiatric Association, 2000). Social or occupational dysfunction must occur, and continuous signs of the disturbance must persist for at least 6 months. If a mood disorder is also present for a substantial portion of the illness, schizoaffective disorder is diagnosed (American Psychiatric Association, 2000). Although the positive symptoms (e.g., hallucinations or delusions) are the most visible and have been the primary target of antipsychotic treatment, the negative symptoms are also distressing for family members, and have a greater impact on functional outcome (Lin et al., 2013).

Epidemiology

The annual incidence of schizophrenia is estimated to be between around 0.5 per 1,000, while the lifetime prevalence is around 5 per 1,000 (Lieberman et al., 2006). Onset is usually between the ages of 15 – 24 for both males and females, although there is a second peak for females at age 55 – 64. More men than women develop the disorder (Thorup, Waltoft, Pedersen, Mortensen, & Nordentoft, 2007). For roughly half of individuals who develop schizophrenia onset is sudden, while for the other half a prodromal phase of months to years is present. The prodromal phase usually involves the development of negative and cognitive symptoms, such as social withdrawal, loss of motivation and initiative, or affective blunting (Picchioni & Murray, 2007). A number of environmental factors are implicated in schizophrenia: being born in winter, obstetric

complications during birth, living in an urban environment, and social isolation all increase an individual's likelihood of developing schizophrenia (Lieberman et al., 2006).

Aetiology and Pathophysiology

Despite considerable research into the aetiology and neuropathology of schizophrenia, much remains unknown. A number of different theories regarding the cause of schizophrenia have focussed on different aspects of the disorder. Within these theories, the role of genetics, environment, neurodevelopment, neurotransmitters, neurodegeneration, or neuroplasticity, have been variously emphasised.

Initially, observation of the deterioration of cognitive function led to the hypothesis that schizophrenia may be a degenerative disease or dementia, and early investigations into schizophrenia involved studies of brain volume post-mortem. Unlike the dementia seen in Alzheimer's disease, clear signs of a disease process such as gliosis are missing in schizophrenia. The most consistently found structural brain difference in schizophrenia is enlarged ventricles, thought to be due to a loss of grey matter, while other observed structural brain changes have been modest (Lieberman et al., 2006). Genetic and family studies reveal schizophrenia has a considerable heritable component, with a 10 fold increase in risk for siblings of those affected, and a monozygotic twin concordance rate of 40% (Picchioni & Murray, 2007). Recently genetic studies have implicated a number of genes in schizophrenia, but so far no single gene has been identified to cause the disorder, indicating that it is likely to be a combination of many genes that contribute to the development of the disease (Doherty, O'Donovan, & Owen, 2012). The neurodevelopmental hypothesis, in contrast, primarily focuses on the impact of environmental factors early in life (particularly pre- and peri-natal) that might have an

impact on brain development, and recent evidence from neuropathology that indicates

altered development rather than neurodegeneration (Piper et al., 2012). A number of

neurotransmitters have been implicated in schizophrenia, most notably dopamine and

glutamate, but also y-aminobutyric acid (GABA), serotonin and acetycholine (Iversen &

Iversen, 2007; Lieberman et al., 2006). Recently, attention has shifted to the possibility

that other brain changes may be contributing to the disorder. For example, change to the

neuronal membrane with reduced levels of phospholipids, possibly from oxidative stress,

might explain the changes to neurotransmitter systems observed in schizophrenia

(Lieberman et al., 2006). In addition, altered neuroplasticity in schizophrenia has also

been implicated (Fitzgerald et al., 2004; Oxley et al., 2004; Voineskos, Rogasch, Rajji,

Fitzgerald, & Daskalakis, 2013).

Bipolar Disorder

Historical Context

Hippocrates (460-337 BC) was one of the earliest physicians to describe

melancholia and mania, although mania had a number of meanings in the classical era,

including to react in a rage, a disease, a divine state, or a temperament (Angst &

Marneros, 2001). It was another Greek physician, however, Aretaeus, who in the 1st

century explicitly linked mania and melancholia, noting "The development of a mania is

really a worsening of the disease (melancholia) rather than a change into another disease"

(cited in Angst & Marneros, 2001, p. 6). It was not until the 19th century that further

progress was made in characterising the disorder. Jean-Pierre Falret published a

description of a disorder he termed "folie circulaire" in 1851 that matches our modern

day concept of bipolar disorder, and in the 1890s Kraepelin labelled the disorder manic-

depressive insanity and distinguished it from the psychoses he labelled dementia praecox

(Angst & Marneros, 2001). Manic-depressive insanity did not originally distinguish

between unipolar and bipolar depression, and this distinction was not made until the

1960s, when it was recognised that the disorders differed not just with regard to

symptoms, but also genetics, gender, course, and premorbid personality (Angst &

Marneros, 2001).

Diagnostic Criteria and Clinical Course

The bipolar disorders are categorised by the DSM-IV-TR as mood disorders,

which involve major depressive episodes and either manic or hypomanic episodes. There

are two major types: Bipolar I Disorder, which is characterised by one or more manic or

mixed episodes usually accompanied by major depressive episodes, and Bipolar II

Disorder, in which major depressive episodes are the prominent feature, accompanied by

at least one hypomanic episode (American Psychiatric Association, 2000). A manic

episode is defined as a distinct period during which there is an abnormally and

persistently elevated, expansive, or irritable mood, which lasts at least a week. In

addition, a list of additional symptoms during mania includes grandiosity, decreased need

for sleep, pressure of speech, flight of ideas, distractibility, increased involvement in

goal-directed activities or psychomotor agitation, and excessive interest in pleasurable

activities with disregard for consequences. Three of these should be present if mood is

elevated or expansive, while four of these must be present if the mood is irritable. The

episode must cause marked impairment in social or occupational functioning, or require

hospitalisation, or is characterised by the presence of psychotic features. A hypomanic

episode is similar except the mood symptoms must last at least four days, not cause social

or occupational dysfunction or require hospitalisation, and psychotic features must not be present. Major depressive episodes involve five of the following symptoms present during a two week period and represent a change from previous functioning: depressed mood, diminished interest in activities, changes to appetite or sleep, psychomotor agitation or retardation, fatigue, feelings of worthlessness, reduced ability to concentrate, or recurrent thoughts of death. In addition, clinically significant distress, or impairment of important areas of functioning must be present. Finally, a mixed episode is diagnosed when the criteria are met for a manic episode and a major depressive episode every day for at least a one-week period.

With regard to clinical course, about 80-90% of patients experience relapse or recurrence of symptoms, with the presence of residual symptoms after the acute episode increasing the likelihood of recurrence. The average number of episodes per year is 0.6 (Hilty, Leamon, Lim, Kelly, & Hales, 2006). Recovery of function is often slower than symptomatic recovery and varies greatly depending on the individual.

Epidemiology

The average onset of Bipolar I disorder is 18 years, while Bipolar II disorder is slightly later at 22 years (Hilty et al., 2006). Treatment is not usually sought for a number of years after onset, and because differential diagnosis is a challenge given the number of symptoms shared with other disorders, the correct diagnosis is made on average 8 years after initial symptoms. Prevalence or Bipolar I disorder is around 1% (Sherazi, McKeon, McDonough, Daly, & Kennedy, 2006), and Bipolar II prevalence is around 2.5%. There is an even gender distribution for Bipolar I, while more females are diagnosed with Bipolar II (Hilty et al., 2006). Family studies indicate that there is a significant heritable

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component to bipolar disorder, with approximately 40% concordance rate for monozygotic twins, and 6% concordance rate for dizygotic twins (Kieseppa, Partonen, Haukka, Kaprio, & Lonnqvist, 2004; McGuffin et al., 2003).

Aetiology and pathophysiology

The cause of bipolar disorder has not been established, but the role of genetics, environment, circadian rhythms, and neurophysiological changes have all been explored. Genetic studies have implicated a large number of genes in bipolar disorder. In particular, genes that are involved in neurotransmitters, including serotonin and dopamine, have been implicated, as well as genes involved in cell maintenance and circadian rhythms (Segurado et al., 2003; Serretti & Mandelli, 2008). Bipolar disorder is more common in urbanised areas, and living in an urban area increases the incidence of both psychosis and depression (Serretti & Mandelli, 2008). Early environmental stress, lower socioeconomic status, and being an ethnic minority are also risk factors for developing bipolar disorder (Sherazi et al., 2006). These observations therefore also indicate the role of the environment in the development of the disorder. Structural neuroimaging studies of bipolar disorder have indicated the presence of enlarged ventricles and deep white matter hyperintensities, but no clear evidence of region-specific structural changes (Kempton, Geddes, Ettinger, Williams, & Grasby, 2008). Studies using magnetic resonance spectroscopy have indicated that there may be changes in bipolar disorder in cell membranes and secondary messenger metabolism, while functional magnetic resonance imaging (fMRI) studies have found differences in activation in limbic and prefrontal brain regions between individuals with bipolar disorder and healthy controls (Strakowski, DelBello, & Adler, 2005). Given the strong connections between prefrontal and limbic

areas, some researchers have suggested that reduced prefrontal modulation of limbic areas may be the cause of mood symptoms in the disorder (Strakowski et al., 2005).

Schizophrenia and Bipolar Disorder as Related Disorders

Despite currently being categorised as separate and unrelated disorders, schizophrenia and bipolar disorder share a number of clinical features. Around 58% of bipolar disorder patients will experience psychotic symptoms during the course of the illness (Lindenmayer, Bossie, Kujawa, Zhu, & Canuso, 2008), and up to 90% of patients with schizophrenia will experience a concurrent mood disorder at some time (American Psychiatric Association, 2000). This is reflected in the diagnosis of schizoaffective disorder. Studies of schizoaffective disorder have revealed that patients' clinical features, course, cognition and outcomes place it intermediate to schizophrenia and bipolar disorder (Amann et al., 2012; Benabarre et al., 2001). In recent years, recognition of this overlap has led to the increase in comparative studies between schizophrenia and bipolar disorder, in the areas of genetics and family studies, cognition, neuroimaging, functional outcome and quality of life.

Genome-wide association studies have identified a number of genes that are associated with increased risk for both schizophrenia and bipolar disorder, although a number of non-shared genetic risk factors have also been identified (Craddock & Owen, 2010). Familial aggregation has been demonstrated for the disorders, and this is substantially due to genetic, rather than environmental factors (Berrettini, 2000; Lichtenstein et al., 2009). Impaired premorbid social functioning has been observed in both disorders, although the level of impairment is more severe in individuals with schizophrenia (Cannon et al., 1997). The same pattern is seen in reductions in functional

outcome and quality of life (Brissos, Dias, Carita, & Martinez-Aran, 2008; Green, 2006;

E. J. Kim et al., 2010; Narvaez, Twamley, McKibbin, Heaton, & Patterson, 2008). A

review of neuroimaging studies comparing bipolar disorder, schizophrenia, and healthy

control participants, indicate that there is both overlap and differences between the neural

circuitry involved in the two disorders (Prossin, McInnis, Anand, Heitzeg, & Zubieta,

2010). Recently, there has been increasing recognition that bipolar disorder has

reductions in general cognition, as well as social cognition, which share similarities to

those experienced in schizophrenia (Brissos et al., 2008; Donohoe et al., 2012). Overall,

studies comparing schizophrenia with bipolar disorder suggest the presence of some

shared underlying neuropathology, which should be further explored for a better

understanding of these two serious disorders.

Chapter 3: Social Cognition

Overview

Social cognition is an umbrella term that refers to the psychological processes that underlie social behaviour, and ultimately contribute to social functioning (Kennedy & Adolphs, 2012). While generally defined as the ability to understand others' intentions, dispositions, and behaviours (Green, Olivier, Crawley, Penn, & Silverstein, 2005), the nature of these processes remain hotly debated. Initially largely consisting of behavioural studies in normal as well as clinical populations, social cognition research is now increasingly utilising more direct measures of brain activity, such as neuroimaging and electrophysiological methods. This is leading to new and exciting insights in the field. The current chapter provides an overview of social cognition: the development of the concept, summary of the core aspects, a review of the two major theories, and likely neural substrates.

The Concept of Social Cognition

The term social cognition emerged during the 1960s as a branch of cognitive psychology, and was therefore initially explored within an information-processing paradigm (Brothers, 1990; Heider, 1967; Penn, Sanna, & Roberts, 2008). The term was quickly adopted by psychologists from a number of different fields, and has since been studied from developmental, personality, neuroscience, and clinical perspectives. The way that social cognition has been defined has been influenced by a number of factors,

including the theoretical perspectives of the researchers studying it, the clinical populations the research has been based on, and the tests that have been developed and used to measure it (Adolphs, 2006; Brune, 2005b). Different aspects of social cognition have often been studied individually without any attempt to integrate them into a single construct. There has also been debate as to how to break down the different aspects of social cognition, and the subsequent terminology used (Preston & de Waal, 2001).

To date, social cognitive research has most often been studied in children (i.e., in a developmental context), or in clinical populations known to have social impairments, such as children with autism, or patients with schizophrenia (Cacioppo, Visser, & Pickett, 2006). Because of this, the focus of studies in this field has often depended on the deficits observed in particular populations. This has made it difficult for a comprehensive and unified theory of social cognition to emerge. For example, studies of social cognition in schizophrenia have highlighted the importance of attribution style (the ability to correctly assign causes of events) in social cognition, as this ability is impaired in schizophrenia, and seems to contribute to the paranoia often present in the disorder (Penn et al., 2008). In contrast, studies of social cognition in autism have often examined imitation, as this skill is often impaired in autism (Hamilton, Brindley, & Frith, 2007).

One way of defining the aspects of social cognition has been by classifying them into more basic and more advanced processes. Blakemore and Frith (2004) propose that social cognition comprises both the more basic processes that we share with other species, and higher level processes that are arguably uniquely human. They hypothesise that the lower level processes include the perception of basic emotions, eye gaze,

biological motion, and goal directed action and agency. The higher level processes are hypothesised to include imitation, theory of mind (ToM), interpretation of complex emotions, empathy, and morality. This theory has been developed from the evolutionary theory of the "social brain", that is that our relatively large brains have evolved for social interaction and understanding that has given us an advantage that allowed our success as a species (Brothers, 1990).

A number of aspects of social cognition have been discussed in the literature, including imitation, affect recognition and processing, attribution style, social perception and knowledge, empathy, ToM, and affective decision-making (Adolphs, 2006; Green et al., 2005; Samamé, Martino, & Strejilevich, 2012). There is potential overlap between some of these concepts, and a discussion of all these is beyond the scope of this thesis. Instead, three core aspects of social cognition, which have been consistently studied in both schizophrenia and bipolar disorder, will be discussed in the following section: affect recognition, empathy, and ToM.

Aspects of Social Cognition

Affect recognition

Affect recognition refers to the ability to perceive and understand emotions in others. Emotion can be perceived through facial expression, voice prosody, and body language. This ability is important for social interaction as it allows individuals to detect subtle emotional cues from others and alter their behaviour accordingly (Green et al., 2005). Most commonly emotion recognition has been measured via the ability to recognise facial affect. Ekman and Friesen (1976) developed the most widely used stimuli to measure facial emotion recognition, which consists of black and white

photographs of universally recognised (basic) emotions: happiness, sadness, anger, disgust, fear and surprise. More recently, in an attempt to achieve more ecological validity, sets of colour photographs which include actors of different races (Tottenham et al., 2009), video stimuli where the actor expresses the emotion dynamically (McDonald, Flanagan, Rollins, & Kinch, 2003), and virtual reality stimuli (E. Kim et al., 2009) have also been used.

Empathy

Empathy is another key area within the social cognition domain, and refers to the reactions of one individual to the observed experiences of another (Davis, 1983). Originally a lay term, there has been much debate over the exact definition of empathy, and whether it itself is a unitary concept or comprised of dissociable abilities (Blair, 2005). Some researchers argue that it can involve an intellectual reaction to another's experience, which involves understanding another's perspective (cognitive empathy), while others argue empathy is an emotional reaction to another's situation (affective empathy) (Davis, 1983). It has been argued that the description of cognitive empathy as the ability to take another person's perspective is very similar to the concept of ToM, and in fact some researchers use the terms cognitive empathy and ToM interchangeably (Derntl, Seidel, Schneider, & Habel, 2012; Rogers, Dziobek, Hassenstab, Wolf, & Convit, 2007). One of these researchers is Blair (2005), who argues that cognitive empathy is synonymous with ToM, and that this skill is independent of affective empathy and motor empathy, which he characterises as the ability to imitate others. While previous researchers have theorised that cognitive empathy is a necessary precursor to affective empathy, Blair gives evidence of dissociation between these two abilities, using

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the disorders of psychopathy (where cognitive empathy is intact but affective empathy impaired) and autism (where affective empathy can be intact but cognitive empathy is impaired). This supposition is supported by imaging studies (Pineda, Moore, Elfenbeinand, & Cox, 2009).

Self-report measures have primarily been used to assess levels of empathy in individuals, and these measures reflect the divergent definitions of empathy. The two major tests that are currently used are the Interpersonal Reactivity Index (IRI; Davis, 1983) and the Balanced Emotional Empathy Test (Mehrabian, 2000). While the Balanced Emotional Empathy Test is primarily a measure of affective empathy, the IRI is based on a multi-dimensional approach to empathy, and so measures both affective and cognitive components of empathy. It has four subscales that measure perspective taking, fantasy seeking, empathic concern, and personal distress. Perspective taking and fantasy seeking are related to the concept of cognitive empathy, while empathic concern and personal distress are related to the concept of affective empathy. Given that self-report measures of empathy are not always reliable (due to inaccurate self-perception or reporting biased by perceptions of social desirability) researchers have also incorporated more physiological techniques, including imaging, EEG, galvanic skin response, and rapid facial mimicry into empathy research. For example, studies have examined brain activation while watching stimuli designed to elicit an empathic response (e.g., while watching a needle being inserted into the hand) in both healthy and clinical populations (Avenanti, Bueti, Galati, & Aglioti, 2005; Singer et al., 2004). The inherently subjective nature of empathy, however, makes the interpretation of physiological measures somewhat difficult, as

physiological changes in response another's distress can be for reasons other than empathy.

ToM

ToM (also known as mentalising or mind-reading), is the ability to represent others' mental states and make inferences about their intentions (Repacholi & Slaughter, 2003). The term was first used by Premack and Woodruff, in their seminal paper that explored whether chimpanzees have the ability to ascribe mental states to others (1978). The authors distinguished ToM from empathy; while empathy was described as an individual imagining himself or herself in another's place and thinking what they would do, ToM was described as an individual imputing intention or knowledge to another, and using that information. However, the authors acknowledged that empathy and ToM have many similarities. While Premack and Woodruff speculated that chimpanzees may have a ToM based on behavioural research, more recent researchers have questioned this evidence and argued that humans are likely the only species to have this advanced form of social cognition (Povinelli & O'Neill, 2000).

Early ToM studies explored the ability in a developmental context. Wimmer and Perner (1983) tested the age at which children develop the ability to understand deception using a paradigm of false-belief. Children were introduced to two characters (for example, Sally and Anne), one of which has a false-belief about the world, or another character's beliefs, depending on the level of complexity being measured (Perner & Wimmer, 1985; Wimmer & Perner, 1983). These levels are referred to as first-, second-, and higher-order belief understanding. First-order belief understanding involves an individual understanding that others can have false beliefs about the world, and can have

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beliefs that are different to their own. Second-order belief understanding is when an individual understands that others can have beliefs about other people's beliefs, (e.g., "he believes that she believes…"), and higher-order belief understanding is more advanced again, "he believes that she believes that he believes..." (Perner & Wimmer, 1985). Experiments with false-belief tasks demonstrated that first-order ToM is usually developed by age 4, while second-order ToM is generally developed by 8 years (Perner & Wimmer, 1985; Wimmer & Perner, 1983). Following studies in normally developing children, researchers began to wonder if children with autism, who had difficulties socially, were impaired on ToM tasks. Baron-Cohen, Leslie and Frith (1985) were the first to explore ToM in children with autism. Using a false-belief task, they showed that the children with autism did have specific difficulties with ToM tasks that were independent of any cognitive dysfunction. The finding of impaired ToM in autism spectrum disorders (ASD) is one of the most consistent in the ToM literature (Baron-Cohen & Goodhart, 1994; Baron-Cohen, Jolliffe, Mortimore, & Robertson, 1997; Baron-Cohen et al., 1994; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001; Happe, 1994; Welsh, Ray, Weeks, Dewey, & Elliott, 2009)

Since then, ToM has also been explored in a number of adult populations, such as those with psychiatric or neurological disorders, or those with specific brain lesions (Baron-Cohen et al., 1997; Frith & Corcoran, 1996; Kosmidis, Aretouli, Bozikas, Giannakou, & Ioannidis, 2008; Tager-Flusberg & Sullivan, 2000). In order to test ToM in adults, researchers generally adapted tasks that had been used in children, or created new tasks with face validity. A number of tasks have been developed which involve the individual understanding stories that involve hinting, irony, metaphor and faux pas

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(Harrington, Siegert, & McClure, 2005; Pickup, 2008; Stone, Baron-Cohen, & Knight, 1998). A move away from verbal story based ToM tasks was the sequencing task, which that involves inferring a character's intention and choosing the most likely card to complete comic strip sequences (Brunet, Sarfati, Hardy-Bayle, & Decety, 2000; Sarfati, Hardy-Bayle, Brunet, & Widlocher, 1997). Another task, which had a different approach, was the Reading the Mind in the Eyes task ("Eyes task"; Baron-Cohen et al., 1997). The original Eyes task involved 25 black and white photos of eyes showing different facial expressions, cut from magazines. The task was designed specifically for use in an autistic population and so used only the eyes to minimise distractions from other parts of the face. Each photo was presented for 3 seconds, and participants were asked to select from two alternate, opposite, mental state terms. Since then the Eyes task has been revised to improve its validity, by lengthening the test and including four multiple choice options, instead of the original two (Baron-Cohen et al., 2001).

Because of the origins of the research, ToM has most often been explored using measures designed initially for children, and the validity of these measures in adults has been challenged (Repacholi & Slaughter, 2003). Further, often the ToM measures have been used without testing for construct validity, leading to the possibility that some of the measures used may have face validity but lack ecological validity (Harrington et al., 2005; Penn & Corrigan, 2001). For example, one study used fMRI to compare brain activation during two ToM tasks, a false-belief task and a task that involves interpreting geometric shapes that depict social interactions, and found that they activated different areas of the brain. The researchers speculated that they are actually measuring different

processes (Gobbini, Koralek, Bryan, Montgomery, & Haxby, 2007), something which is not necessarily evident in behavioural studies of ToM.

Recently, researchers have recognised that ToM involves processes that can be affective (recognising emotional cues) or cognitive (using verbal or non-emotional body language cues), and that these processes may be dissociable (Shamay-Tsoory, Aharon-Peretz, & Levkovitz, 2007; Shamay-Tsoory, Shur, Barcai-Goodman, et al., 2007). One task that enables the dissociation of affective from cognitive ToM is the "Yoni task". The Yoni task is a cartoon computer based task that involves mental state attribution based on verbal and eye gaze cues (cognitive component), as well as emotional expression (affective component) (Shamay-Tsoory & Aharon-Peretz, 2007). Research using this task in groups with specific brain lesions, and also in individuals with schizophrenia, has indicated that affective and cognitive ToM processes are dissociable (Shamay-Tsoory & Aharon-Peretz, 2007; Shamay-Tsoory, Aharon-Peretz, et al., 2007; Shamay-Tsoory, Shur, Barcai-Goodman, et al., 2007). Recent research has explored affective and cognitive aspects of ToM in clinical populations (Montag et al., 2011; Montag et al., 2010), but more research is needed to allow greater understanding of these ToM processes and how they might be differentially affected in diverse populations.

Social Cognition as a Unitary Concept

While different aspects of social cognition have been shown to be distinct from a behavioural perspective, recent evidence discussed later in this chapter indicates that the different social cognitive abilities involve some shared underlying neural networks and similar cognitive processes (Adolphs, 2001; Amodio & Frith, 2006). Despite the

development of better techniques for understanding the different elements of social

cognition, how we actually form and use these skills is still in dispute.

Theories of Social Cognition

Currently, there are two major theoretical conceptualisations of how human

beings understand others: theory theory (TT) and simulation theory (ST) (Brune, 2005b;

C. E. Kerr, 2008). While TT focuses on the advanced aspects of social cognition,

specifically ToM abilities, ST also accounts for the more basic aspects of social

cognition. In recent years a substantial body of literature has tackled the question of

which theory is supported better by the available evidence.

Theory theory

TT is a meta-representational model of mentalising, in which an individual

develops "hypotheses" about another's mental state using higher-order reasoning (Brune,

2005b; Frith, 1992). Theory theorists refer to this kind of mentalising as a kind of "folk

psychology", where children develop representations about the world, and then revise

them as new evidence becomes apparent to them that contradicts their current

conceptualisations (Gopnik, Capps, & Meltzoff, 2000). These theories about the world

are argued to be implicit, so that an individual is not aware that they have them. A

number of different versions of TT have been developed.

Based on Fodor's modular view of brain organisation (1983) and observations

from autism, some earlier theorists argued there must be theory of mind module "ToMM"

in the brain, solely responsible for mental state attributions (A. M. Leslie & Roth, 1993;

A. M. Leslie & Thaiss, 1992). These theorists argued that because autism is a developmental disorder, and social deficits are evident from a very early age, the ToMM must be innate and separate from other forms of cognition and intelligence. Like language or the visual system, proponents of a ToMM proposed that a particular region in the brain must be genetically programmed to develop into a specialised meta-representational area, and that this ability is fixed throughout life.

More recently, influenced by increasing knowledge of neural networks from imaging studies, proponents of TT have moved away from a modular view, towards a network view (Kennedy & Adolphs, 2012). For example Gopnik, Capps and Meltzoff argue that while human beings have an innate capacity for ToM, this capacity is related to a more general ability to theorise, and that rather than being located in a specific region in the brain, it is distributed throughout the brain (Gopnik et al., 2000). These authors argue that there are two kinds of innate structures in the brain that allow for ToM: initial theories and an innate theory-formation system. They postulate that babies are born with innate initial theories, which are modified over time using the theory-formation system. They argue that either, or both, of these structures can be dysfunctional. Gopnik et al. (2000) cite evidence from autism research that has shown that some autistic children have trouble forming theories about anything, mental states or otherwise, which could be a sign that the theory-formation system is not working properly. Research into ToM deficits in other disorders have also added to TT. Following a review of ToM literature, Corcoran proposed that ToM involves both the cognitive skills of if-then conditional reasoning and autobiographical memory (Corcoran, 2001).

The TT view that individuals predict mental states based on theory-based reasoning has been criticised for a number of reasons. First, critics argue that TT is too complex to account for the automatic, instinctual way that human beings appear to understand others, and does not explain the emotional element in understanding others (Heal, 1995). Another criticism is that children are able to make predictions about others' intentions and actions well before they are able to explain how they arrived at the prediction, making it unlikely that they are using theory based reasoning to make the prediction, implicit or otherwise (Freeman, 1995). Further, some critics argue that if ToM is based on cognitive if-then conditional reasoning, it does not explain how social cognition can be dysfunctional, independent of other types of intellectual functioning. Some researchers argue for a simpler explanation, and one that also explains other aspects of social cognition: a theory based on mental simulation.

Simulation theory

Proponents of simulation theory (ST) posit that mental states in others are understood by attributing mental states to oneself, through replicating or mirroring the mental life of others on a neural level (Gallese & Goldman, 1998; C. E. Kerr, 2008). Proponents of this theory, also called embodied simulation, argue that human beings' understanding of the mental states of another person are direct and automatic, and therefore involves more of a perceptual process, rather than a cognitive one. This concept was first proposed in the early 20th century by philosophers who discussed it as part of phenomenology, such as Merleau-Ponty (1962) and Husserl (1913) (cited in Welton, 1999). Proponents of phenomenology argued that we understand others through our own

perceptions and experiences. Merleau-Ponty wrote: "When I turn towards perception, and pass from direct perception to thinking about that perception, I reenact it" (Merleau-Ponty, 1962, p. 351). He also suggested this social cognition was an automatic process, citing babies' automatic imitation of others as evidence that it is not conscious reasoning which allows for our understanding of other people. More recently, this concept of social cognition has re-emerged due to the discovery of mirror neurons in the premotor cortex of the macaque brain, which are active both when an action is carried out, and when that same action is merely observed (Gallese, Fadiga, Fogassi, & Rizzolatti, 1996; Gallese & Goldman, 1998). The fact that mirror neurons were first identified in primates, and later found in humans, provided a potential link that between the more basic social cognition of primates, and how that might have evolved into the more advanced ToM skills that human beings take for granted (Gallese & Goldman, 1998). In their recent model of empathy, Pineda, Moore, Elfenbeinand and Cox (2009) conceptualise social cognition as a hierarchical model of mirroring, with more basic processes laying the foundation for more advanced processing. In the authors' framework of mirroring and social cognition, automatic mirroring processes such as motor contagion, motor empathy and mimicry are more fundamental in the hierarchy, emotional empathy is more advanced, and at the top of the hierarchy lies theory of mind and cognitive empathy.

ST has been criticised for a number of reasons. First, critics ask how individuals are able to predict what the beliefs, desires and behaviours might be for people very different to ourselves (Davies & Stone, 1995). ST is also criticised for being based on circular logic. Critics argue that because ST is based on an individual imagining him or herself in another's place, any attempt to simulate another person's mental state must

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involve knowledge of another's mental state to start with. The critics ask where that knowledge of the other's mental state came from that is used in the simulation? Proponents of TT argue that the mental state knowledge comes from ToM (Borg, 2007; Fuller, 1995).

TT and ST: Compatible or Mutually Exclusive?

Some researchers have suggested that a combination of both TT and ST could account for social cognition, distinguishing between the perceptual and the cognitive elements of social cognition, and suggesting that ST and mirror neurons could account for the perceptual process, but that the cognitive process employs other parts of the brain (Pineda & Hecht, 2009; Van Overwalle & Baetens, 2009).

Research into children with ASD and Williams Syndrome have supported a dissociation between these two elements of social cognition, as children with ASD tend to be impaired on both emotion processing and ToM, but children with Williams Syndrome appear to be impaired only on ToM (Tager-Flusberg & Sullivan, 2000). Recent research has investigated mirror system activation in healthy adults and has supported this distinction between the two types of social processing. They found mirror systems were most active when participants were completing an emotion processing task, and less active when participants completed a cartoon sequencing task designed to measure ToM (Pineda & Hecht, 2009). Further, Salvatore, Dimaggio, and Lysaker (2007) analysed TT and ST in light of a case study of a patient with schizophrenia who suffered from ToM deficits. Rather than lacking a ToM, or having impaired reasoning abilities, the patient had many theories of other people but could not accurately predict which was

the most correct. The authors argue that the best model for these social cognitive deficits is a faulty simulating system, but intact higher-order reasoning. While this evidence supports dissociation between these two processes that contribute to ToM, it does not indicate that simulation is purely empathy, as the patient "Alberto" was struggling to make cognitive inferences, despite having apparently intact higher-order reasoning.

Neural Substrates of Social Cognition

As the behavioural aspects of social cognition have been increasingly studied, interest has grown in the neural mechanisms of social cognition, to the point where recently a new discipline has been conceived: social cognitive neuroscience (Singer, 2006). Despite this, research into the neural substrates of different aspects of social cognition is still in its infancy, and has been primarily explored to date using correlational imaging techniques (Benedetti et al., 2009; Fletcher et al., 1995; K. R. Leslie, Johnson-Frey, & Grafton, 2004; Ohnishi et al., 2004; Vogeley et al., 2001; Vollm et al., 2006).

Evidence from functional imaging and lesion studies exploring the recognition of facial emotion, in contrast to face processing, indicates that right somatosensory cortices are particularly implicated (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Adolphs & Tranel, 2003; Pitcher, Garrido, Walsh, & Duchaine, 2008). In addition, recognising angry and fearful facial expressions also activates the amygdala (Adolphs & Tranel, 2003).

The neural substrates of empathy have recently been explored in a number of studies. Singer et al. (2004) investigated the regions of the brain involved in empathy for pain using fMRI, and found that parts of the limbic system, including the anterior insula (AI) and rostral ACC, as well as the brainstem and cerebellum, were activated both when

experiencing pain and empathising with another's pain. They also found that activity in the AI and ACC correlated with the participants' empathy scores. Other regions that were involved in perceiving pain, such as the somatosensory and sensorimotor cortices, and caudal ACC, were not found to be involved in empathy. The researchers concluded that the parts of the pain network involved in the affective, but not the sensory, aspects of pain were implicated in empathy. However, another study used a potentially more sensitive measure of brain function, transcranial magnetic stimulation (TMS), to measure activity in the sensorimotor part of the pain network, and found it was also involved in empathy for pain. In this study, participants watched videos of needles being inserted into hands and feet, which were designed to elicit empathic reactions, and measured the corticospinal motor representations of hand muscles (Avenanti et al., 2005). The authors found that the corticospinal motor neurons for the hand were inhibited when participants viewed the painful stimulus, which was similar to the reaction of neurons during the actual experience of pain. The authors concluded that the motor system is an important part of the neural network involved in registering empathy. This finding supports the simulation theory of social cognition.

Leslie, Johnson-Frey and Grafton (2004) investigated the neural substrates of imitation and empathy using fMRI, and also found sensorimotor areas to be implicated. Leslie et al. found that the passive viewing of facial emotion activated the right ventral premotor area, whereas imitation triggered bilateral activation. Other areas found to be implicated in imitation included Broca's area (left inferior frontal gyrus), right superior temporal gyrus, supplementary motor area (SMA), posterior temporo-occipital cortex, and cerebellar areas.

The first brain region to be implicated in ToM processing was the orbitofrontal cortex (OFC). Baron-Cohen and colleagues explored the neural substrates of ToM in healthy adults using SPECT imaging (1994). The study involved participants reading words and identifying them as mental state words or non-mental state words. A region of interest technique was utilised in analysing the imaging data, and the right OFC had a higher blood flow level when participants thought about mental state words, compared to a control area, the frontal polar cortex. This study was limited in that it used a region of interest analysis, that is, only the OFC was analysed for activation, and so other areas were not considered. Further, the mental state recognition task had not previously been used as a ToM task, and as it did not explicitly involve subscribing ToM to others, it is difficult to know how valid it is as a measure of ToM.

Fletcher et al. (1995) used the more sensitive PET imaging to study the neural correlates of ToM in 6 healthy adults while they completed a story comprehension ToM task. The researchers looked at the pattern of activation across the whole brain, rather than examining only a region of interest, and did not find a significant increase in orbitofrontal activation compared to the control conditions. Rather, a higher level of activation was observed in the medial prefrontal cortex (mPFC) (Brodmann's Area 8), and anterior and posterior cingulate cortices (ACC/PCC).

Castelli, Happe, Frith and Frith (2000) also used PET to study brain activations of 6 participants while they watched animations with intentional movement patterns, designed to evoke ToM, compared to control animations. Similar to Fletcher et al. (1995), Castelli et al. found increased activation in the mPFC in the ToM animations. They also found

significant activation of the temporo-parietal junction (TPJ), including the superior

temporal sulcus (STS), the basal temporal regions and the extrastriate cortex.

As studies implicated more brain areas in ToM processing, researchers began to

speculate about the specific roles of each region. Vogeley et al. (2001) explored whether

representing self and other mental states utilized the same or different neural networks.

The researchers found that activities designed to elicit thoughts of self mental states

activated the right TPJ, including the inferior parietal lobule (IPL) and parietal

operculum, while thoughts of other people's mental states led to increased activity in the

ACC and left temporopolar cortex. Both self and other representations also activated the

ACC, but in different patterns of activation. A significant interaction between the self and

other mental representations was observed in the right prefrontal cortex.

Many of the recent studies of the neural substrates of social cognition have looked at

particular processes in isolation, and have not explored the connectivity between

implicated regions. A few studies, however, have compared different aspects of social

cognition and their neuroanatomical correlates from a network perspective. Vollm et al.

(2006) used both ToM and empathy stimuli to test patterns of fMRI activation. The

researchers found overlapping but distinct neural networks. The overlapping areas

included the mPFC, TPJ, and temporal poles. Empathy activated the paracingulate, ACC,

PCC and amygdala. ToM activated the lateral OFC, middle frontal gyrus, cuneus and

superior temporal gyrus.

In his review of the neural substrates of theory of mind, Abu-Akel (2003) presents

a potential model of TOM processing that has distinct areas of processing for self mental

states, other mental states, and areas that allow integration of the two for full

understanding of ToM. The author suggests that information pertaining to other's mental states are first represented in the IPL and STS regions, passed to paralimbic and limbic structures such as the ACC for emotional processing and integration of this emotional information with incoming sensory information. This information is then relayed to dorsal and lateral regions of the PFC where conscious interpretation takes place, and decisions regarding the information are executed. This model does not mention, however, the medial frontal cortex, which has been shown to be involved in social cognitive processing, and in fact has been argued to be the most important region in social cognition (Amodio & Frith, 2006).

Pineda et al. (2009) also propose a neuroanatomical circuit underlying social cognition. Their model is based on ST, and the mirror neuron system, and is hierarchical in nature. In the authors' model, social information is first received via primary and association visual and auditory cortices. Emotional information is automatically registered in the amygdala, and information regarding intentions of actions is passed through to the STS. Information then travels from the STS to mirror neurons in the IPL and inferior frontal cortex (including Broca's Area and the lateral OFC), and then onto further neurons with mirror like properties in the AI and premotor areas. Information in the AI is sent to the ACC and mPFC, which is combined with information sent from the amygdala to integrate the cognitive, motor and affective elements of social cognition. This model places mirror neurons at almost every level of the social cognitive neural circuitry, and while some studies have supported the key role mirror neurons play in social cognition (Ohnishi et al., 2004; Schulte-Ruther, Markowitsch, Fink, & Piefke,

2007), further research is needed to validate this model, and the role of the mirror

systems in general.

Chapter 4: Mirror Systems

Overview

Since their discovery two decades ago, mirror neurons have excited scientists because they offer a potentially simple and intuitive explanation for how humans understand others. In humans, invasive methods of assessing mirror systems are generally not ethical, so a number of other non-invasive techniques have been designed to putatively measure mirror systems. Some research has now also begun to explore potential relationships between mirror systems and social cognitive measures. The current chapter provides an introduction to mirror systems, outlines the primary measures of mirror systems in humans, and reviews the literature exploring mirror systems and social cognition.

Introduction to the Mirror System

Mirror neurons, neurons that respond both when a particular goal-directed action is undertaken and when a similar action is observed, were first discovered in the ventral premotor cortex (area F5) of the macaque monkey (Gallese et al., 1996; G. Rizzolatti, Fadiga, Gallese, & Fogassi, 1996). These neurons were first thought to be purely motor neurons, that were specialised to fire differentially to different goal-directed actions, such as holding, grasping, and bringing food to the mouth (G. Rizzolatti et al., 1988). Di Pellegrino et al. discovered that some of these neurons would fire in area F5 both when the monkey carried out a specific action (for example, grasping a peanut) and when the monkey observed the experimenter carrying out the same action (Di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992). Two types of these so-called mirror neurons were

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discovered. *Strictly congruent* mirror neurons were those that would discharge for the same action, either executed or observed. *Broadly congruent* mirror neurons would, in addition, discharge for actions that were either logically related, or achieve the same goal (Gallese et al., 1996). The broadly congruent mirror neurons were twice as populous as the strictly congruent mirror neurons. The neurons wouldn't fire with the hand on its own, or the target on its own, indicating that it was the goal-directed action, rather than the movement per se, that was important. Another finding related to the mirror neuron system was that these neurons would not only respond to the sight of the goal-directed action, but also the sound related to it (for example, the sound of paper tearing) (Kohler et al., 2002). This discovery indicated that these neurons were important for understanding the meaning of actions.

Fadiga, Fogassi, Pavesi and Rizzolatti (1995) used TMS to putatively test whether mirror neurons were present in humans, and found the same pattern of activation that had been detected in the monkey experiments. That is, they found a pattern of increased activity in the motor areas during the observation and execution of goal-directed hand actions, but not during observation of the control movements.

More recent research has found that neurons with mirror properties appear to be present in a number of areas of the brain. fMRI has been used in a number of studies to explore these "mirror systems", and has indicated that the regions with mirror properties are found in the caudal section of the inferior frontal gyrus (pars opercularis), the inferior premotor cortex (Brodmann's Area 44), parts of the parietal cortex including the IPL, and the STS (Brune et al., 2008; Iacoboni & Mazziotta, 2007; Malhi et al., 2008; Malhi et al., 2007; Montgomery & Haxby, 2008; Schulte-Ruther et al., 2007). Together, these areas

are known as the mirror system. Furthermore, regions with mirror-like properties have been found in other areas of the brain associated with the perception of stimuli, for example in the insula, where neurons fire both when experiencing disgust and watching others experience the emotion (Wicker et al., 2003).

Measuring Mirror Systems

While single-unit recordings using implanted electrodes have been used to measure mirror neuron activity in macaque monkeys, this method is too invasive for use in humans. In humans, the mirror system has been indirectly measured using a number of non-invasive methods, including stimulation, electrophysiological, and imaging methods (G. Rizzolatti & Craighero, 2004).

The first way the mirror system was tested in humans was using single pulse TMS (Fadiga et al., 1995). TMS is a non-invasive technique that involves indirect electric stimulation of the cortex via a magnetic coil. Based upon Faraday's principle of electromagnetic induction, a rapidly changing magnetic field is generated by passing a very brief high-current alternating electric pulse through an insulated wire coil (Haraldsson, Ferrarelli, Kalin, & Tononi, 2004). When the coil is placed against the scalp, the magnetic field passes through the skull and induces a weak electrical current, which can induce an action potential. When an appropriate stimulation intensity is applied to an area of the motor cortex, motor-evoked potentials (MEPs) can be recorded from contralateral extremity muscles that correspond to that area of the motor cortex (e.g., the muscles of the hand). When mirror neurons in the IFG/premotor cortex are active (e.g., when observing someone complete a goal-directed action with their hand), this increases the neural inputs into the motor cortex, increasing the excitability of the

motor cortex, which when stimulated results in larger MEPs in the distal muscles of the hand (Enticott, Hoy, et al., 2008; Enticott, Johnston, Herring, Hoy, & Fitzgerald, 2008). The level of muscle activity can be recorded via electromyogram (EMG). Single pulse TMS is generally safe and well tolerated (Rossi, Hallett, Rossini, & Pascual-Leone, 2009).

Another common method used to measure mirror system activity is via electroencephalogram (EEG). At rest, sensorimotor neurons spontaneously fire in synchrony, leading to large amplitude EEG oscillations in the mu frequency band (alpha: 8-13 Hz and beta: 15-20 Hz) (Oberman et al., 2005). When an action is performed, these neurons fire asynchronously, resulting in decreased power of the mu-band oscillations, known as mu suppression. Similar to the pattern seen in single-unit recordings in macaques, mu suppression has been found to be stronger when executing an action, compared to merely observing an action (Woodruff & Maaske, 2010). Mu power recorded from scalp electrodes at locations C3, CZ, and C4 of the International 10-20 system of electrode placement is suppressed during both the execution and observation of actions, indicating that mu rhythm is related to frontal mirror system activity (Oberman et al., 2005; Pineda, 2005).

Imaging techniques, such as positron emission tomography (PET) and fMRI have also been used to measure activity in the mirror system (Brunet et al., 2000; Kaplan & Iacoboni, 2006; Montgomery & Haxby, 2008; Ohnishi et al., 2004). These techniques are important as they allow researchers to examine brain activity in a holistic manner and see patterns of brain activation. A limitation of imaging techniques, however, is that although they have good spatial resolution, they generally have poor temporal resolution.

Despite good evidence that these measures provide insights into mirror neuron function, little research has explored if they are all reliably measuring the same construct. One study investigated single-pulse TMS and mu rhythm EEG as measures of mirror system function in the primary motor cortex and found that while they both seemed independently to measure mirror system function, they did not correlate in individuals as was expected (Lepage, Saint-Amour, & Theoret, 2008). The authors speculated that the two measures might be detecting distinct processes, that is, the TMS induced MEPs might reflect motor activity, whereas mu rhythms might signify the sensory aspects of the motor resonance system. More studies are needed, however, to further compare the different measures, and to better understand exactly what aspect of brain function the different techniques are testing.

Mirror Systems and Social Cognition

As well as mirror neurons responding both to the execution and observation of an action, research with macaque monkeys also indicated that mirror neurons respond to the goal of an action, rather than the action itself (Fogassi et al., 2005). Fogassi et al. studied individual mirror neurons in the inferior parietal lobule of the macaque monkey. They trained the monkey to grasp a piece of food either to eat, or to place it in a container. The hand movement to grasp the food was the same regardless of the condition, yet the mirror neurons fired differentially depending on the subsequent goal of the grasping. Studies of mirror neurons in humans have found that they too code for intention of an action, rather than the action itself (Iacoboni et al., 2005; Kaplan & Iacoboni, 2006). Iacoboni et al. (2005) used fMRI to study patterns of neural activation in 23 participants while they watched video clips. The clips were either of a hand grasping action without a context

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(action condition), scenes containing objects with no action (context condition), and hand grasping actions in two different contexts (intention condition). The intention condition was the only condition with enough information to understand the probable intention of the hand grasping (either for drinking or for cleaning). In the premotor mirror neuron areas, a significantly larger activation was observed in the intention condition, compared to the other conditions. Furthermore, the drinking intention condition yielded significantly higher activation than the cleaning intention condition, indicating that the two different intentions implied in the context were being differentially coded in the mirror system.

The finding that the mirror system appears to code for the intention of an action, whether it be one's own action, or another's action, led researchers to speculate that the mirror system may be related to social cognition (Hamilton et al., 2007; Lepage & Theoret, 2007; Oberman & Ramachandran, 2007; Giacomo Rizzolatti & Fabbri-Destro, 2008; Schulte-Ruther et al., 2007). Gallese and Goldman (1998) suggested that mirror neurons could support the simulation theory of social cognition, as the mirror system offers a simple, neurophysiological way that individuals can understand others. This has led to speculation that dysfunction of the mirror neuron system may be responsible for disorders in which social cognitive deficits are a defining characteristic, such as ASD (Dapretto et al., 2006; Iacoboni & Mazziotta, 2007; Oberman & Ramachandran, 2007; Welsh et al., 2009). Oberman et al. (2005) examined mirror system function in participants with high-functioning ASD using EEG. Mu suppression was measured in ten participants with ASD and ten control participants while they watched videos of a moving hand, a bouncing ball, visual noise, and while moving their own hand. While mu

suppression was present in control participants when they either moved their own hand, or watched the video of a moving hand, mu suppression was only present in ASD participants when they moved their hand. The absence of mu suppression in participants with ASD during the observation of another hand moving, indicated that the mirror system is dysfunctional in individuals with ASD. Another study, however, did not find a significant suppression of mu rhythms in participants with ASD, despite poor performance on ToM tasks (Avikainen, Kulomaki, & Hari, 1999). The authors concluded that impaired social cognition in ASD was not because of a faulty mirror system. However, the study had a small sample size (5 ASD participants and 8 control participants), and a lack of power may account for the results. In fact, an fMRI study comparing children with high-functioning autism and those who were normally developing found that they performed equally well when imitating and observing emotional expressions, but showed reduced activity in the inferior frontal gyrus (pars opercularis), a key area of the mirror system (Dapretto et al., 2006). The authors also found that this apparent reduction in mirror system activity was related to increased social dysfunction. Recently, studies have found associations between mirror systems and emotion recognition (Enticott, Johnston, et al., 2008), and in schizophrenia, first-order ToM but not second-order ToM (Mehta, Basavaraju, Thirthalli, & Gangadhar, 2012). In contrast, studies have failed to find any relationship between mirror systems and empathy (Enticott, Kennedy, Bradshaw, Rinehart, & Fitzgerald, 2011; McCormick et al., 2012). More research is needed to elucidate the relationships between mirror systems and different aspects of social cognition.

The role of the mirror system in facilitating social cognition has been challenged by a number of researchers (Borg, 2007; Jacob, 2009; Southgate & de C. Hamilton, 2008). Borg argues that rather than facilitating "mind-reading", mirror neurons are more likely to facilitate understanding of action intention. That is, when mirror neurons fire while observing someone reaching to grasp a cup, they may be facilitating understanding that the person is intending to drink (i.e. it is an intentional action), but not *why* they intend to drink (i.e. because they are thirsty). Another criticism of mirror neurons is that they do not, to our knowledge, have a way of distinguishing between whether a goal-directed action is self-generated or generated by another agent (Abu-Akel, 2003). This would make it difficult for mirror neurons to facilitate understanding of others as distinct from ourselves. Further, Gallese and Goldman's (1998) conception of how mirror neuron function underlies social cognition does not allow for a situation where a person is able to attribute mental states to others, but not to themselves, yet there have been cases of individuals with schizophrenia who could perform effectively on ToM tasks, but have trouble with self-attribution. One possibility, however, is that when the mirror systems are not functioning properly, ToM tasks can still be completed, albeit by less efficient neural processes. Given the implication of mirror systems in social cognitive processes, and the observation of social deficits in schizophrenia and bipolar disorder, exploring mirror systems in these disorders is an exciting new avenue for research.

Chapter 5: Social Cognition and Mirror Systems in Schizophrenia and Bipolar Disorder

Overview

Schizophrenia features prominent social deficits, and recent research has indicated they are more prevalent in bipolar disorder than was previously believed (Olley et al., 2005). There is growing evidence for a range of social cognitive deficits in both schizophrenia and bipolar disorder. Some initial research indicates mirror systems may be impaired in these disorders, which might be contributing to these deficits. The following chapter provides a review of social cognition in schizophrenia and bipolar disorder, a summary of research exploring mirror systems in these disorders, and concludes with a synthesis of the literature, and rationale for the current thesis.

Social Cognition in Schizophrenia

In schizophrenia, deficits have been observed in ToM, facial emotion recognition, and empathizing ability (Brune, 2005a; Harrington et al., 2005; Shamay-Tsoory, Shur, Harahi, & Levkovitz, 2007).

Studies examining ToM in schizophrenia have more often found second-order, but not first-order, ToM reasoning to be impaired (Harrington et al., 2005). ToM deficits in schizophrenia appear to be different to those of autism, in that people with schizophrenia make mental state attributions, but people with autism do not. Frith (1992) suggested this is because while people with autism lack meta-representations necessary for ToM, people with schizophrenia have present but faulty meta-representations, and the delusions and paranoia that are common in schizophrenia are a symptom of this problem. Frith and Corcoran (1996) tested ToM ability in people with schizophrenia and found

those with paranoid delusions, and behavioural symptoms, to be impaired in this skill.

They found no significant impairment in those participants with primarily passivity

symptoms, and remitted patients, compared to healthy controls, which supported Frith's

theory of ToM in schizophrenia. However, other studies have found that remitted

patients, individuals with ultra high risk of developing schizophrenia, and even relatives

of schizophrenia sufferers show reduced performance on more advanced social cognitive

tasks, compared to the general population (Chung, Kang, Shin, Yoo, & Kwon, 2008).

This indicates that social cognitive deficits are trait, rather than state deficits, which may

become worse during the acute phases of the disorder. Some researchers have suggested

that those with primarily positive symptoms may make a one type of ToM error (e.g.,

faulty mental state attributions, so-called "over-mentalising"), whereas those with

primarily negative symptoms may make ToM errors due to "under-mentalising", that is,

reduced or absent mental state attributions (Montag et al., 2011). Recently, studies have

begun to examine whether affective and cognitive ToM is differentially affected in

schizophrenia. Two studies using the computer based Yoni task found evidence for

reduced affective ToM, but not cognitive ToM in schizophrenia (Shamay-Tsoory,

Aharon-Peretz, et al., 2007; Shamay-Tsoory, Shur, Barcai-Goodman, et al., 2007), but

one recent study using video-based stimuli found evidence for reductions in both

emotional and cognitive ToM in the disorder (Montag et al., 2011). These conflicting

findings indicate the need for further research into this area.

Less research has explored empathy in schizophrenia. A number of studies using

the self-report IRI have found that cognitive empathy, but not affective empathy, to be

impaired in this disorder (McCormick et al., 2012; Montag, Heinz, Kunz, & Gallinat,

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2007; Shamay-Tsoory, Shur, Harahi, et al., 2007; Sparks, McDonald, Lino, O'Donnell, & Green, 2010). One study, however, has found schizophrenia patients to be reduced on another measure of affective empathy (Shamay-Tsoory, Shur, Harahi, et al., 2007)

Reductions in facial emotion processing have been found in schizophrenia (Brune, 2005a; Mandal, Pandey, & Prasad, 1998). In a review of emotion recognition studies in schizophrenia, patients in all studies showed overall deficits in emotion processing, however, a number of studies identified a selective deficit in recognising negative emotions (Mandal et al., 1998). While some researchers argue that individuals with schizophrenia have an impairment specific to negative emotions, others argue that the negative emotions used in the studies were more difficult to identify than the positive emotions, and therefore this distinction was due to task difficulty (Mandal et al., 1998). Research into face processing has indicated that while healthy individuals rely on holistic, configural processing to recognise faces, people with schizophrenia tend to rely on individual facial features (Joshua & Rossell, 2009), indicating that altered face processing might contribute to emotion recognition difficulties. Given that individuals with schizophrenia also have difficulty with recognising affective prosody (Hoekert, Kahn, Pijnenborg, & Aleman, 2007), it is likely that some general emotion deficits are present in the disorder. Nevertheless, the relationships between emotion and face processing, and other types of social and general cognition, have not yet been fully explored.

While a number of social cognitive deficits have been established in schizophrenia, the reasons for these deficits are under debate. Research has consistently found that general cognition, especially aspects of executive functioning, including

higher-order attention, working memory, set-shifting and strategic planning, are impaired in people with schizophrenia. Some researchers have argued that these deficits may account for the social cognitive problems this population experiences (Langdon, Coltheart, Ward, & Catts, 2001). As people with schizophrenia have been found to have biases in terms of remembering episodes in their life, and lowered cognitive performance, Corcoran and Frith suggested that problems with conditional reasoning and autobiographical memory could account for their poor performance on social cognitive tasks, particularly ToM tasks (Corcoran, 2001; Corcoran & Frith, 2003). However, one case study highlighted another possibility: that the mirror system is not working properly in people with schizophrenia. This study indicated that patients utilise alternative networks in order to mentalise, which are less efficient, and somewhat faulty, leading to the misattributions, paranoia and delusions so common in schizophrenia (Salvatore et al., 2007). Further challenging the view that cognitive deficits account for impairments in ToM, a recent review has found ToM and executive functioning to be largely independent (Pickup, 2008). Given many studies have only explored particular aspects of social and general cognition, a more comprehensive investigation into these relationships is warranted.

While the relationship between general cognitive deficits and functional outcomes in schizophrenia has been extensively studied and these have been found to be negatively related (Green, 2006), less research has examined the relationship between social cognition and functional outcome. Nevertheless, recent research examining this relationship have indicated that not only do social deficits have a negative impact on everyday functioning, there are indications that social cognition actually mediates the

relationship between cognitive ability and functional outcome (Bell, Tsang, Greig, & Bryson, 2009; Brune, Abdel-Hamid, Lehmkamper, & Sonntag, 2007; Couture, Penn, & Roberts, 2006). One study has indicated that emotion processing is significantly related to work functioning and independent living in schizophrenia, after controlling for conceptual disorganisation (Kee, Green, Mintz, & Brekke, 2003), indicating that it is an important factor in functional outcomes. However, the study did not consider the impact of other types of social cognition on functional outcomes. One important measure of outcome for patients is quality of life, which is a subjective measure of their current satisfaction with their life, as opposed to objective measures of function, such as employment and independent living. In schizophrenia, reductions have been detected in quality of physical health, psychological well-being, social relationships and environment (Maat, Fett, Derks, & Group Investigators, 2012; Narvaez et al., 2008). To date only one study has explored the relationship between aspects of social cognition (emotion recognition and cognitive ToM) and quality of life in schizophrenia. Improved ToM, along with more severe symptoms, were related to reduced quality of life (Maat et al., 2012). One possibility for these findings is that improved ToM might be associated with better insight into the presence functional issues, and this increased awareness might be leading to reduced satisfaction with current circumstances. Support for this hypothesis comes from studies exploring general cognitive function and quality of life: Improved cognitive function has been associated with poorer perception of quality of life in schizophrenia participants (Kurtz & Tolman, 2011; Narvaez et al., 2008). One other study, however, showed that improvements in emotion recognition were associated with

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self-reported improved quality of social relationships (Sachs et al., 2012). It is clear that the relationship between social cognition and quality of life needs further investigation.

Social Cognition in Bipolar Disorder

There is evidence that individuals with bipolar disorder show reductions in aspects of social cognition.

With regard to emotion recognition, results have been mixed. In euthymic bipolar disorder, some studies have indicated that only selective emotions are reduced, such as fear (Martino, Strejilevich, Fassi, Marengo, & Igoa, 2011), while other studies have found no differences (Hassel et al., 2008; Robinson et al., 2008; Shamay-Tsoory, Harari, Szepsenwol, & Levkovitz, 2009). A recent meta-analysis indicated that reductions are present, but with small effect sizes (Samamé et al., 2012). With regard to empathy, two studies reported that individuals with bipolar disorder reported less perspective taking (cognitive empathy) than healthy controls, but more negative reactions to others in distress (affective empathy) (Derntl et al., 2012; Shamay-Tsoory et al., 2009). This indicates that these aspects of empathy may be differentially affected in the disorder.

An initial study of ToM in both the acute and remitted phases of bipolar disorder, using a cartoon false-belief task, indicated that only patients in the acute phase were impaired (N. Kerr, Dunbar, & Bentall, 2003). However more recent studies, utilising more challenging tasks, have found evidence for subtle ToM deficits even when patients are in remission (Inoue, Tonooka, Yamada, & Kanba, 2004; McKinnon, Cusi, & MacQueen, 2010; Wolf, Brune, & Assion, 2010). Some studies have found euthymic bipolar disorder participants to be impaired only on particular types of mentalising tasks (Donohoe et al., 2012; Olley et al., 2005), indicating that only certain aspects of ToM

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might be reduced in this population. One study assessed ToM in euthymic bipolar

disorder patients using a faux pas task, and found that patients' performance was intact

when asked what went wrong in the story emotionally, but was reduced when asked what

when wrong cognitively (Shamay-Tsoory et al., 2009). This gave an indication that

cognitive ToM, but not affective ToM, might be reduced in this population. Montag et al.

(2010) found evidence for cognitive but not affective ToM reductions in euthymic bipolar

disorder by using a video-based task. In contrast to these findings, two studies have

evaluated ToM abilities in bipolar disorder using the Eyes task, which could be

considered affective ToM, and found impairments (Bora et al., 2005; Donohoe et al.,

2012). It might be that in bipolar disorder, the affective ToM deficits are more subtle, and

the Eyes task is more sensitive for detecting these impairments. These inconsistent

findings indicate that more research is needed into cognitive and affective ToM in

euthymic bipolar disorder.

The relationship between neurocognitive and social cognitive impairments in

euthymic bipolar disorder has been explored in some recent studies. While one study

concluded that neurocognitive impairments might account for social cognitive deficits

(Martino et al., 2011), others have found that social cognitive impairments are at least

partially independent of neurocognitive deficits (Bora et al., 2005; Wolf et al., 2010),

with one possibility being that neurocognitive deficits may contribute to poor function in

some aspects of social cognition in the disorder, but not others.

Overall, reduced social cognition has been associated with poor functional

outcomes in a number of disorders, including schizophrenia and bipolar disorder, and so

understanding what underlies these deficits is of importance (Couture et al., 2006).

Recently, there has been speculation that the social cognitive deficits present in schizophrenia and bipolar disorder may be due to a mirror system deficit.

Mirror Systems in Schizophrenia

Given the hypothesised link between social cognition and mirror systems, some researchers have explored mirror systems as a potential contributor to the social cognitive deficits observed in schizophrenia. One imaging study found that participants with schizophrenia showed abnormal activation of mirror system regions while viewing emotional stimuli (Quintana, Davidson, Kovalik, Marder, & Mazziotta, 2001). A twin study of mu suppression using magnetoencephaology (MEG) found evidence for reduced suppression in schizophrenia patients, compared with their disconcordant twin (Schurmann et al., 2007). Enticott, Hoy et al. (2008) explored whether the mirror system was impaired in schizophrenia using TMS. They applied TMS to the motor cortex and measured motor facilitation during action observation in 15 participants with schizophrenia and 15 healthy control participants. Results showed that in the schizophrenia participants, motor facilitation was reduced, indicating a possible mirror system deficit. The social cognitive ability of these participants was not assessed in this study, however, so the extent to which this mirror system deficit could be related to their social cognition is unknown. Another study (Varcin, Bailey, & Henry, 2010) explored rapid facial mimicry in patients with schizophrenia. Rapid facial mimicry occurs during the observation of faces displaying emotion and happens at an automatic level, and occurs even when faces are presented subliminally. It has been related to the simulation account of empathy and the mirror system. In this study, Varcin and colleagues presented participants with faces showing either happy expressions or angry expressions, and EMG

was used to measure muscle activity on the face. In contrast to the healthy control participants, they found atypical facial mimicry reactions in individuals with schizophrenia. Varcin et al. concluded that this could be related to deficits in the mirror system. Recently, McCormick et al. (2012) used EEG to measure mu suppression as a putative measure of mirror system function, along with cognitive and affective empathy, in 16 participants with schizophrenia (8 with current psychotic symptoms) and 16 healthy control participants. Contrary to expectations, they found that mu suppression was increased in patients with actively psychotic symptoms, compared to healthy controls and patients without current psychotic symptoms. In comparison to controls, the participants with schizophrenia reported higher levels of distress in response to others suffering, and the authors argued that mirror system over-activation in psychotic patients might contribute to their symptoms. In this study, however, psychotic patients showed slightly increased mu suppression in all conditions, not just those designed to elicit a mirror neuron response. This indicated that perhaps rather than an over-active mirror system, psychotic patients might have a generally heightened response to visual stimuli. To date, studies exploring mirror systems in schizophrenia have all had small samples, and limited, if any, measures of social cognition.

Mirror Systems in Bipolar Disorder

Given that some aspects of social cognition are reduced in bipolar disorder, to a similar extent to schizophrenia (Donohoe et al., 2012), it is plausible that mirror system impairments may be present in bipolar disorder. To date, only one study has attempted to study the mirror system in individuals with euthymic bipolar disorder (E. Kim et al., 2009). Kim and colleagues used fMRI to scan 14 patients with euthymic bipolar disorder

and 14 healthy controls while they undertook a virtual reality social cognition task that incorporated both cognitive and affective aspects. They found that while the bipolar disorder patients performed with similar accuracy to healthy controls, their response time was slower, indicating less efficient processing. Further, mirror system regions were less active in the bipolar disorder group compared to the control group. This is the first study to indicate that the mirror system may in fact be dysfunctional in this population, and that this may be related to impaired social cognition. Nevertheless, further research is needed to confirm this finding, and explore a possible relationship between mirror system function and social cognition in the disorder.

Rationale for Thesis

Following is a summary of the information presented in the previous chapters, and outline of the research question for the current thesis:

- Schizophrenia and bipolar disorder are two severe mental illnesses that have poor functional outcomes and quality of life, even during times of symptom remission. The disorders share a number of clinical and epidemiological features, and genetic and neurophysiological research indicates potential overlap between the disorders.
- Social cognition comprises a number of processes that are important for social functioning. While one major theory (theory theory) argues that higher-order reasoning abilities underlie social cognition, another, more recent theory (simulation theory) posits that social cognition is a more automatic process involving simulation on a neural level.

- The discovery of mirror neurons, that respond the same way when a particular goal-directed action is undertaken, and when a similar action is observed, support simulation theory, and has led to speculation that a faulty mirror system could underlie the social cognitive deficits present in a number of disorders.

- Despite a significant body of research indicating that aspects of social cognition are impaired in schizophrenia and bipolar disorder, the exact nature and impact of these deficits, as well as the neuropathology that underlies them, is still not well understood.

- Given the proposed association between social cognition and mirror systems, it is possible that a dysfunctional mirror system may underlie these social cognitive deficits.

- While a few studies of mirror systems have been conducted in schizophrenia or bipolar disorder to date, no study has comprehensively explored mirror systems in both disorders and related these deficits to aspects of social cognition

Therefore, the goal of the current thesis was to better understand the nature and impact of social cognitive deficits in schizophrenia and euthymic bipolar disorder, and comprehensively assess mirror system function as a possible contributor to these deficits.

As such, the specific aims of this thesis are to:

- Assess social cognition in schizophrenia and euthymic bipolar disorder samples, compared to a healthy control group, and relate these deficits to neurocognitive, clinical, and quality of life variables (Studies One and Two).

- Compare mirror system function across the three groups using a multimodal
  approach (using EEG and TMS), and examine any relationships between mirror
  system function and other aspects of social cognition (Study Three and Additional
  Analyses).

Do Social Cognitive Deficits Underpin Reduced Quality of Life in Schizophrenia?

Explanatory Notes

The following chapter comprises a study that has been submitted for publication in Schizophrenia Research. This study comprehensively compared a schizophrenia sample with a healthy control group on a number of aspects of social cognition and quality of life, and examined the relationships between any social cognitive deficits identified with quality of life, neurocognitive deficits, and clinical variables. This is the first time the relationship between a range of social cognitive variables and different aspects of quality of life have been explored in schizophrenia in this level of detail.

Monash University

Declaration for Thesis Chapter Six

Declaration by candidate

In the case of Chapter Six, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Designed the study and protocol, recruited the participants and collected the data. Entered and analysed the data, and interpreted the results. Wrote the manuscript.	85

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Dr Peter Enticott	Advised on study design, recruitment, provided guidance regarding data analysis, advised on draft manuscript	5
Dr Kate Hoy	Advised regarding recruitment, assisted with data analysis, and gave feedback on manuscript	5
Prof Paul Fitzgerald*	Advised on study design, provided guidance regarding recruitment queries, statistical analysis and interpretation. Provided feedback on draft manuscript	5

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	██████████	Date 1/7/13
Main Supervisor's Signature	██████████	Date 1/7/13

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

Do social cognitive deficits underpin reduced quality of life in schizophrenia?

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Abstract:

Individuals with schizophrenia have reduced quality of life, even in the absence of

psychotic symptoms. While previous studies have established relationships between

quality of life and reduced cognitive function in schizophrenia, there is little research

exploring the relationship between social cognition and aspects of quality of life. The

current study aimed to comprehensively investigate social cognitive deficits in

schizophrenia and examine the relationship of these deficits with quality of life, as well

as neurocognition and clinical symptoms. 20 individuals with schizophrenia and 22 age-

and gender-matched healthy controls completed measures of affective and cognitive

ToM, emotion recognition, empathy, quality of life, and neurocognition. Individuals with

schizophrenia showed reduced accuracy on measures of cognitive ToM and recognition

of anger, as well as reduced quality of life in all domains. There was no relationship

between social cognitive deficits and either severity of clinical symptoms or

neurocognitive deficits. Quality of life was not related to social cognitive deficits, but

rather to severity of current symptoms. It is possible that level of insight might be

mediating the relationship between social cognition and quality of life, and this should be

explored in future research.

Keywords:
Schizophrenia, social cognition, affect recognition, theory of mind, quality of life.

1.   Introduction

Outcomes for individuals with schizophrenia are often poor, even during times of symptom remission (Green, 2006; Maat et al., 2012; Narvaez et al., 2008). Health care planners for patients with schizophrenia now recognise the need to measure not only objective measures of functional outcome but also subjective measures of wellbeing (Skevington et al., 2004). One possible contributor to poor quality of life in schizophrenia are impairments in social cognition, as these remain even during remission of clinical symptoms (Harrington et al., 2005; Penn et al., 2008). While impairments in social cognition have been linked to objective functional outcome in schizophrenia, there is a paucity of research exploring the relationship between social cognition and subjective quality of life (Couture et al., 2006; Sparks et al., 2010).

Social cognition comprises a broad range of abilities, including emotion recognition, theory of mind (ToM), and empathising abilities (Penn et al., 2008). Individuals with schizophrenia show differences in emotion recognition, most often difficulties recognising facial expressions displaying negative emotions (Brune, 2005; Mandal et al., 1998). They can also show differences in some aspects of empathy, most commonly reductions in taking others perspectives and increases in feelings of distress in response to others' suffering (Derntl et al., 2012; McCormick et al., 2012; Montag et al., 2007; Shamay-Tsoory et al., 2007c; Sparks et al., 2010). In addition, aspects of ToM - the ability to make predictions about an individual's mental state - are reduced in schizophrenia. ToM can be first-order (inferring another's mental state) or second-order (predicting another's mental state inferences), and includes both cognitive and affective processes (Pickup, 2008; Shamay-Tsoory and Aharon-Peretz, 2007). Second-order ToM

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deficits have been consistently found in individuals with schizophrenia (for a review, see Harrington et al., 2005), and recent studies measuring cognitive and affective ToM indicate that individuals with the disorder have deficits in affective but not cognitive ToM (Shamay-Tsoory et al., 2007a; Shamay-Tsoory et al., 2007b), although evidence for both cognitive and affective ToM deficits in schizophrenia has recently emerged (Montag et al., 2011).

With regard to quality of life, reductions have been detected in physical health, psychological well-being, social relationships and environment (Maat et al., 2012; Narvaez et al., 2008). Only one study to date has explored the relationship between aspects of social cognition (emotion recognition and cognitive ToM) and quality of life in schizophrenia patients. They found that reduced quality of life was associated with increased symptom severity but *improved* ToM (Maat et al., 2012). The authors suggest that better ToM might be associated with more insight into the functional difficulties caused by their symptoms, and therefore reduced satisfaction with current circumstances. This is supported by studies that have explored general cognitive function and quality of life, with better cognitive function predicting poorer perception of quality of life in schizophrenia participants (Kurtz and Tolman, 2011; Narvaez et al., 2008). While Maat et al. had a very large sample which allowed them to run highly powered regression analyses, they only examined overall quality of life, rather than examining possible differences between domains. Given that another study found that improvements in emotion recognition were associated with better quality of life in the social relationships domain (Sachs et al., 2012), research which examines the relationships between aspects of social cognition and different domains of quality of life is needed. To date, no study

has comprehensively investigated the relationship between all aspects of social cognition and quality of life in schizophrenia. Because clinical variables are known to have an impact on outcomes in the disorder, these were also included as correlates in the current study.

The current study aimed to provide a comprehensive assessment of social cognition and quality of life in schizophrenia, and explore the relationships between these variables. We compared schizophrenia patients with healthy controls on a range of social cognitive variables (affective and cognitive ToM, empathy and emotion recognition), quality of life domains and neurocognitive variables. We then examined the relationships between social cognition, clinical variables and quality of life in patients.

2. Method

2.1. Participants

The study sample consisted of 20 participants with a DSM-IV diagnosis of either schizophrenia or schizoaffective disorder (SZ=13, SAD=7) and 22 healthy control participants. Participants were aged between 24 and 66 years old. Clinical participants were recruited through advertising at the Alfred Hospital, and via a database of participants at the Monash Alfred Psychiatry Research Centre. Healthy control participants were recruited via advertising at Monash University and the Alfred Hospital. The study was designed in accordance with the Declaration of Helsinki and was approved by the ethics committees of Monash University and the Alfred Hospital. All participants provided informed consent. Exclusion criteria comprised a history of head injury, neurosurgery or neurological disorder, or a current diagnosis of substance dependence.

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Clinical diagnosis was confirmed using the MINI International Neuropsychiatric Interview (Sheehan et al., 1998), and the MINI screen was used to confirm no diagnosis of any current mental illness for healthy control participants. One participant with schizophrenia and one participant with schizoaffective disorder had co-morbid obsessive-compulsive disorder. No participants with schizophrenia or schizoaffective disorder had any significant extra-pyramidal side effects (i.e., overall score of <10 on the Simpson-Angus Scale and Abnormal Involuntary Movements Scale). For the schizophrenia group, current symptom severity was estimated using The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), which was administered by a trained clinician. Chlorpromazine equivalence (CPZe) for antipsychotic medications was calculated using equivalence ratios provided in Humberstone, Wheeler and Lambert (2004), and Woods (2003). Demographic and clinical characteristics are shown in Table 1. Clinical participant data (including diagnosis, medication and CPZe) are outlined in Table 2.

Table 1
Demographic and clinical data

	Schizophrenia (n=20)	Controls (n=22)	Statistics
Age (years)	45.05 (11.87)	39.09 (13.37)	t=1.52, p=.136
Age range (years)	24-62	26-66	
Gender (m/f)	(11/9)	(12/10)	X^2=.001, p=.976
Years of education*	13.35 (2.28)	15.82 (2.34)	t=3.45, p=.001
Mean Age at Onset	22.77 (8.38)		
PANSS Positive	15.15 (5.97)		
PANSS Negative	16.30 (5.80)		
PANSS General	34.25 (7.95)		
AIMS	0.40 (1.19)		
Simpson-Angus	1.85 (1.53)		

Significant at the .01 level

Table 2
Clinical participant information

Participant #	Diagnosis	Gender	Age	Medication/dosage	CPZe
1	SAD	M	31	Fluphenzine Depot 12.5mg fortnightly	150
2	SCZ	M	24	Olanzapine 7.5mg	227.27
3	SCZ	F	45	Amisulpride 100mg; Quetiapine 25mg	66.67
4	SCZ	F	29	Clozapine 550mg; Olanzapine 25mg	1307
5	SAD	M	51	Aripiprazole 30mg; Duloxetine 10mg; Clozapine 300mg	700
6	SCZ	M	46	Amisulpride 600mg	300
7	SCZ	F	59	Aripiprazole 30mg	400
8	SCZ	F	60	Quetiapine 100mg; Amisulpride 100mg	116.67
9	SAD	F	47	Olanzapine 5mg; Fluoxetine 60mg	151.52
10	SAD	F	31	Aripiprazole 40mg; Quetiapine 50mg; Benztropine 2mg; Clomipramine Hydrochloride 75mg	566.66
11	SAD	M	34	Risperidone 3mg; Sodium Valproate 1000mg; Lithium 1000mg	272.72
12	SAD	M	45	Olanzapine 15mg; Aripiprazole 30mg	854.54
13	SAD	M	49	Sodium Valproate 1000mg; Aripiprazole 70mg	933.33
14	SCZ	M	61	Trifluoperazine 15mg; Duloxetine 60mg	750
15	SCZ	F	33	Escitalopram 20mg; Risperidone 2mg	181.81
16	SAD	F	53	Ziprasidone 220mg; Quetiapine 25mg; Citalopram 5mg	383.34
17	SCZ	M	55	Olanzapine 10mg; Sertraline 50mg	303.03
18	SCZ	M	51	Clozapine 500mg; Lithium 500mg	500
19	SCZ	M	35	Escitalopram 20mg; Aripiprazole 15mg	200
20	SCZ	F	62	Risperidone 2mg	181.81

2.2. Social cognitive assessment

2.2.1. Yoni task

ToM was assessed using this computerised cartoon task (Shamay-Tsoory et al., 2007b). The Yoni task has been described extensively elsewhere (Shamay-Tsoory et al., 2007a; Shamay-Tsoory et al., 2007b). A simple cartoon face "Yoni" thinks or feels something in relation to one of four objects or faces also displayed on the screen, and participants have to select the right item based on verbal and eye gaze cues. The task measures first and second order "cognitive" and "affective" ToM. To account for the attentional demands of the task, a "physical" control task was also included, which requires no mentalising, but

has similar demands on attention and working memory to the ToM tasks. Accuracy and response time (RT) in milliseconds was recorded for each trial.

2.2.2. NimStim Static Faces Task

Facial emotion recognition was measured using this computerised task, which comprises static face stimuli showing either happy, angry, fearful, sad, disgusted or surprised expressions selected from the NimStim Set of Facial Expressions (Tottenham et al., 2009). In total 48 stimuli were presented in a pseudo-random order, with each of the six emotions displayed eight times (four male and four female faces). On each trial a face would flash up displaying a particular emotion, and participants were asked to select, using the keyboard, which of the six emotions they felt best fit the expression presented.

2.2.3. Interpersonal Reactivity Index

Self-reported empathy was assessed using the Interpersonal Reactivity Index (IRI; Davis, 1983), a 28 item measure which comprises four 7-item subscales: Perspective Taking, Fantasy Seeking, Empathic Concern and Personal Distress.

2.3. Quality of life assessment

The abbreviated version of the World Health Organisation Quality of Life scale (WHOQOL-BREF; The WHOQOL Group, 1998) was used to measure quality of life. WHOQOL-BREF is a self-report measure that divides quality of life into scores on four indices: Physical health, psychological wellbeing, social relationships and environment quality.

2.4. Neurocognitive assessment

General cognitive functioning was estimated using the Repeatable Battery for the

Assessment of Neuropsychological Status (RBANS), a brief paper-and-pencil

neurocognitive battery (Randolph, 1998). The battery comprises 12 subtests, which

contribute to five indices: Immediate Memory, Visuospatial/Constructional ability,

Language, Attention, and Delayed Memory. The RBANS has been demonstrated to be

valid and reliable measure for cognition in schizophrenia (Loughland et al., 2007; Wilk et

al., 2004). Executive functioning was measured using the Hayling and Brixton tests

(Burgess and Shallice, 1997). The Hayling sentence completion test is a response

initiation and suppression task that assesses the ability to inhibit automatic responses. The

Brixton test is a rule detection task, which measures both rule attainment and cognitive

flexibility. Configural face processing was evaluated using a Fractured Faces Task

described elsewhere (Joshua and Rossell, 2009). This task is designed to test to what

extent participants rely on configural or featural face processing and compares

performances recognising famous faces on intact faces compared to faces where the

configural face information has been disrupted in the context of maintained featural

information.

2.5. Data analysis

Data were analysed using statistical software package SPSS version 20. Between group

analyses were conducted using a series of one-way ANOVAs, or Mann-Whitney U tests

where assumptions of normality were violated. Where measures had a number of

subscales, Bonferroni adjusted alpha levels were employed to control for family-wise

error. In order to replicate the analyses in Shamay-Tsoory et al. (2007b) ANCOVA was

used to explore the cognitive and affective ToM performances between groups, with performance on the control condition serving as the covariate. Although our ToM data were not normally distributed, ANCOVA has been shown to be relatively robust to violations of normality where sample sizes are similar (Tabachnick and Fidell, 2007). Relationships between social cognitive deficits and general cognitive deficits were explored using Spearman's correlations, as were relationships between social quality of life, social cognitive variables and symptom severity.

3. Results

3.1. Demographic and clinical characteristics

There were no significant differences in age or gender between the samples. The groups varied on years of formal education, with healthy individuals completing significantly more years of education than participants with schizophrenia.

3.2. Between group differences

ToM: As can be seen in Table 3, clinical participants made more errors than control participants in all second order conditions. After covarying for the 2nd order physical control condition using ANCOVA, the difference in accuracy between participants with schizophrenia and healthy controls remained significant in the 2nd order cognitive condition ($F(1,32)=5.66$, $p=.023$), and approached significance in the 2nd order affective condition ($F(1,32)=4.132$, $p=.050$). Adjusted means and standard errors are displayed in Figure 1. No significant between-group differences were observed in any of the first order conditions. There was no significant difference in response times between groups in any of the conditions.

Table 3
Between groups comparisons for facial affect recognition and ToM

	Healthy participants		Schizophrenia		Test statistic	p value	Adjusted alpha
	n	Mean (SD)	n	Mean (SD)			
Facial emotion Acc							
Anger accuracy	**22**	**6.50 (1.60)**	**20**	**4.95 (1.23)**	$\chi^2=3.16$	**p=.002***	$\alpha<.008$
Disgust accuracy	22	6.00 (1.60)	20	4.45 (2.39)	$\chi^2=2.17$	p=.030	$\alpha<.008$
Fear accuracy	22	3.45 (1.73)	20	2.90 (1.71)	$\chi^2=1.17$	p=.242	$\alpha<.008$
Happy accuracy	22	7.72 (0.55)	20	7.90 (0.31)	$\chi^2=1.12$	p=.259	$\alpha<.008$
Sad accuracy	22	6.41 (1.65)	20	5.15 (1.50)	$\chi^2=2.57$	p=.010	$\alpha<.008$
Surprise accuracy	22	6.31 (1.13)	20	6.15 (1.69)	$\chi^2=.13$	p=.896	$\alpha<.008$
Facial emotion RT (ms)							
Anger RT	22	1482 (522)	20	2226 (1419)	$\chi^2=2.37$	p=.018	$\alpha<.008$
Disgust RT	22	1290 (371)	20	2195 (1961)	$\chi^2=2.32$	p=.021	$\alpha<.008$
Fear RT	22	1925 (532)	20	2314 (1795)	$\chi^2=.53$	p=.597	$\alpha<.008$
Happy RT	22	1138 (563)	20	1133 (581)	$\chi^2=.05$	p=.960	$\alpha<.008$
Sad RT	22	1494 (439)	20	2085 (1097)	$\chi^2=1.84$	p=.066	$\alpha<.008$
Surprise RT	22	1142 (298)	20	1666 (1488)	$\chi^2=.49$	p=.623	$\alpha<.008$
Yoni Accuracy scores							
1st order physical	16	7.75 (0.78)	19	7.37 (1.34)	$\chi^2=1.02$	p=.481	$\alpha<.008$
1st order cognitive	16	12.00 (0)	19	11.74 (0.56)	$\chi^2=1.92$	p=.301	$\alpha<.008$
1st order affective	16	11.75 (0.45)	19	11.63 (0.68)	$\chi^2=.26$	p=.857	$\alpha<.008$
2nd order physical	16	11.0 (2.31)	19	9.47 (2.29)	$\chi^2=2.68$	p=.009	$\alpha<.008$
2nd order cognitive	**16**	**21.63 (2.73)**	**19**	**17.84 (4.34)**	$\chi^2=2.77$	**p=.005***	$\alpha<.008$
2nd order affective	**16**	**27.06 (2.84)**	**19**	**24.00 (3.57)**	$\chi^2=2.74$	**p=.006***	$\alpha<.008$
Yoni RT							
1st order physical	16	2388 (464)	19	3599 (2003)	$\chi^2=2.15$	p=.031	$\alpha<.008$
1st order cognitive	16	3064 (992)	19	4285 (2094)	$\chi^2=1.72$	p=.088	$\alpha<.008$
1st order affective	16	3454 (830)	19	4541 (2536)	$\chi^2=.56$	p=.589	$\alpha<.008$
2nd order physical	16	5648 (1541)	19	6349 (2886)	$\chi^2=1.36$	p=.182	$\alpha<.008$
2nd order cognitive	16	8378 (2162)	19	8972 (3348)	$\chi^2=.29$	p=.781	$\alpha<.008$
2nd order affective	16	6943 (1700)	19	8302 (3572)	$\chi^2=.73$	p=.481	$\alpha<.008$

Note: To control for family wise error where subscales are employed, a Bonferroni adjusted alpha level is specified.
*Significant at the Bonferroni corrected alpha level
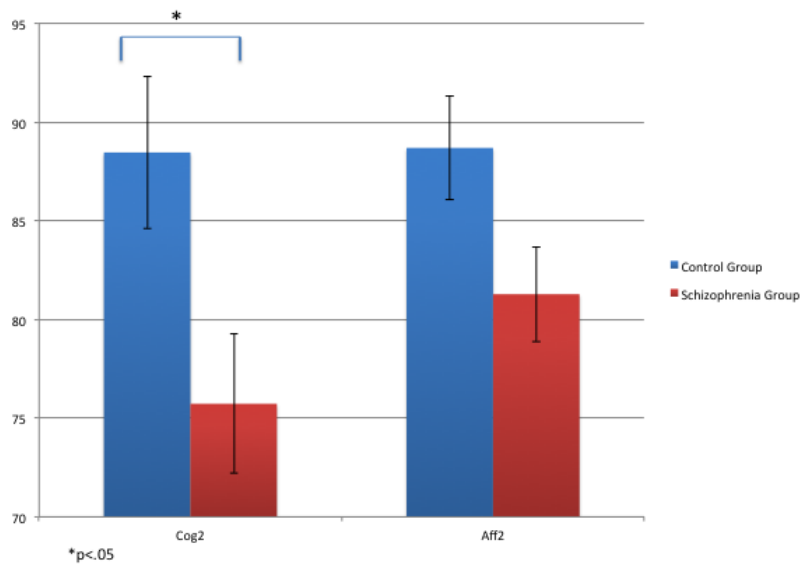
Figure 1. Mean percentage correct for each group on second order affective and cognitive theory of mind conditions (ANCOVA adjusted for control condition)

Facial emotion recognition: Individuals with schizophrenia were significantly less accurate when identifying angry facial expressions compared to healthy controls (*p*=.002). A reduction in accuracy for recognising sad and disgusted faces was also detected but this was not significant after Bonferroni correction. There were no significant group differences when participants identified fearful, happy or surprised faces. There were no significant differences in response time between patients and controls when identifying any of the facial emotions. These results are displayed in Table 3.

Self-reported empathy: Participants with schizophrenia reported higher levels of Personal Distress than healthy controls (*p*=.01), but there were no significant differences between groups on reported levels of perspective taking, fantasy seeking, or empathic concern (Table 4).

Table 4
Self-reported quality of life and empathy ratings

	Healthy participants		Schizophrenia		Test statistic	*p* value	Adjusted alpha
	n	Mean (SD)	*n*	Mean (SD)			
WHOQOL-BREF							
Physical	**22**	**14.91 (2.24)**	**20**	**13.00 (2.29)**	***F*=7.42**	***p*=.01***	*α<.013*
Psychological	**22**	**14.77 (1.57)**	**20**	**12.60 (2.33)**	***F*=12.79**	***p*=.001****	*α<.013*
Social relationships	**22**	**15.04 (2.65)**	**20**	**12.45 (3.38)**	***F*=7.76**	***p*=.008****	*α<.013*
Environment	**22**	**16.36 (1.29)**	**20**	**14.30 (3.01)**	***F*=8.61**	***p*=.006****	*α<.013*
IRI							
Perspective taking	22	17.92 (4.51)	20	15.60 (5.13)	*F*=2.09	*p*=.156	*α<.013*
Fantasy Seeking	22	15.72 (5.21)	20	11.80 (5.72)	*F*=5.28	*p*=.027	*α<.013*
Empathic Concern	22	19.68 (3.73)	20	18.65 (4.25)	*F*=.45	*p*=.505	*α<.013*
Personal Distress	**22**	**11.24 (4.32)**	**20**	**15.40 (6.06)**	***F*=7.20**	***p*=.011***	*α<.013*

General cognitive functioning: As displayed in Table 5, performances of individuals with schizophrenia were significantly below those of healthy controls on the indices of visuospatial/constructional abilities (*p*=.001), attention (*p*=.001), and delayed memory

(*p*=.009). There was no significant difference between patients and controls on immediate

memory or language indices.

Table 5
Performances on cognitive and executive function measures

	Healthy participants		Schizophrenia		Test statistic	*p* value	Adjusted alpha
	n	Mean (SD)	*n*	Mean (SD)			
RBANS							
Immediate Memory	22	107.05 (17.02)	20	96.85 (15.86)	*F*=4.01	*p*=.052	*α*=.01
Visuospatial	**22**	**114.41 (9.49)**	**20**	**97.05 (14.18)**	**_F_=22.09**	**_p_<.001****	*α*=.01
Language	22	104.09 (10.60)	20	94.50 (12.90)	*F*=6.98	*p*=.012	*α*=.01
Attention	**22**	**113.64 (15.45)**	**20**	**88.30 (19.52)**	**_F_=21.96**	**_p_<.001****	*α*=.01
Delayed Memory	**22**	**107.73 (12.33)**	**20**	**95.45 (16.33)**	**_F_=7.65**	**_p_=.009****	*α*=.01
Haylings A (control)	21	5.81 (0.68)	19	5.05 (1.13)	χ^2=2.29	*p*=.022	*α*=.017
Haylings B (RT)	21	5.86 (0.57)	19	5.74 (0.73)	χ^2=.471	*p*=.638	*α*=.017
Haylings C (accuracy)	21	6.52 (1.69)	19	6.00 (1.73)	χ^2=1.47	*p*=.143	*α*=.017
Brixton	**22**	**7.68 (2.31)**	**20**	**5.55 (2.26)**	**χ^2=3.102**	**_p_=.002****	*α*=.05
Face processing	19	11.79 (5.31)	19	11.68 (4.85)	*F*=.004	*p*=.949	*α*=.05

Note: To control for family wise error where subscales are employed, a Bonferroni adjusted alpha level is specified.

Executive functioning: Individuals with schizophrenia made more errors than healthy

controls on the Brixton test (*p*=.002). Patients and controls showed similar speed and

accuracy when asked to inhibit automatic responses (Haylings B and C). These results are

also shown in Table 5.

Configural face processing:

The mean difference for each group in number of famous faces identified when

configural face information was intact compared to when configural face information was

disrupted is displayed in Table 5. No significant difference between groups was apparent.

Quality of life

As shown in Table 4, individuals with schizophrenia reported lower levels of quality of

life, compared with healthy controls, on all four indices: Physical health (*p*=.01),

psychological wellbeing (*p*=.001), social relationships (*p*=.008), and environment quality

(*p*=.006).

3.3. Relationships between social cognitive and general cognitive deficits

To explore what relationship the delayed memory, visuospatial, attentional, facial emotion recognition or cognitive flexibility deficits might have with 2nd order affective and cognitive ToM, Spearman's correlations were performed. In the schizophrenia group, there were no significant relationships evident between any of these variables (Table 6). There was also no relationship between clinical symptoms and the ToM measures. In the healthy control group, only accuracy in recognising angry faces was related to affective ToM. There were no relationships in either group between memory, attention, visuospatial or cognitive flexibility ability and ToM.

Table 6
Spearman correlations between affective and cognitive ToM variables, and identified social cognitive and general cognitive deficits

	Schizophrenia group		Healthy control group	
	Aff2	Cog2	Aff2	Cog2
Anger Acc	.431	.361	**.755***	.503
Brixton	.080	.098	-.053	-.111
RBANS Delayed Memory	.323	.193	-.011	-.218
RBANS Attention	.225	.055	-.061	-.412
RBANS Visuospatial	.286	-.037	.237	.011
PANSS Positive	.129	-.194		
PANSS Negative	-.260	.040		
PANSS General	-.328	.023		

*Significant at the Bonferroni alpha adjusted level of p<.01

3.4. Relationships between quality of life, social cognitive deficits and clinical symptoms

As can be seen from Table 7, in the schizophrenia group, severity of clinical symptoms was generally negatively associated with aspects of quality of life. Specifically, positive symptoms were associated with the social and environmental domains, negative symptoms were associated with physical, psychological and social domains, and general psychopathology symptoms were associated with the physical, social and environmental domains. There was no significant relationship between affective or cognitive ToM, or accuracy in recognising anger, and quality of life.

Table 7
Correlations between clinical, social cognitive variables, and social quality of life in schizophrenia group

| | WHOQOL-BREF domain | | | |
| | Physical | Psychological | Social | Environmental |
	r	r	r	r
PANSS positive	-.347	-.322	**-.639***	**-.602***
PANSS negative	**-.674****	**-.566***	**-.580***	-.281
PANSS general	**-.636***	-.485	**-.786****	**-.669****
Aff2	-.089	-.044	.124	.035
Cog2	-.027	-.100	.194	.217
Anger Accuracy	.150	.352	.335	.081

Note: Bonferroni corrected alpha level of p<.01
*p<.01, **p<.001

4. Discussion

In the present study, schizophrenia participants showed reduced accuracy in second order cognitive ToM and reduced recognition of the facial expression of anger, with a trend towards reduced affective ToM and reduced recognition of sad and disgusted faces. All domains of quality of life were also significantly reduced in patients, however, the social cognitive deficits observed in patients were unrelated to quality of life. Rather quality of life was related to severity of current symptoms.

4.1. Social cognition in schizophrenia

Our finding that schizophrenia patients showed reduced cognitive ToM, and a trend towards reduced affective ToM compared to controls was in contrast to previous studies which found a selective impairment in affective ToM but not cognitive ToM using the Yoni task (Shamay-Tsoory et al., 2007a; Shamay-Tsoory et al., 2007b). Schizophrenia is a heterogeneous disorder with a wide range of presenting clinical symptoms, and one possibility to explain this discrepancy might be differing symptom profiles of the participants with schizophrenia. There is some indication that negative symptoms may be negatively related to affective ToM and positive symptoms may be negatively related to

cognitive ToM (Montag et al., 2011; Shamay-Tsoory et al., 2007b). Our sample size was not sufficient to split the clinical group based on predominant positive or negative symptoms, but future research should do to this better understand these relationships. Another finding of interest in the current study was a strong relationship between accuracy in recognising angry facial expressions and affective ToM in the healthy control group that was not present in the schizophrenia sample. This supports the theory that in healthy populations, affective ToM relies on the recognition of facial affective cues, and indicates that in individuals with schizophrenia this may be disrupted. These individuals may therefore be using different and less efficient brain processes to solve these tasks. Individuals with schizophrenia reported more personal distress in response to emotional situations, which is consistent with some earlier studies, and has been likened to social discomfort, rather than empathy for others per se (Sparks et al., 2010). We did not find any significant difference between the patient and control group on any of the other empathy scales, which was somewhat unexpected, given that perspective taking has been found to be reduced in some previous studies (Montag et al., 2007; Shamay-Tsoory et al., 2007c). Accuracy of self-ratings regarding empathy have been shown to vary in schizophrenia, depending on a number of factors including insight, ability to recognise others' emotions, and clinical symptoms (Lysaker et al., 2013), and it is possible that our sample were not accurate at rating their own levels of empathy. Future studies into empathy in schizophrenia could include imaging methods, in addition to self-report, in order to study brain activation during empathy tasks in schizophrenia.

4.2. *Quality of life and social cognition in schizophrenia*

The findings of our study indicate that there is a not a direct relationship between deficits in social cognition and any aspects of quality of life in schizophrenia. Rather, severity of positive, negative and general psychopathology symptoms had a strong impact on different aspects of quality of life. This lack of relationship is not entirely consistent with the findings of Sachs et al. (2012) who found that both social quality of life and emotion recognition improved following an affect recognition training program. This study did not report correlations between affect recognition performance and social quality of life at baseline, however, and also reported significant reductions in negative symptoms following the treatment. It is possible that rather than a linear relationship between affect recognition and quality of life, a mediating factor such as negative symptom severity might play an important role. The findings of Maat et al. (2012) support this possibility, as they found a significant interaction between ToM and symptom severity with respect to quality of life, with individuals with intact ToM but severe clinical symptoms having the worst quality of life. They hypothesised that intact ToM is generally associated with better insight, which has been associated with more dissatisfaction with poor function associated with the disorder. The current study did not include a measure of insight, but future research should include this as a possible mediating factor in the relationship between social cognition and quality of life.

4.3. *Limitations*

One limitation of the current study was that we did not include an objective measure of function, and so it is difficult to know the functional impact of the social cognitive

deficits we identified in the schizophrenia sample, and the relationship between those functional impacts and quality of life. Further, our sample size was not large enough to allow us to split the group on the basis of predominant symptoms and explore the relationship of symptoms to social cognitive deficits more comprehensively. In general, our modest sample size and conservative approach to statistical analysis means that the current study may have been underpowered to detect some of the more subtle deficits and relationships in the groups. Replication of these results in a larger sample would address this concern.

A further limitation, similar to most clinical research of this nature, is that all patients in the current study were medicated. Previous studies of effects of medication on social cognition have found that antipsychotic medication may improve social cognition (Penn et al., 2009; Sumiyoshi et al., 2009), and although the current study did not reveal any relationship between chlorpromazine equivalent and social cognitive variables, future research could explore the possible differential effects of different medications on social cognition.

4.4 Conclusions

To summarize, the current study aimed to comprehensively assess a number of aspects of social cognition, as well as aspects of quality of life in schizophrenia, and examine any relationships between these variables. We found that schizophrenia patients showed impairments cognitive ToM and recognising angry faces, as well as reductions on all domains of quality of life. The social cognitive deficits were not related to clinical symptoms or any neurocognitive deficits. Quality of life was not related to the social cognitive deficits, but rather to severity of current symptoms. It is possible that level of

insight might be mediating the relationship between social cognition and quality of life, and this should be explored in future research.

Author Disclosure

Contributors

SCA designed the study, collected and analysed the data, and wrote the first draft of the manuscript. PGE assisted with the design of the study and data collection, and oversaw the data analysis. KEH advised regarding patient recruitment, data analysis and interpretation of the results. PBF oversaw the study, advised regarding the recruitment of participants, and interpretation of the results. All authors have contributed to and approved the manuscript.

Conflict of Interest

PBF has received equipment for research from Medtronic, MagVenture A/S and Brainsway Ltd and research funding from Cervel Neurotech. All other authors declare that they have no conflicts of interest.

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Chapter 7: Study Two

Social cognition and quality of life in bipolar disorder

Explanatory Notes

Chapter 7 contains a study that has been submitted for publication in Psychiatry Research. Study 1 established the presence of a number of impairments in social cognition, as well as reductions in quality of life, in participants with schizophrenia, and showed that in this sample the quality of life reductions were strongly related to clinical variables, but not social cognitive or neurocognitive variables. Research has indicated that aspects of social cognition are reduced in bipolar disorder; however, very little research has comprehensively assessed social cognition and quality of life in this disorder. Study 2 comprehensively investigated aspects of social cognition and quality of life in a bipolar disorder sample, compared with healthy controls. Because mood symptoms have been shown to exacerbate any social cognitive difficulties in bipolar disorder, only euthymic bipolar participants were included, in order to examine social cognitive impairments as potential trait deficits. This is the first time the relationships between a number of facets of social cognition and different aspects of quality of life have been assessed in bipolar disorder.

Monash University

Declaration for Thesis Chapter Seven

Declaration by candidate

In the case of Chapter Seven, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Designed the study and protocol, recruited the participants and collected the data. Entered and analysed the data, and interpreted the results. Wrote the manuscript.	85

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Dr Peter Enticott	Advised on study design, recruitment, provided guidance regarding data analysis, advised on draft manuscript	5
Dr Kate Hoy	Advised regarding recruitment, assisted with data analysis, and gave feedback on manuscript	5
Prof Paul Fitzgerald*	Advised on study design, provided guidance regarding recruitment queries, statistical analysis and interpretation. Provided feedback on draft manuscript	5

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature		Date 1/7/13
Main Supervisor's Signature		Date 1/7/13

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

Investigating social cognition and quality of life in euthymic bipolar disorder

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Abstract:

While social cognitive deficits and reduced quality of life have both been detected in euthymic bipolar disorder, results to date have been mixed. The relationship between social cognitive deficits and quality of life in patients is also unclear. This study aimed to clarify which aspects of social cognition are altered in this disorder and understand the relationship of any deficits to quality of life. We used a well-controlled measure of cognitive and affective Theory of Mind (ToM), Yoni task, as well as measures of emotion recognition, empathy, quality of life and neurocognition in16 participants with euthymic bipolar disorder and 20 healthy controls. Patients showed reduced second order cognitive but not affective ToM, increased affective empathy, and no deficits in facial affect recognition. There were deficits seen in neurocognition in the patient group which were found to be related to cognitive ToM. Quality of life was also reduced in patients, and this was associated with depressive symptoms and disease duration but not social cognitive deficits. It is likely that there are mediating factors in the relationship between social cognition and quality of life.

1. Introduction

Individuals with bipolar disorder report reduced function and quality of life, even during remission of mood symptoms (Brissos et al., 2008; Wingo et al., 2009; Yen et al., 2008). With regard to quality of life, reductions have been reported in physical health, psychological wellbeing, quality of social relationships, and quality of the physical environment (Brissos et al., 2008; Yen et al., 2008). Despite increasing recognition of the importance of quality of life in patient outcomes, the factors contributing to quality of life reductions in euthymic bipolar disorder are still unclear. Significant cognitive impairments, particularly in the domains of attention, memory, and executive function, have been detected in euthymic bipolar disorder (Mann-Wrobel et al., 2011; Torres et al., 2007), and have been linked to reduced objective functioning in this population (Martino et al., 2009; Wingo et al., 2009). Additionally, one study has found evidence for neurocognitive reductions and reduced subjective quality of life (Brissos et al., 2008). Another emerging area of research in euthymic bipolar disorder which could have some relevance to quality of life is that of social cognition.

Social cognition refers to a group of processes that allow individuals to recognise, understand and respond to socially relevant information. These processes include basic facial emotion recognition, empathy, and theory of mind (ToM; Adolphs, 2001). ToM is the ability to predict what another individual might be thinking or feeling (Ang and Pridmore, 2009). In recent years, a distinction has been made between the affective aspects of ToM (decoding another's emotional state based on visual and verbal cues) and cognitive aspects of ToM (using reasoning skills to predict another's mental state) (Shamay-Tsoory and Aharon-Peretz, 2007).

In euthymic bipolar disorder, studies of social cognition have found evidence for both ToM deficits and subtle emotion recognition difficulties (Samamé et al., 2012). Some studies have found selective ToM impairments in euthymic bipolar disorder (Donohoe et al., 2012; Olley et al., 2005), indicating that only certain aspects of ToM might be affected. Specifically, there have been two studies that have shown that cognitive ToM but not affective ToM was reduced in euthymic bipolar disorder participants, (Montag et al., 2010; Shamay-Tsoory et al., 2009). However, an additional investigation reported reduced performance in patients on the "Eyes task," which involves decoding mental states from eye cues, and could therefore be classified as an affective ToM task (Donohoe et al., 2012).

One ToM task has been designed to specifically discriminate between affective and cognitive ToM, involving minimal language and executive demands, and with a physical condition to control for attention and comprehension (Shamay-Tsoory and Aharon-Peretz, 2007). This computerised task, named the Yoni task, has been shown to distinguish between affective and cognitive ToM deficits in a number of clinical groups (Shamay-Tsoory and Aharon-Peretz, 2007; Shamay-Tsoory et al., 2007a; Shamay-Tsoory et al., 2010; Shamay-Tsoory et al., 2007b). The Yoni task has never been used to assess ToM in a bipolar disorder group. One other aspect of social cognition that has been explored in this clinical group is empathy. Two studies have assessed this domain using a self-report measure called the Interpersonal Reactivity Index (IRI; Derntl et al., 2012; Shamay-Tsoory et al., 2009). Both found that individuals with bipolar disorder reported less perspective taking than healthy controls, but more negative reactions to others in distress. Perspective taking is generally regarded as an aspect of "cognitive" empathy,

and personal distress is regarded as an aspect of "affective" empathy, indicating that these aspects of empathy may be differentially affected in the disorder. Despite this growing evidence of changes to social cognitive functioning in bipolar disorder, the impact of this on quality of life has not yet been investigated. The current study aimed to systematically assess social cognition in euthymic bipolar disorder, and explore any relationships with reductions in quality of life. In addition, measures of neurocognition and clinical variables were also included as possible correlates to both social cognition and quality of life. We hypothesised that cognitive ToM and perspective taking, as an aspect of cognitive empathy, would be reduced in the clinical group, and that reductions in quality of life would be related to deficits in neurocognition, as well as social cognition.

2. Methods

2.1. Participants.

Participants were 16 individuals with Bipolar I Disorder (n=11) or Bipolar II Disorder (n=5), as diagnosed according to DSM-IV criteria (American Psychiatric Association, 2000), and 20 healthy controls. The age of participants ranged from 24 to 65 years. Individuals with bipolar disorder were recruited through advertising at the Alfred Hospital, and via a database of previous participants at the Monash Alfred Psychiatry Research Centre. Control participants were recruited via advertising at Monash University and the Alfred Hospital.

The study was designed in accordance with the Declaration of Helsinki and ethical approval was obtained from Monash University and the Alfred Hospital. All participants provided informed consent. Exclusion criteria comprised a history of head injury, neurosurgery or neurological disorder, or a current diagnosis of substance

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dependence or other Axis I disorder. Clinical diagnosis was confirmed using the MINI International Neuropsychiatric Interview (Sheehan et al., 1998), and the MINI screen was used to confirm no diagnosis of any current mental illness for healthy control participants. For the bipolar disorder group, euthymia was defined as a rating of less than 8 on the Hamilton Depression Scale (HAMD-21) (Hamilton, 1960), and less than 6 on the Young Mania Rating Scale (YMRS) (Young et al., 1978). Demographic and clinical characteristics are shown in Table 1. Clinical participant data (including diagnosis and medication) are outlined in Table 2.

Table 1
Demographic and clinical data

	Bipolar disorder (n=16)	Controls (n=25)	Statistics
Age (years)	41.63 (12.72)	38.10 (12.53)	$t=-.83, p=.411$
Age range (years)	24-65	24-64	
Gender (m/f)	(4/12)	(10/10)	$X^2=2.39, p=.126$
Years of education*	14.50 (1.79)	15.60 (2.39)	$t=1.53, p=.136$
Mean Age at Onset	20.27 (6.02)		
HAMD	3.31 (2.57)		
YMRS	1.38 (1.75)		

Table 2
Clinical participant information

Participant #	Diagnosis	Gender	Age	Medication/dosage
1	BP-I	M	41	Sodium Valproate 1000mg; Quetiapine 25mg
2	BP-I	M	27	Sodium Valproate 1000mg; Olanzapine 2.5mg
3	BP-I	F	35	Lithium 1500mg; Quetiapine 300mg
4	BP-I	F	38	Quetiapine 200mg; Sodium Valproate 500mg
5	BP-II	M	37	Lithium 1350mg
6	BP-I	F	58	Asenapine 10mg; Venlafaxine 525mg; Lithium 500mg
7	BP-II	F	59	Venlafaxine 450mg; Agomelatine 50mg; Amisulpride 200mg; Lithium 750mg
8	BP-I	F	34	Quetiapine 350mg; Aripiprazole 20mg; Lamotrigine 50mg
9	BP-II	M	28	Lithium 1000mg
10	BP-I	F	28	None
11	BP-I	M	65	None
12	BP-II	F	24	Sodium Valproate 1000mg; Quetiapine 400mg; Lamotrigine 100mg
13	BP-I	F	51	Sodium Valproate 1000mg; Duloxetine 60mg
14	BP-II	F	49	Duloxetine 10mg; Aripiprazole 30mg;
15	BP-I	F	39	Olanzapine 10mg; Fluvoxamine 100mg
16	BP-I	F	53	Lithium 1000mg; Quetiapine 100mg

2.2. Tasks.

Social cognitive function

ToM was assessed using the Yoni task (Shamay-Tsoory et al., 2007b). This computerised cartoon task assesses the ability to judge mental and affective states based on verbal and eye gaze cues. A cartoon outline of a face (named Yoni) is positioned in the middle of the screen, with four pictures of either objects or faces placed around the screen. For each trial, participants must decide which object or face Yoni is referring to by reading a phrase at the top of the screen and/or using eye gaze and face expression cues. The task measures both first and second order "cognitive" and "affective" ToM, depending on the complexity and nature of the cue (e.g., purely cognitive or with an emotional component). To account for the attentional demands of the task, a "physical" control task is also included, which requires no mentalising, but has similar attention and working memory demands to the ToM trials. Further details of the Yoni task, including screen shots, are included in Shamay-Tsoory et al. (2007a). This task has previously been used in schizophrenia and individuals with prefrontal lesions to dissociate between cognitive and affective ToM (Shamay-Tsoory et al., 2007a; Shamay-Tsoory et al., 2007b). Accuracy and response time in milliseconds (ms) was recorded for each trial.

Facial emotion recognition was measured using the NimStim Static Faces Task. This computerised task comprises static face stimuli showing either happy, angry, fearful, sad, disgusted or surprised expressions selected from the NimStim Set of Facial Expressions (Tottenham et al., 2009). This task was presented on a laptop computer and took approximately 5 minutes to complete. In total 48 stimuli were presented in a pseudo-random order, with each of the six emotions displayed eight times (four male and four

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female faces). On each trial a face would flash up displaying a particular emotion, and participants were asked to select, using the keyboard, which of the six emotions they felt best fit the expression presented.

Empathy was assessed using the Interpersonal Reactivity Index (IRI; Davis, 1983), a 28 item self-report measure which comprises four 7-item subscales: Perspective Taking (tendency to adopt the psychological viewpoint of others), Fantasy Seeking (tendency to get involved in fictional situations), Empathic Concern (tendency to experience feelings of compassion and sympathy for others) and Personal Distress (tendency to experience distress in response to others' suffering).

Neurocognitive function

Current cognitive functioning was estimated using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a brief paper-and-pencil neurocognitive battery (Randolph, 1998). The battery comprises 12 subtests that contribute to five indices: Immediate Memory, Visuospatial/Constructional ability, Language, Attention, and Delayed Memory. While originally developed as a neuropsychological assessment for dementia patients (Randolph et al., 1998), the RBANS has been demonstrated to be valid and reliable measure of current cognitive functioning in bipolar affective disorder (Dickerson et al., 2004).

Executive functioning was measured using the Hayling and Brixton tests (Burgess and Shallice, 1997). The Hayling sentence completion test is a response initiation and suppression task that assesses the ability to inhibit automatic responses. The Brixton test is a rule detection task, which measures both rule attainment and cognitive flexibility.

Both the Haylings and Brixton tests have been found to have adequate reliability and validity for both healthy and neurological lesion groups (Burgess and Shallice, 1997).

Quality of Life

The abbreviated version of the World Health Organisation Quality of Life scale (WHOQOL-BREF; The WHOQOL Group, 1998) was used to measure self-reported quality of life. The WHOQOL-BREF comprises 26 items and assesses four aspects of quality of life: Physical health, psychological wellbeing, social relationships and environment quality.

2.3. Data analysis

Data were analysed using statistical software package SPSS version 20. Between group analyses were undertaken using a series of one-way ANOVAs, or Mann-Whitney U tests where data was non-normally distributed. Where measures had a number of subscales, Bonferroni adjusted alpha levels were used to correct for family-wise error. Consistent with Shamay-Tsoory et al. (2007a), ANCOVA was used to compare the cognitive and affective ToM performances between groups, with performance on the control condition serving as the covariate. Although our ToM data were not normally distributed, ANCOVA has been shown to be relatively robust to violations of normality where sample sizes are similar (Tabachnick and Fidell, 2007). Pearson correlations were used to explore any relationships between social cognitive reductions and general cognitive deficits, as were relationships between social quality of life, social cognitive variables and symptom severity.

3. Results

3.1. Demographic and clinical characteristics

Demographic and clinical characteristics of the groups are displayed in Table 1. There were no significant differences between the groups on age, gender, or years of education.

3.2. Neurocognitive results

As can be seen from Table 3, the bipolar group performed below the healthy control group on the RBANS domains of immediate memory (p=.003), attention (p=.004), and delayed memory (p=.002). In contrast, there was no difference between groups on the RBANS visuospatial skills or language domains. With regard to executive functioning, individuals with bipolar disorder showed reduced scores on the Brixton test (p=.01), indicating reduced cognitive flexibility. Clinical participants performed similarly to healthy controls on the Haylings subtests, which measure cognitive inhibition.

Table 3
Performances on neurocognitive measures

	Healthy participants Mean (SD)	Bipolar Disorder Mean (SD)	Test statistic	p-value	Adjusted alpha
RBANS					
Immediate Memory	**105.10 (12.41)**	**91.00 (14.13)**	**F=10.15**	**p=.003***	**α<.01**
Visuospatial	111.85 (11.15)	106.94 (14.78)	F=1.29	p=.263	α<.01
Language	102.65 (10.63)	96.25 (13.00)	F=2.65	p=.113	α<.01
Attention	**112.95 (15.75)**	**93.38 (22.36)**	**F=9.48**	**p=.004***	**α<.01**
Delayed Memory	**106.75 (12.00)**	**92.25 (13.63)**	**F=11.51**	**p=.002***	**α<.01**
Haylings A	5.79 (0.66)	5.31 (1.49)	χ^2=-1.47	p=.230	α<.017
Haylings B	5.88 (0.54)	5.63 (1.71)	χ^2=.15	p=.909	α<.017
Haylings C	6.58 (1.61)	5.63 (2.45)	χ^2=-1.21	p=.243	α<.017
Brixton	**7.84 (2.27)**	**5.75 (2.49)**	**χ^2=-2.58**	**p=.010***	**α<.05**

3.3. Social cognitive results

3.3.1 ToM

With regard to the Yoni data, after including the physical control condition as a covariate in the between groups ToM analysis, adjusted means and standard errors are shown in Figure 1.
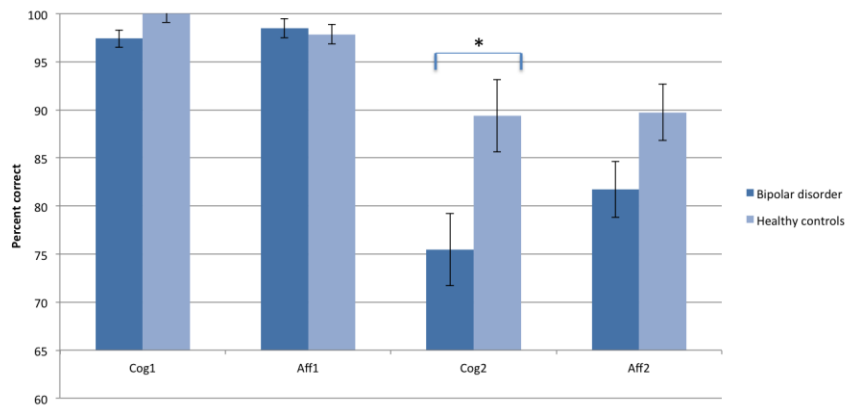
Fig. 1. Adjusted Yoni ToM means and standard errors

Accuracy in the 2nd order physical condition had a significant impact on the accuracy in the 2nd order cognitive ToM condition, $F(1,32)=4.89$, $p=.035$; however, the reduced cognitive ToM in the bipolar group remained when the physical condition was included as a covariate, $F(1,32)=6.819$, $p=.014$. The 2nd order physical control condition was also significantly related to performance on the affective ToM condition, $F(1,32)=7.422$, p=.011; however, after including the physical condition as a covariate, the difference between the groups only approached significance, $F(1,32)=3.514$, $p=.071$. There was no relationship between 1st order physical condition and 1st order cognitive or affective conditions. There was also no significant difference between groups on the 1st order affective condition after covarying the physical condition $F(1,32)=.196$, $p=.661$,

however there was a trend towards significance for the 1st order cognitive ToM condition,

$F(1,32)=7.117$, $p=.052$. There was no significant difference between groups on response

time for any of the conditions (see Table 4).

Relationships between second order cognitive ToM deficits and the observed

reductions in attention, immediate memory, delayed memory, and Brixton scores, as well

as mood symptoms were examined. In the bipolar disorder group, scores in the 2nd order

cognitive ToM condition were positively related to RBANS attention (r=.553, p=.026),

immediate memory (r=.504, p=.046) and Brixton scores (r=.525, p=.037), but not delayed

memory (r=.293, p=.272), HAMD (r=.170, p=.529) or YMRS (r=.134, p=.620) ratings.

In healthy controls, there was no relationship between the neurocognitive variables and

second order cognitive ToM (Attention: r=-.412; Immediate memory: r=.496; Delayed

memory: r=-.218; Brixton: r=-.111, all p>.05).

3.3.2. Emotion recognition

As can be seen from Table 4, on the NimStim task, there were no differences in

accuracy or response time between the groups when classifying any of the six emotions.

3.3.3. Empathy

On the IRI, bipolar disorder participants reported significantly higher levels of

empathic concern than healthy controls (*p*=.001). There were no differences between

patients and controls on the perspective taking, fantasy seeking, or personal distress

scales. These results are displayed in Table 4.

Table 4
Social cognition scores

	Healthy participants Mean (SD)	Bipolar Disorder Mean (SD)	Test statistic	p-value	Adjusted alpha
Nimstim Accuracy					
Anger accuracy	6.48 (1.50)	6.13 (2.00)	χ^2=-.89	p=.404	α<.008
Disgust accuracy	6.00 (1.53)	5.50 (2.10)	χ^2=-.47	p=.648	α<.008
Fear accuracy	3.40 (1.66)	3.56 (1.90)	χ^2=.19	p=.863	α<.008
Happy accuracy	7.72 (0.54)	7.75 (0.57)	χ^2=.00	p=1.00	α<.008
Sad accuracy	6.44 (1.56)	5.63 (1.63)	χ^2=-1.67	p=.109	α<.008
Surprise accuracy	6.40 (1.12)	6.44 (1.15)	χ^2=-.07	p=.962	α<.008
Nimstim RT					
Anger RT (ms)	1401 (544)	1625 (793)	χ^2=-.67	p=.519	α<.008
Disgust RT (ms)	1268 (399)	1601 (767)	χ^2=-.83	p=.422	α<.008
Fear RT (ms)	1816 (524)	1708 (739)	χ^2=-1.21	p=.236	α<.008
Happy RT (ms)	1081 (562)	968 (273)	χ^2=-.13	p=.912	α<.008
Sad RT (ms)	1425 (399)	1543 (632)	χ^2=.00	p=1.00	α<.008
Surprise RT (ms)	1073 (296)	1242 (573)	χ^2=-.61	p=.560	α<.008
Yoni RT					
Cog1 RT	3064 (992)	3047 (945)	χ^2=.113	p=.926	α<.008
Aff1 RT	3454 (830)	3295 (1596)	χ^2=-1.43	p=.160	α<.008
Phy1 RT	2388 (464)	2789 (974)	χ^2=1.21	p=.239	α<.008
Cog2 RT	8378 (2162)	7591 (2529)	χ^2=-1.02	p=.309	α<.008
Aff2 RT	6942 (1700)	6577 (2076)	χ^2=-.68	p=.515	α<.008
Phy2 RT	5648 (1541)	5268 (1795)	χ^2=-1.09	p=.287	α<.008
IRI					
Perspective taking	17.92 (4.51)	18.69 (6.02)	F=.17	p=.687	α<.013
Fantasy Seeking	15.72 (5.21)	12.75 (6.45)	F=2.74	p=.107	α<.013
Empathic Concern	**19.68 (3.73)**	**24.31 (3.03)**	**F=14.17**	**p=.001***	**α<.013**
Personal Distress	11.24 (4.32)	11.50 (5.06)	F<.001	p=1.00	α<.013

RT=response time

3.4. Quality of life

As can be seen in Table 5, bipolar disorder participants reported significantly

lower quality of life in the psychological wellbeing domain, compared to healthy controls

(p=.002). While clinical participants reported lower quality of life in their physical health,

this was not significant after a Bonferroni correction. There was no difference between

patients and controls in the quality of their social relationships, or their environment. In

the bipolar group, reductions in quality of life in the psychological wellbeing domain

were associated with longer disease duration (r=.67, p=.006) and higher levels of

depressive symptoms on the HAMD ($r=.78$, $p<.001$), but not manic symptoms, social

cognitive or neurocognitive deficits (see Table 6).

Table 5
Quality of life scores

	Healthy Controls Mean (SD)	Bipolar Disorder Mean (SD)	Test statistic	p-value	Adjusted alpha
WHOQOL-BREF					
Physical	15.16 (2.34)	13.00 (2.03)	*F*=4.51	*p*=.041	*α<.013*
Psychological	**14.92 (1.61)**	**12.25 (2.59)**	***F*=11.45**	***p*=.002**	***α<.013***
Social relationships	15.16 (2.75)	14.81 (3.25)	*F*=.01	*p*=.970	*α<.013*
Environment	16.48 (1.29)	15.88 (1.86)	*F*=.30	*p*=.588	*α<.013*

Table 6
Correlations between psychological quality of life and clinical, social cognitive and neurocognitive variables in bipolar disorder group

	WHOQOL-BREF Psychological domain	
	r	*p*
Disease duration	**-.670****	**.006**
YMRS score	-.425	.100
HAMD score	**-.783****	**<.001**
Cog2	-.275	.303
RBANS Immediate memory	-.237	.376
RBANS Attention	.123	.649
RBANS Delayed memory	.016	.954
Brixton	-.276	.301

4. Discussion

This study aimed to explore a number of aspects of social cognition in euthymic

bipolar disorder, and examine relationships between any social cognitive deficits with

quality of life. We found that the clinical participants showed a selective deficit in second

order cognitive ToM but not affective ToM, and that this ToM deficit was related to

deficits in attention, memory and executive function. In addition, emotion recognition

was intact and compared to controls, and patients reported higher levels of an aspect of

affective empathy. With regard to quality of life, we found that while reduced

psychological quality of life was reported in the bipolar disorder sample, this was not

related to social cognitive or neurocognitive deficits. Rather, this reduction was related levels of depressive symptomatology and disease duration.

Our finding of reduced second order cognitive but not affective ToM is consistent with the findings of Shamay-Tsoory et al. (2009) and Montag et al. (2010). Whereas the results of these previous studies could have arguably been impacted by verbal comprehension or reasoning ability, or in the case of Montag et al., by extra cues provided in the situational context of each vignette, the current study used a task that was specifically designed to eliminate these confounds. Our study, therefore, provides clearer evidence that cognitive ToM is affected in euthymic bipolar disorder, to a greater extent than affective ToM. In addition to the ToM deficit, the bipolar disorder participants also showed reduced immediate memory, attention, delayed memory, and cognitive flexibility. Some researchers have suggested that poor ToM performance may be underpinned by more general neurocognitive deficits. In the current study, significant correlations were apparent between the neurocognitive deficits and cognitive ToM in the patient group, but there was no relationship however between ToM performance and neurocognition in healthy controls. A possible explanation for this differentiation is that in healthy individuals ToM may be independent from neurocognitive functioning, but that in bipolar disorder, dysfunction in the mentalising network may be leading to a greater reliance on other neurocognitive abilities to compensate. Alternatively, reduced variation in scores in the control group, due to better performance, may have masked the relationship between neurocognition and ToM in healthy individuals. In our study, due to the modest sample size, the inclusion of the neurocognitive variables as covariates in the ToM ANCOVAs would have resulted in an unacceptable loss of power. Future research

with a larger sample should undertake this analysis, as well as conduct functional neuroimaging to better understand biological aspects of the relationship between neurocognition and cognitive ToM. Another finding of note was the increased empathic concern reported in our patient group but not of perspective taking or personal distress, as this was somewhat different to previous studies in euthymic bipolar disorder (Derntl et al., 2012; Shamay-Tsoory et al., 2009). The personal distress and empathic concern subscales of the IRI have been referred to collectively as "affective empathy" (Shamay-Tsoory et al., 2007c), and Shamay-Tsoory et al. also reported a trend toward higher levels of empathic concern in their sample, so our results are not completely inconsistent with previous findings. Cognitive empathy has been related to affective ToM (Shamay-Tsoory et al., 2007b), and given that we did not find evidence for affective ToM reductions in bipolar disorder in our study, it might be that only some individuals with bipolar disorder have dysfunction in brain areas that underlie both cognitive empathy and affective ToM.

In the current study, participants with bipolar disorder reported reduced quality of life with regard to psychological wellbeing, and a trend toward reduced physical health. Previous studies of quality life in euthymic bipolar disorder had found reductions in physical, psychological and social quality of life (Brissos et al., 2008; Yen et al., 2008). Both previous studies of quality of life in bipolar disorder included patients with much lower education level than participants in the current study. It is possible that different socio-demographic factors could account for better quality of life in some domains in our clinical group. Interestingly, reduced psychological quality of life in patients was related only to depressive symptoms and disease duration, and not to the ToM or neurocognitive deficits identified. While previous research has revealed a relationship between social

cognition and functional outcome in euthymic bipolar disorder, this is the first study to examine social cognition and quality of life. The finding in the current study that social cognition was unrelated to quality of life variables could be for a number of reasons. Perceptions of quality of life are subjective and although improvements in social cognition might lead to improvements in objective function, it does not necessarily follow that quality of life will improve to the same degree. There is evidence that social cognition is poorer during mood episodes, and negative impacts on personal and work relationships occurring during these episodes might have a lasting impact. While functional recovery following the mood episode might be relatively fast, relationship issues caused by the mood episode may take longer to resolve, and therefore current social cognitive ability may not show a direct relationship with current quality of life. The association between longer disease duration and quality of life might reflect the impact of multiple mood episodes on outcomes that impact quality of life. Longitudinal research into social cognition, mood, functional outcome and quality of life might help to elucidate these relationships. Another explanation for our results is that poor insight, which is related to neurocognitive function, might be having an impact on perceptions of quality of life. That is, an individual's better insight into limitations may lead to a lowered perception of quality of life, despite better functional outcomes. Although neurocognition was not related to social cognition in this study, insight was not specifically measured. This should be included as a possible mediating factor in future research to better understand the relationships between social cognition and quality of life

This study had a number of limitations. Mood ratings were not completed for healthy control subjects. While all clinical participants met the criteria for euthymia,

previous research has highlighted the potential importance of subclinical mood symptoms, and assessment of mood in control participants would have allowed for a direct comparison of these symptoms between groups. Another limitation of the current study is the absence of a premorbid IQ measure. While groups were matched on education, a premorbid IQ measure would have confirmed that the neurocognitive and ToM deficits detected are part of the disease profile, rather than some premorbid difference in intellectual capacity. Further, our small sample size and conservative statistical analysis increased the risk of a Type II error in our study, and it is possible we missed some subtle differences between groups, particularly in affective ToM and physical quality of life, where trends were detected. It will be important to replicate our findings in a larger sample. Finally, the clinical participants in this study were taking a variety of different medications, which could be a confounding factor in this study. While a previous study found that medication type did not have an impact on social cognitive performance in euthymic bipolar disorder (Shamay-Tsoory et al., 2009), more research is needed into the impact of psychotropic medication on social cognition in this disorder.

In conclusion, this study assessed social cognition in euthymic bipolar affective disorder, and its relationship to quality of life. We found a significant deficit in cognitive ToM, which was related to neurocognitive deficits. These relationships were absent in healthy controls, indicating that bipolar patients might be recruiting neurocognitive networks to attempt to compensative for deficits in mentalising. Psychological quality of life was reduced in patients, and this was associated with depressive symptoms and disease duration but not social cognitive deficits, indicating that social cognition does not have a direct relationship with quality of life. Future research should use longitudinal

designs and investigate possible mediating factors, such as insight, to better understand

the relationship between social cognition and quality of life in bipolar disorder.

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Chapter 8: Study Three

Evidence for reduced mirror system activity in euthymic bipolar disorder but not schizophrenia

Explanatory Notes

This chapter includes a manuscript submitted for publication in Bipolar Disorders. Studies 1 and 2 had established that aspects of social cognition were reduced in both schizophrenia and bipolar disorder. Study 3 investigated mirror system functioning in these disorders as a potential contributor to these deficits. While a small number of studies had previously examined mirror system function in each disorder individually, using a variety of measures, with conflicting results, Study 3 compared mirror system activity in schizophrenia, bipolar disorder, and healthy controls using a novel multimodal approach using both EEG and TMS simultaneously. In addition, a ToM measure was also included, in order to more directly examine the relationship between any mirror system reductions and a social cognitive measure.

Monash University

Declaration for Thesis Chapter Eight

Declaration by candidate

In the case of Chapter Eight, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Assisted with the study design and protocol, created the mirror system video stimuli, recruited the participants and collected the data. Entered and analysed the data, and interpreted the results. Wrote the manuscript.	80

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Dr Peter Enticott	Advised on study design, recruitment, provided assistance with data acquisition, provided guidance regarding data analysis, advised on draft manuscript	5
Dr Kate Hoy	Advised regarding recruitment, assisted with data analysis, and gave feedback on manuscript	5
Dr Richard Thomson	Assisted with EEG/TMS protocol, provided guidance regarding EEG data processing and analysis, provided feedback on draft manuscript	5
Prof Paul Fitzgerald*	Advised on study design, provided guidance regarding recruitment queries, statistical analysis and interpretation. Provided feedback on draft manuscript	5

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	⬛	Date 1/7/13
Main Supervisor's Signature	⬛	Date 1/7/13

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

Evidence for reduced mirror system activity in euthymic bipolar disorder but not schizophrenia

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Abstract:

Objective: Dysfunctional mirror systems have been proposed to contribute to the social cognitive deficits observed in both schizophrenia and bipolar disorder. A few studies have explored mirror system activity in either schizophrenia or bipolar disorder, using various techniques such as TMS (levels of motor resonance) or EEG (levels of mu suppression) with mixed results. This study aimed to use a novel multimodal approach (i.e. including both TMS and EEG) to further explore mirror systems and social cognition in both schizophrenia and bipolar disorder.

Method: Fifteen individuals with bipolar disorder, 19 individuals with schizophrenia, and 20 healthy controls participated in this study. Single-pulse TMS was applied to M1 during the observation of hand movements (goal-directed or interacting) designed to elicit mirror system activity. Single EEG electrodes (C3, CZ, C4) recorded brain activity. Participants also completed a theory of mind task.

Results: Both patient groups showed significantly reduced cognitive ToM but not affective ToM. Participants with bipolar disorder showed significantly less mu suppression than healthy controls, while participants with schizophrenia had intermediate levels of mu suppression and were not significantly different from either group. Despite a significant relationship between mu suppression and motor resonance, there were no significant between-group differences on levels of motor resonance, or type of stimuli (goal-directed or interactive).

Conclusions: Reduced mirror system activity may be present in bipolar disorder, to a greater degree than schizophrenia, and may contribute to social cognitive difficulties. These deficits may have, at least partly, a different basis to those seen in schizophrenia.

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Social cognition comprises a number of processes, including emotion processing, empathy and theory of mind (ToM), which allow an individual to perceive, comprehend and respond to the intentions and behaviours of others (1, 2). ToM refers to the ability to attribute mental states to oneself and others, and can involve processes that are cognitive (inferential reasoning) or affective (interpreting non-verbal cues) (3, 4). These inferences regarding mental states can be first-order (e.g., "He thinks that…") or second-order (e.g., "He thinks that she thinks that…") (5). Research has indicated that ToM impairments are present, to varying degrees, in both bipolar disorder and schizophrenia (6-8). These deficits are thought to be related to functional outcome and reduced quality of life (9-12). In bipolar disorder, ToM impairments have been found during both acute episodes and the euthymic stage of the disorder (8, 13), with one study reporting deficits in cognitive ToM, but not affective ToM (14). Reductions in ToM have also been consistently demonstrated in schizophrenia (4, 7, 15, 16), with some recent studies suggesting that patients with schizophrenia are selectively impaired on affective ToM (4, 17). There are similarities in the ToM deficits in bipolar disorder and schizophrenia. The largest study to have directly compared ToM in these disorders found that what would be considered affective ToM was similarly reduced in both disorders, while patients with schizophrenia showed more pronounced mental state reasoning (cognitive ToM) deficits (6). Despite progress in characterising these deficits in bipolar disorder and schizophrenia, the neural basis of these impairments remains unclear.

One system posited to underlie many social cognitive skills is the mirror system (18). A key component of this system are mirror neurons, which become both active during the observation and execution of a motor action. Mirror neurons are present in the premotor

cortex/inferior frontal gyrus and the inferior parietal lobule (19). Because mirror neurons have been shown to code for the intention of an action, rather than the motor movement per se, it has been theorised that they might help to facilitate understanding others' intentions (20). In this way mirror systems may play a key role in higher order social cognitive processes, including ToM. Support for the theory that mirror systems may help to facilitate social cognitive processes is found in autism spectrum disorder research. Autism spectrum disorder is a neurodevelopmental disorder characterised by social impairments, and not only have mirror system deficits been found in this population (21, 22), but the severity this impairment has been found to be related to the severity of social impairment (23, 24).

Two of the most used methods to measure mirror system function in humans involve electroencephalogram (EEG) and transcranial magnetic stimulation (TMS). At rest, sensorimotor neurons spontaneously fire in synchrony, leading to large-amplitude EEG oscillations in the mu frequency band (8-13 Hz) over scalp locations C3, CZ, and C4. Because the mu rhythm is suppressed when neurons in motor regions are activated, EEG studies of mirror systems use this suppression over the sensorimotor cortex during the observation of movement as an index of mirror neuron activity (18, 25). TMS, applied to the primary motor cortex to induce a motor evoked potential (MEP) in a muscle of the hand, has been used as an alternative method of measuring mirror system activity. The size of a MEP reflects the level of activity in the motor cortex and associated brain areas. When an individual views a transitive movement (e.g., hand interacting with an object in a goal-directed way), TMS induced MEPs are larger than when at rest, or when viewing an intransitive movement (e.g., hand moves without a target object evident) (26, 27). This

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difference in MEP amplitude is called motor resonance and has also been used as a putative measure of mirror system activity (28, 29). A recent study found that viewing interacting hand movements judged to have an emotional component (such as one hand moving away from another hand in a way that is judged to be "rejecting") also increases motor resonance to a similar level to that of a transitive movement (30). Further, a study explored mu suppression levels when viewing video clips with varying levels of social interaction, and showed that stimuli with a social interaction component resulted in more mu suppression than a non-interacting stimuli (18). There does not appear to be a close relationship between EEG mu suppression and TMS motor resonance indicating that these techniques might measure different aspects of the action-observation network (31). These, and similar methods, have been used to investigate mirror systems in disorders other than ASD, with emerging work in both bipolar disorder and schizophrenia.

A few studies have explored mirror systems in schizophrenia to date. For example, a study of mu suppression using magnetoencephalography (MEG) found evidence for reduced mirror system activity in patients compared to disconcordant twins (32). Similarly, a TMS study found that 15 patients with schizophrenia had lower levels of motor resonance compared to a healthy control group (29), and a study of rapid facial mimicry, thought to be a reflection of mirror system activation, was found to be abnormal in a schizophrenia sample (33). No behavioural measures were included in these studies, so the relationship between the mirror system impairments and social cognition was not clear. In contrast, McCormick and colleagues compared schizophrenia patients with high levels of psychotic symptoms with those with residual symptoms, and healthy controls, and found evidence for *increased* left-sided mu suppression in the psychotic group (34).

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Mu suppression levels in their control group, however, were not significantly different from baseline, indicating that in this study, the healthy control group may not have demonstrated adequate mirror system activation to be an appropriate comparison group. McCormick et al. also correlated mu suppression with self-reported empathy and found no relationship. One study exploring the relationship between TMS motor resonance and social cognitive variables in non-medicated schizophrenia patients found correlations between both emotion recognition and first order ToM, and MEP amplitude. Second-order ToM however, which is more commonly impaired in schizophrenia, was not found to be related to MEP amplitude. These authors also did not report whether there was evidence for reductions of the mirror system in this patient group (35). Only one previous study has investigated mirror systems in bipolar disorder (36). Kim and colleagues used fMRI to explore activation of mirror neuron regions and found that participants with euthymic bipolar disorder had slower response times and showed less activation in relevant regions while completing a social cognitive task, in comparison with healthy control participants.

The current study aimed to further explore the possibility that mirror system dysfunction might be present in bipolar disorder and schizophrenia, and that this might contribute to the ToM difficulties observed in the disorders. Given the presence of conflicting findings, both when exploring mirror systems in bipolar disorder and schizophrenia, and when comparing studies that have used EEG mu suppression or TMS motor resonance, the current study sought to investigate mirror systems in both bipolar disorder and schizophrenia, using EEG and TMS. We compared motor resonance when viewing transitive stimuli and interactive stimuli. We also compared ToM abilities in our groups,

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in order to explore any relationship between ToM performances and mirror system functioning. We hypothesised that we would find mirror system reductions in both patient groups, and that these reductions would be related to reductions in ToM performance.

Materials and methods

Participants

15 participants diagnosed with bipolar disorder (BD-I = 10, BD-II = 5), 19 participants diagnosed with either schizophrenia or schizoaffective disorder (SCZ = 12, SAD = 7),and 20 age- and gender-matched healthy control participants took part in this study. Both clinical groups were recruited through a participant database of the Monash Alfred Psychiatry research centre, and through advertising at the Alfred Hospital. Healthy control participants were recruited through advertising at Monash University and the Alfred hospital. The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committees of the Alfred hospital and Monash University. All participants provided informed consent. Participants were aged between 22-65 years. Those with a history of seizures, serious head injury or neurosurgery, metal implanted in the cranium, or pregnant women, were excluded from the study, in keeping with current TMS safety guidelines (37). Participants who met criteria for current substance dependence were also excluded from the study. For the clinical groups, diagnosis was confirmed using the MINI International Neuropsychiatric Interview (38), while healthy control participants completed the MINI screen to confirm no current

mental illness. One participant with schizophrenia and one participant with

schizoaffective disorder had co-morbid obsessive-compulsive disorder.

All participants with bipolar disorder were in the euthymic phase of the disorder. This

was defined as rating ≤ 7 on the Hamilton Depression Scale (HAMD-21) (39), and ≤ 5 on

the Young Mania Rating Scale (YMRS) (40). Participants with schizophrenia or

schizoaffective disorder were only included if they showed no significant extra-pyramidal

side effects (i.e., overall score of <10 on the Simpson-Angus Scale and Abnormal

Involuntary Movements Scale). Severity of current symptomatology was measured using

the Positive and Negative Syndrome Scale (PANSS), which was administered by a

trained clinician. Demographic and clinical characteristics are shown in Table 1. Healthy

control participants had significantly more years of formal education than schizophrenia

participants, but not bipolar participants. Clinical participant data (including diagnosis

and medication) are outlined in Table 2.

Table 1
Demographic and clinical data

	Schizophrenia (n=19)	Bipolar disorder (n=15)	Controls (n=20)	Statistics
Age (years)	44.16 (11.49)	40.87 (12.79)	37.05 (13.21)	F=1.58, p=.22
Age range (years)	24-61	24-65	22-64	
Gender (m/f)	(11/8)	(4/11)	(10/10)	X^2=3.46, p=.18
Years of education*	**13.53 (2.20)**	**14.67 (1.72)**	**15.70 (2.23)**	**F=5.28, p=.008**
Mean Age at Onset	22.41 (8.49)	20.71 (5.97)		
PANSS Positive	15.26 (6.11)			
PANSS Negative	15.79 (5.48)			
PANSS General	33.95 (8.05)			
AIMS	0.42 (1.22)			
Simpson-Angus	1.68 (1.38)			
HAMD		3.53 (2.30)		
YMRS		1.46 (1.89)		

Significant at the .01 level

Table 2
Clinical participant information

Participant #	Diagnosis	Gender	Age	Medication/dosage
1	SAD	M	31	Fluphenzine Depot 12.5mg
2	SCZ	M	24	Olanzapine 7.5mg
3	SCZ	F	45	Amisulpride 100mg; Quetiapine 25mg
4	SCZ	F	29	Clozapine 550mg; Olanzapine 25mg
5	SAD	M	51	Aripiprazole 30mg; Duloxetine 10mg; Clozapine 300mg
6	SCZ	M	46	Amisulpride 600mg
7	SCZ	F	59	Aripiprazole 30mg
8	SCZ	F	60	Quetiapine 100mg; Amisulpride 100mg
9	BP-I	M	41	Sodium Valproate 1000mg; Quetiapine 25mg
10	BP-I	M	27	Sodium Valproate 1000mg; Olanzapine 2.5mg
11	BP-I	F	35	Lithium 1500mg; Quetiapine 300mg
12	BP-I	F	38	Quetiapine 200mg; Sodium Valproate 500mg
13	BP-II	M	37	Lithium 1350mg
14	SAD	F	47	Olanzapine 5mg; Fluoxetine 60mg
15	SAD	F	31	Aripiprazole 40mg; Quetiapine 50mg; Benztropine 2mg; Clomipramine Hydrochloride 75mg
16	SAD	M	34	Risperidone 3mg; Sodium Valproate 1000mg; Lithium 1000mg
17	SAD	M	45	Olanzapine 15mg; Aripiprazole 30mg
18	SAD	M	49	Sodium Valproate 1000mg; Aripiprazole 70mg
19	SCZ	M	61	Trifluoperazine 15mg; Duloxetine 60mg
20	BP-I	F	58	Asenapine 10mg; Venlafaxine 525mg; Lithium 500mg
21	BP-II	F	59	Venlafaxine 450mg; Agomelatine 50mg; Amisulpride 200mg; Lithium 750mg
22	SCZ	F	33	Escitalopram 20mg; Risperidone 2mg
23	SAD	F	53	Ziprasidone 220mg; Quetiapine 25mg; Citalopram 5mg
24	SCZ	M	55	Olanzapine 10mg; Sertraline 50mg
25	SCZ	M	51	Clozapine 500mg; Lithium 500mg
26	BP-I	F	34	Quetiapine 350mg; Aripiprazole 20mg; Lamotrigine 50mg
27	BP-II	M	28	Lithium 1000mg
28	BP-I	F	28	None
29	BP-I	M	65	None
30	SCZ	M	35	Escitalopram 20mg; Aripiprazole 15mg
31	BP-II	F	24	Sodium Valproate 1000mg; Quetiapine 400mg; Lamotrigine 100mg
32	BP-I	F	51	Sodium Valproate 1000mg; Duloxetine 60mg
33	BP-II	F	49	Duloxetine 10mg; Aripiprazole 30mg;
34	BP-I	F	39	Olanzapine 10mg; Fluvoxamine 100mg

ToM task

Aspects of ToM were measured using the Yoni task (4). This computerised cartoon task

is based on a task previously described by Baron-Cohen (41), and assesses the ability to

judge mental and affective states based on verbal and eye gaze cues. This task has been

described extensively elsewhere (4, 17). The task comprises first and second order

"cognitive" and "affective" ToM conditions. There is also a "physical" control condition,

which has similar attentional and working memory demands to the other conditions, but

no mentalising component. For each participant, accuracy and response time (RT) in milliseconds was recorded for each trial.

TMS & EEG experiment

Participants were comfortably seated 1.5 m from a 22" LCD monitor set at eye level for the duration of the procedure.

Single pulse TMS (Magstim-200 stimulator; Magstim Company Ltd, United Kingdom) was administered to the left primary motor cortex (M1) using a hand-held, 70 mm figure-of-eight coil that was rested gently on the scalp. Motor-evoked potentials (MEPs) were recorded using Ag/AgCI surface electrodes placed over the right first dorsal interosseous (FDI) muscle in a belly-tendon montage. Resting motor threshold was defined as the minimum stimulation intensity required to evoke a peak-to-peak MEP of >50 µV in at least 3 out of 5 consecutive trials. EMG signals were amplified using PowerLab/4SP (AD instruments, Colorado Springs, Co), and sampled at 5000 Hz via a CED Micro 1401 mk II analogue-to-digital converting unit (Cambridge Electronic Design, Cambridge, UK). Single EEG electrodes were placed on C3, CZ and C4 according to the International 10-20 system of electrode placement. The reference electrode was positioned on the left mastoid bone, and the ground electrode was placed on the forehead. Electro-oculogram (EOG) electrodes were also placed above and below the eyes, and to the left and right of the eyes, to detect artifact from eye movements. EEG was recorded using Scan 4.3 Acquisition Software (Neuroscan, Charlotte, USA), and amplified using Neuroscan Synamps System. EEG was digitised at 1000 Hz, with a bandpass filter of 0.1-100Hz. All electrode impedances were below 10 kΩ.

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Participants were first administered 10 TMS pulses (at 120% RMT) while at rest (viewing a black screen); this served as measure of general corticospinal excitability (CSE) for each participant. TMS was then administered and EEG recorded during the presentation of ten short videos designed to either elicit mirror system activation, or serve as control stimuli. The videos were modelled on stimuli used in previous TMS investigations of the mirror system (29, 30, 42) and comprised: two static (i.e., motionless) hands, either from the same person or different people; a hand reaching out and clasping a mug (transitive); a hand pantomiming clasping a mug, but without the mug present (intransitive); and two interactive movements, one with hands from two different people, and a similar movement carried out by one person. For all videos, the time point of the TMS stimulation was based on the optimal index finger/thumb position used in previous research (29, 30, 43). For some of the videos (static and interacting hands), an additional TMS stimulation was triggered earlier in the movement for an additional comparison. A screenshot of each clip, taken at the point of TMS stimulation, is provided in Figure 1 along with an accompanying description of each movement. Participants were presented with a quasi-random sequence of the eight aforementioned video clips (i.e., fixed sequence, which appeared to be in random order). In total, each clip was presented 10 times, with a 2-second gap (black screen) between each clip.
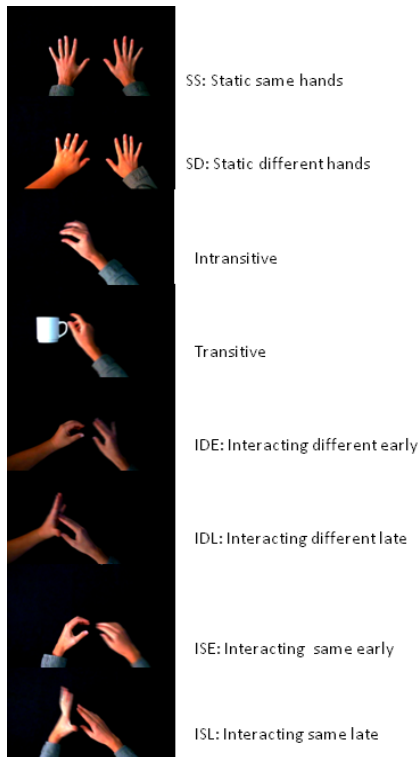
Figure 1. Screen shots of each video clip used to either elicit mirror system activation, or serve as control conditions

A light sensor device was employed to time-lock the TMS pulse to each video clip. Upon light detection, a trigger was sent from this device (5V TTL pulse via BNC connector) to the stimulator. This was achieved by embedding a black square in the upper left corner of each video clip, over which the light sensor was placed. At a specified point in each clip, this black square flashed white for 200 ms. The light sensor device detected this, and triggered a TMS pulse. A second trigger was then sent from the stimulator to the EMG device to signal EMG recorder.

EEG was acquired continuously during the videos. To prevent artefact from the TMS stimulation affecting the EEG trace, a sample and hold circuit was employed (44).

EEG analysis

Offline analyses of EEG data were performed using Scan 4.3 (Compumedics, Melbourne, Australia). In order to have sufficient epochs for analysis, all the videos that contained biological movement (intransitive, transitive, interacting different, interacting same) were used for analysis. For all the conditions which included biological movement, EEG was segmented into epochs of 2048ms length, around the trigger indicating the TMS pulse. From the black screen between each video, epochs of 1024ms were also segmented, which served as a reference period. A total of 80 movement condition epochs and 118 reference epochs were initially segmented for each participant. Ocular artifact reduction was conducted using an off-line threshold reduction algorithm (NeuroScan Inc). Epochs were then visually inspected and any epochs with any non-cerebral artefact still remaining were removed from the analysis. After data processing, the mean number of epochs retained across the movement conditions was 60.02 (SD=12.33), and across the reference periods was 96.27 (19.82). A Fast Fourier Transform (FFT) was used to calculate absolute power for the mu rhythm (8-13 Hz) band. Mu suppression was measured as the log ratio of power during the movement conditions relative to the power during the baseline condition (reference period): log10 ((([reference-movement condition]/reference) x 100).

TMS analysis:

Trials in which there was EMG detected muscle activity within 200 ms of the TMS pulse were excluded from the analysis (less than 1% of trials). Median peak-to-peak amplitude (mV) was calculated for each of the eight video conditions, as well as the ten "baseline" pulses before the video sequence. Motor resonance was calculated as MEP amplitude

relative to the baseline condition: ([FDI observation mV – baseline mV]/baseline mV) x

100. Due to non-normally distributed data, a log10 transform was then applied. Mixed

between-within ANOVAs were performed to compare the different conditions across the

three participant groups.

All statistical analyses were performed using SPSS 20.0. Unless otherwise specified, the

level of significance was set a $p<.05$ (two tailed).

Results

ToM

Means, standard deviations and ANOVA results for both accuracy and response time on

the Yoni task are presented in Table 3.

There was a significant difference in accuracy between groups on the second order

cognitive ToM task. Post-hoc comparisons revealed that both the bipolar group and

schizophrenia group had significantly reduced accuracy on second order cognitive ToM,

in comparison to the control group. There were no significant differences in accuracy on

the physical control conditions, indicating that this difference was not due to reduced

comprehension or attention in the clinical participants. Second order affective ToM was

intact, as was first order cognitive and affective ToM accuracy in the clinical groups.

Response time did not significantly vary between the participants in any of the

conditions.

Table 3
Mean (SD) of accuracy and response time (ms) for each condition of the Yoni task

Condition	Schizophrenia (n=18)	Bipolar disorder (n=15)	Controls (n=13)	F	p	η^2
Phy1 Acc	7.61 (.85)	7.67 (.62)	7.69 (.86)	.04	.957	.002
Phy1 RT	3286.46 (1512.47)	2723.71 (971.31)	2327.21 (483.17)	2.82	.071	.11
Cog 1 Acc	11.83 (.38)	11.67 (.62)	12.00 (.00)	2.13	.131	.09
Cog1 RT	3972.59 (1636.44)	3038.03 (1018.48)	3037.70 (1026.76)	2.83	.070	.11
Aff1 Acc	11.72 (.58)	11.80 (.56)	11.69 (.48)	.15	.861	.007
Aff1 RT	4202.88 (2122.92)	3273.57 (1650.01)	3541.20 (900.63)	1.31	.280	.05
Phy2 Acc	9.44 (2.36)	10.67 (1.80)	10.85 (2.54)	1.89	.164	.08
Phy2 RT	6824.05 (2923.93)	5047.05 (1616.94)	5287.21 (1421.63)	3.21	.050	.13
Cog2 Acc*	**18.17 (4.22)**	**18.20 (4.70)**	**21.62 (2.87)**	**3.33**	**.045**	**.15**
Cog2 RT	8909.79 (3434.06)	7627.29 (2613.38)	8269.93 (2356.53)	.80	.456	.03
Aff2 Acc	24.17 (3.60)	24.40 (4.79)	27.00 (3.06)	2.3	.113	.096
Aff2 RT	8089.42 (3549.56)	6594.00 (2147.66)	6934.29 (1616.94)	1.39	.260	.06

*Significant at the .05 level
Note: RT=response time, Acc=accuracy. Conditions were Phy1=1st order physical, Cog1=1st order cognitive, Aff1=1st order affective, Phy2=2nd order physical, Cog2=2nd order cognitive, Aff2=2nd order affective.

EEG results

In order to explore the level of mu suppression across C3, CZ and C4 in the three groups, a mixed between-within subjects ANOVA was conducted. There was a significant main effect of group, $F(2,42)=3.313$, $p=.046$, $\eta^2=.16$. Bonferroni corrected post hoc tests reveal that participants with bipolar disorder showed significantly less mu suppression than control participants, $p=.042$. Participants with schizophrenia were intermediate and not significantly different from either group (Figure 2). There was no main effect of electrode placement, indicating that the level of mu suppression was similar across the three electrodes, and no electrode x group interaction, meaning all groups had similar patterns of mu suppression across the three electrodes, (Main effect Electrode: $F(2,42)=.03$, $p=.973$, $\eta^2=.000$; Electrode*Group: $F(4,82)=.823$, $p=.514$, $\eta^2=.034$).
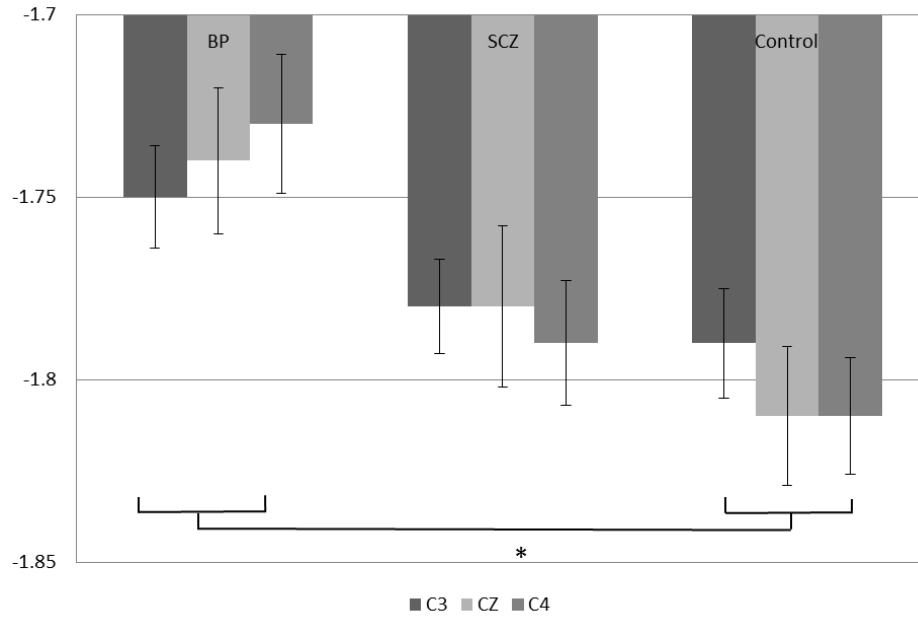
Figure 2. Mu suppression for each group across electrodes (*p<.05)

TMS results

Means and standard deviations of the transformed MEP amplitude change from baseline

for each group is presented in Table 4.

Table 4
Mean (SD) of Log transformed MEP change from baseline for each condition

	Schizophrenia (n=18)	Bipolar disorder (n=14)	Controls (n=18)
Intransitive	2.04 (.32)	1.98 (.32)	2.10 (.40)
Transitive	2.04 (.51)	1.92 (.31)	1.91 (.45)
SS	2.05 (.33)	2.00 (.23)	2.07 (.38)
SD	2.03 (.30)	2.00 (.28)	2.04 (.38)
ISE	2.05 (.34)	1.94 (.29)	2.03 (.41)
ISL	2.09 (.34)	1.93 (.29)	2.09 (.42)
IDE	2.02 (.30)	1.97 (.30)	2.06 (.44)
IDL	2.01 (.38)	1.93 (.23)	2.11 (.43)

When comparing the intransitive condition to the transitive condition across the three

participant groups, no significant interaction or main effects were apparent (Interaction:

$F(2,47)=1.137$, $p=.329$, $\eta^2=.046$; Main effects: $F(2,47)=.264$, $p=.77$, $\eta^2=.01$). Further, no

significant group differences across the static and interaction conditions, either with the early or late trigger time, were detected (Trigger*Condition*Group: $F_{(6,90)}=.716$, $p=.64$, $\eta^2=.046$; Trigger*Condition: $F_{(3,45)}=1.647$, $p=.192$, $\eta^2=.099$; Condition*Group: $F_{(6,90)}=1.11$, $p=.36$, $\eta^2=.069$, Trigger*Group: $F_{(2,47)}=2.83$, $p=.069$, $\eta^2=.11$; Main effects Condition: $F_{(3,45)}=1.20$, $p=.32$, $\eta^2=.07$; Main effects Trigger, $F_{(1,47)}=.34$, $p=.56$, $\eta^2=.007$).

There was also no difference between the three groups in MEP amplitude for the baseline condition, $F_{(2,48)}= .73$, $p=.488$, $\eta^2=.032$, indicating similar cortical excitability when at rest.

Relationships between EEG, TMS & ToM measures

Motor resonance was averaged across all conditions with biological movement, to be equivalent to our EEG mu suppression measure, and the relationship between these two variables was explored using a Pearson product-moment correlation. A significant relationship was revealed, where increased mu suppression was associated with increased MEP amplitude, $r=.339$, $n=42$, $p=.028$.

Pearson correlations examining the relationship between both mirror system measures and ToM performances were calculated (Table 5).

No significant correlations were apparent when using a Bonferroni adjusted alpha level of .002 adjusted alpha level.

Table 5
Pearson r values of correlation between mirror system and ToM measures

Yoni condition	Mu suppression N=41	MEP amplitude N=44
Acc 1st order physical	$r=.070, p=.666$	$r=.168, p=.274$
RT 1st order physical	$r=-.458, p=.003$	$r=-.262, p=.085$
Acc 1st order cognitive	$r=.128, p=.425$	$r=-.362, p=.016$
RT 1st order cognitive	$r=-.192, p=.230$	$r=-.329, p=.029$
Acc 1st order affective	$r=.202, p=.206$	$r=.320, p=.034$
RT 1st order affective	$r=-.295, p=.061$	$r=-.264, p=.084$
Acc 2nd order physical	$r=-.015, p=.926$	$r=.051, p=.742$
RT 2nd order physical	$r=-.316, p=.044$	$r=-.344, p=.022$
Acc 2nd order cognitive	$r=-.001, p=.996$	$r=.086, p=.579$
RT 2nd order cognitive	$r=-.224, p=.160$	$r=-.232, p=.130$
Acc 2nd order affective	$r=.060, p=.710$	$r=.330, p=.029$
RT 2nd order affective	$r=-.091, p=.571$	$r=-.264, p=.084$

Discussion:

This study used both TMS and EEG as well as stimuli that were either goal-directed or interacting to compare mirror systems in bipolar disorder and schizophrenia. Additionally, ToM was also compared in these groups. We found evidence for reduced mu suppression in the bipolar disorder participants but not schizophrenia participants. While the bipolar disorder group showed significantly less mu suppression compared to healthy controls, the schizophrenia group showed an intermediate level of suppression, which was not significantly different from either group. Despite a moderate correlation between EEG mu suppression and TMS motor facilitation, indicating an overlap in the underlying brain process, there was no significant difference in motor facilitation between our groups. There was a reasonably high level of variability in levels of motor facilitation in all groups, which may have contributed to this null finding.

The finding of dysfunctional mirror systems in bipolar disorder, as measured using EEG mu suppression, is consistent with Kim et al. (36) and indicates that individuals with bipolar disorder may have reduced activity of the observation/execution matching

system. This may help account for the selective social cognitive deficits that persist even in the euthymic state of the disorder. Previous research suggests that remitted bipolar disorder patients tend to make errors on ToM tasks which involve "under-mentalising" (reductions or lack of mental state reasoning), rather than "over-mentalising" (incorrect mental state reasoning) (45). As mirror system dysfunction has been found most consistently in individuals on the autism spectrum, whose ToM deficits are characterised by "under-mentalising", it might be that the ToM difficulties experienced by bipolar patients, while subtle, may involve a similar neural basis to those on the autism spectrum. Previous research has indicated that schizophrenia patients with predominantly "positive" symptoms have been shown to make more ToM errors due to "over-mentalising", while those with predominantly "negative" symptoms tend to make "under-mentalising" errors (46). Previous studies into mirror systems in schizophrenia have found evidence for either underactive mirror systems (29, 32) or in the case of psychotic patients, overactive mirror systems (34). These conflicting findings may reflect differences in the sample characteristics in these studies, reflective of the heterogeneity of the disorder. The relatively small sample size of the current study did not allow for an examination of mirror system functioning based on symptom clusters, but exploring this in future research will be an important step in understanding mirror systems in schizophrenia. Our results showed significantly reduced cognitive ToM ability in bipolar disorder and schizophrenia, compared to controls. In contrast, affective ToM was not significantly reduced in either patient group. This finding of selectively reduced cognitive ToM in bipolar disorder is consistent with previous literature (14, 45). However, our finding of cognitive but not affective ToM deficits in schizophrenia was somewhat unexpected, as

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previous studies have tended to demonstrate either global ToM deficits (46), or selective affective ToM impairments (4). Compared to other studies exploring social cognition in schizophrenia, our sample size was fairly small, so we may have lacked the power to detect more subtle group differences which may be present.

We failed to find any significant correlations between our mirror system measures and our ToM measures after a conservative Bonferroni correction. One possibility for this is that the relationship between mirror systems and social cognition may differ between our groups. It is possible that some compensatory mechanism is present in our patient groups, which allows for social cognitive function in the absence of a fully functioning mirror system. We should note that despite the diverse number of skills that make up social cognition, the current study only examined two aspects of ToM. It is possible that mirror systems may play a more important role in other aspects of social cognition, such as emotion processing or empathy. The ToM task we used did not distinguish between errors due to under-mentalising or over-mentalising, and if mirror system dysfunction is associated with one type of mentalising error more than another, this may account for the lack of relationship overall. Given the wide range of social cognitive measures in use in social cognition research, investigators have expressed concern that many of the current measures in use may not be sensitive or specific enough to detect all social cognitive deficits (8), and this may be the case with our task. However, given that the Yoni task has been used in a number of other studies, and was found to be significantly correlated with another social cognitive measure in one study (47), it is likely that the Yoni task has adequate construct validity. One possible explanation for our results is that mirror systems do not play a direct role in social cognition, as has been hypothesised. While

some previous literature has found a relationship between mirror system activity (as measured via TMS induced motor response) and social cognitive measures (35, 42), other studies have also failed to find relationships between mirror system measures and social cognition (30, 34). Overall, despite an increasing number of studies exploring mirror systems or social cognition across a number of disorders, a much smaller number of studies have examined relationships between these variables. This may be due an underreporting of null findings, or these analyses may not have been undertaken. Regardless, our results indicate that the relationship between the mirror system and social cognition is not yet clear, and further exploration of how mirror systems might contribute to different elements of social cognition is needed in future research.

One limitation of the current study, shared by most research into clinical populations, is the possible effects of medication on our results. Studies examining the effects of antipsychotic medication on social cognition and brain function have mixed findings (48-50). The majority of studies examining the effect of neuroleptic medication on cortical excitability have found no effect (51, 52), and our study showed no difference in cortical excitability between our groups. The effect of neuroleptic medication on the mirror system is as yet unknown, however, and future research should examine this relationship. A further limitation of the current study is the modest sample size. While our sample size was similar to other studies exploring the mirror systems in these populations, we lacked the power necessary for subgroup analysis.

In conclusion, our findings indicate that individuals with bipolar disorder, more so than individuals with schizophrenia, may have underactive mirror systems. This may be contributing to some of the social cognitive deficits present in bipolar disorder; however,

given the absence of a relationship between our social cognitive measure and mirror

system measures in this study, the functional significance of mirror system impairment

needs further exploration.

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Chapter 9: Additional Analyses

In addition to the results reported in Chapters 6, 7 and 9, some additional analyses were carried out in order to add to the thesis as a whole. Specifically, because the two clinical groups were examined separately with regard to social cognition in Chapters 6 and 7, and only the Yoni task variables were compared across all three groups in Chapter 8, additional analyses were carried out comparing all three groups on the remaining measures of social cognition, to allow for a direct comparison between clinical groups. In addition, while Chapter 8 contained the results of correlation analyses examining the relationship between the mirror system variables and ToM variables across the whole sample, additional analyses were also undertaken to examine the relationships between the mirror system measures and other aspects of social cognition. These results are reported below.

Between Group Comparison on Social Cognitive Variables

Data were analysed using SPSS version 20. Participants with schizophrenia, those with bipolar disorder, and healthy controls were compared on facial emotion recognition (NimStim Static Faces task), and self-reported empathy (IRI). Because the group sizes differed in these analyses, compared to those included in Chapters 6, 7 and 8, demographic and clinical characteristics for this sample are displayed in Table 1. The schizophrenia participants had significantly less years of formal education than healthy control participants.

Table 1
Demographic and clinical data across the three groups

	Schizophrenia (n=20)	Bipolar disorder (n=16)	Controls (n=25)	Statistics
Age (years)	45.05 (11.87)	41.63 (12.72)	37.08 (13.69)	$F=2.17$, $p=.124$
Age range (years)	24-62	24-65	21-66	
Gender (m/f)	(11/9)	(4/12)	(13/12)	$X^2=3.86$, $p=.145$
Years of education*	13.35 (2.28)	14.50 (1.79)	15.68 (2.23)	$F=6.60$, $p=.003$
Mean Age at Onset	22.77 (8.38)	20.27 (6.02)		$F=.94$, $p=.340$
PANSS Positive	15.15 (5.97)			
PANSS Negative	16.30 (5.80)			
PANSS General	34.25 (7.95)			
AIMS	0.40 (1.19)			
Simpson-Angus	1.85 (1.53)			
HAMD		3.31 (2.57)		
YMRS		1.38 (1.75)		

Significant at the .01 level

Due to violations of normality, Kruskal-Wallis tests were used to compare the three groups on these social cognition variables, and any significant findings were explored post-hoc using Mann-Whitney U tests. With regard to self-reported empathy, a series of one-way ANOVAs were used to compare the three groups on these subscales. Because subscales within measures were analysed, Bonferroni adjusted alpha levels were employed, to adjust for family wise error. These results are displayed in Table 2. After applying a Bonferroni adjusted alpha level, the three groups differed overall on accuracy of recognising the facial emotion of anger, and on self-reported empathic concern and personal distress in response to others suffering. Post-hoc tests revealed that the participants with schizophrenia had significantly more difficulty recognising anger than either the healthy control ($p=.001$) or bipolar disorder ($p=.016$) participants. Participants with bipolar disorder reported significantly more empathic concern for others than either participants with schizophrenia ($p<.001$) or healthy controls ($p=.001$). In contrast, individuals with schizophrenia reported significantly more personal distress in response

to others' suffering than the healthy control group (*p*=.027), and participants with bipolar

disorder were not significantly different to either group.

Table 2
Performances on social cognition measures across the three groups

	Healthy Controls		Bipolar Disorder		Schizophrenia		Test statistic	*p*	Post-hoc test
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)			
Facial emotion Acc									
Anger accuracy	**25**	**6.48 (1.50)**	**16**	**6.13 (2.00)**	**20**	**4.95 (1.23)**	χ^2=11.69	**p=.003**	**SZ<HC=BP**
Disgust accuracy	25	6.00 (1.53)	16	5.50 (2.10)	20	4.45 (2.39)	χ^2=5.23	p=.07	
Fear accuracy	25	3.40 (1.65)	16	3.56 (1.90)	20	2.90 (1.71)	χ^2=1.77	p=.41	
Happy accuracy	25	7.72 (.54)	16	7.75 (.58)	20	7.9 (.31)	χ^2=1.52	p=.47	
Sad accuracy	25	6.44 (1.56)	16	5.62 (1.62)	20	5.15 (1.50)	χ^2=8.35	p=.02	
Surprise accuracy	25	6.40 (1.12)	16	6.44 (1.15)	20	6.15 (1.69)	χ^2=.33	p=.85	
Facial emotion RT (ms)									
Anger RT	25	1436 (512)	16	2227 (1419)	20	1625 (793)	χ^2=7.43	p=.02	
Disgust RT	25	1249 (373)	16	1602 (768)	20	2195 (1961)	χ^2=6.67	p=.04	
Fear RT	25	1876 (523)	16	1708 (739)	20	2314 (1794)	χ^2=2.36	p=.31	
Happy RT	25	1118 (535)	16	968 (274)	20	1133 (581)	χ^2=.11	p=.95	
Sad RT	25	1433 (447)	16	1543 (632)	20	2085 (1097)	χ^2=5.20	p=.07	
Surprise RT	25	1112 (302)	16	1242 (573)	20	1666 (1488)	χ^2=.77	p=.68	
IRI									
Perspective Taking	25	17.92 (4.51)	16	18.69 (6.02)	20	15.60 (5.13)	F=1.85	.17	
Fantasy Scale	25	15.72 (5.21)	16	12.75 (6.45)	20	11.80 (5.72)	F=2.88	.06	
Empathic Concern	**25**	**19.68 (3.73)**	**16**	**24.31 (3.03)**	**20**	**18.65 (4.25)**	**F=11.32**	**<.001**	**BP>SZ=HC**
Personal Distress	**25**	**11.24 (4.32)**	**16**	**11.50 (5.06)**	**20**	**15.40 (6.06)**	**F=4.21**	**.02**	**SZ>HC**

Note: Adjusted alpha based on a Bonferroni correction for multiple comparison are as follows: NimStim Faces task and
Yoni task, α<.008. IRI task, α<.013.

Correlations between mirror system measures and social cognitive measures

Additional Pearson correlations were carried out which investigated any

relationships between the mirror system measures (overall mu suppression and motor

resonance) and the facial emotion recognition variables and self-reported empathy

subscales in the overall sample. These results are shown in Table 3. After a Bonferroni

adjusted alpha level of .003 was employed to control for the number of multiple

correlations run using each mirror system measure, no significant correlations were

apparent.

Table 3
Pearson r values of correlation between mirror system and emotion recognition and empathy measures within the whole sample

Social cognitive measure	Mu suppression N=47	MEP amplitude N=49
Facial Emotion Accuracy		
Anger Accuracy	$r=.014, p=.927$	$r=.077, p=.598$
Disgust Accuracy	$r=-.032, p=.833$	$r=-.072, p=.625$
Fear Accuracy	$r=.187, p=.208$	$r=.178, p=.221$
Happy Accuracy	$r=.023, p=.876$	$r=-.172, p=.238$
Sad Accuracy	$r=.306, p=.036$	$r=.210, p=.147$
Surprise Accuracy	$r=-.080, p=.594$	$r=-.249, p=.084$
Facial Emotion RT		
Anger RT	$r=.020, \quad p=.893$	$r=.108, p=.470$
Disgust RT	$r=-.035, p=.814$	$r=.082, p=.585$
Fear RT	$r=.055, p=.706$	$r=.167, p=.262$
Happy RT	$r=-.011, p=.939$	$r=.167, p=.262$
Sad RT	$r=-.055, p=.708$	$r=-.090, p=.547$
Surprise RT	$r=.044, p=.762$	$r=.156, p=.294$
IRI		
Perspective Taking	$r=.072 \ p=.633$	$r=-.177 \ p=.224$
Fantasy Scale	$r=.107, p=.472$	$r=.212, p=.144$
Empathic Concern	$r=-.219, p=.139$	$r=-.122, p=.404$
Personal Distress	$r=-.024, p=.873$	$r=.007, p=.961$

Note: Bonferroni corrected alpha level of $\alpha=.003$

Chapter 10: General Discussion

General Overview and Summary of Findings

For a majority of individuals with schizophrenia or bipolar disorder, social and vocational function and quality of life are poor, even during times of symptom remission. Some recent research has identified reductions in aspects of social cognition in these disorders, which may contribute to poor outcomes in these individuals. Despite this, the exact nature of these deficits, impact on quality of life, and possible underlying brain pathology, remain unclear. One possible brain network posited to contribute to social cognition is the mirror system; however, very little research has explored this system in schizophrenia or bipolar disorder to date.

The goal of this thesis was to better understand the nature and impact of social cognitive deficits in schizophrenia and euthymic bipolar disorder, and comprehensively assess mirror system function as a possible contributor to these deficits. In order to achieve this goal, we first measured social cognition in schizophrenia and euthymic bipolar disorder samples, compared to a healthy control group, and related these deficits to neurocognitive, clinical, and quality of life variables (Studies One and Two). These findings helped to clarify which social cognitive deficits were present in each patient group, any relationships they had to other cognitive and clinical variables, and what their impact might be on patients' quality of life. We then compared mirror system function across the three groups using a multimodal approach (using EEG and TMS), and examined any relationships between mirror system function and other aspects of social cognition (Study Three and Additional Analyses). Overall, while there was evidence for

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reductions in aspects of social cognition and quality of life in both patient groups, only

bipolar disorder participants showed evidence of reduced mirror system function. The

social cognitive deficits identified in the patient groups did not show direct relationships

with either quality of life variables or mirror system measures. The following provides a

summary of the results of each study, a discussion of how these results might be

interpreted and the overall conclusions of this thesis.

Study One: Assessment of social cognition and relationship to quality of life in

schizophrenia

The first study aimed to understand the characteristics of social cognitive deficits

in schizophrenia, their relationship to neurocognitive and clinical variables, and their

impact quality of life. While all these variables have been examined in different

combinations in previous studies of schizophrenia, this study was novel in the

comprehensive approach which was taken in attempting to understand social cognition in

schizophrenia: not only which aspects were reduced, and the neurocognitive and clinical

correlates of these deficits, but also what impact the social cognitive deficits might have

on quality of life in patients. Individuals with schizophrenia and healthy controls were

compared on affective and cognitive ToM, emotion recognition, and empathy, as well as

a number of different neurocognitive domains. In contrast to previous research, we found

that cognitive ToM was significantly reduced in schizophrenia patients, as well as

recognition of anger, and there was a trend toward reduced affective ToM. In patients,

these deficits were unrelated to either neurocognitive deficits or clinical symptoms. While

the healthy controls showed a significant relationship between recognition of anger and

affective ToM, this relationship was absent in the clinical group, possibly indicating that

affective processing networks may be disrupted in schizophrenia. This study was the first to examine the relationships between quality of life and these particular aspects of social cognition, as well as neurocognitive and clinical variables. Patients with schizophrenia reported reduced quality of life in all domains, but these reductions were not related to social cognitive impairments, or neurocognitive impairments. Rather, clinical symptoms were strongly related to quality of life, with higher levels of positive, negative, and general psychopathology symptoms associated with lower levels of quality of life. The strong relationships between severity of symptoms and quality of life might be obscuring any relationships between social cognition and quality of life in this clinical group. It is also conceivable that other factors such as level of insight may be mediating the relationships between social cognition and quality of life variables.

Study Two: Assessment of social cognition and relationship to quality of life in bipolar disorder

Study two compared participants with euthymic bipolar disorder and healthy controls on affective and cognitive ToM, emotion recognition and empathy, as well as quality of life. This was the first study to use the well-controlled Yoni task to compare affective and cognitive aspects of ToM in bipolar disorder, and our results showed that compared with healthy controls, participants with bipolar disorder showed deficits in cognitive but not affective ToM. A trend toward reduced affective ToM, however, was also detected in the bipolar disorder group. Emotion recognition was intact, and one aspect of affective empathy (Empathic Concern) was increased. The bipolar disorder group displayed neurocognitive deficits in the domains of attention, memory and cognitive flexibility and these were related to reductions in cognitive ToM. When quality

of life was compared between groups, ratings on the psychological wellbeing domain were reduced in individuals with bipolar disorder, while there was a trend to reductions in the physical health domain. A novel aspect of this study was the examination of relationships between quality of life reductions and social cognitive deficits in patients with bipolar disorder. No relationship was evident between social cognitive deficits or neurocognitive deficits and quality of life, rather quality of life was related to depressive symptoms and disease duration. It was suggested that due to the episodic nature of bipolar disorder, changes to quality of life during acute episodes, such as changes to job status or breakdown in relationships, may have a lasting impact so that quality of life is not reflective of current ability to function, or alternatively other variables such as insight might be mediating the relationship between social cognition and quality of life.

Study Three: Exploration of mirror system function in bipolar disorder and schizophrenia using EEG and TMS, and its relationship to theory of mind.

Given the establishment of social cognitive deficits in both clinical groups in studies one and two, including second order cognitive theory of mind deficits being present to a similar extent in both disorders, study three sought to investigate mirror system function in schizophrenia and bipolar disorder as possible contributor to these deficits. This study compared schizophrenia, bipolar disorder, and healthy controls on mirror system activity using a novel multimodal approach using both EEG and TMS simultaneously. Further, both goal-directed and interactive hand movements were included as stimuli designed to induce mirror system activity. Bipolar disorder participants showed significantly reduced mu suppression compared to healthy controls, with schizophrenia participants having an intermediate level of mu suppression, not

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significantly different from either group. This novel finding indicates that the observation/execution matching system, which is a key element of the mirror system, may be underactive in euthymic bipolar disorder patients, to a greater extent than schizophrenia. It was suggested that mirror systems might function differently in individuals with schizophrenia depending on their predominant clinical symptoms. This is the first time mirror systems have been assessed using EEG or TMS in bipolar disorder, and the first time mirror systems have been explored in both schizophrenia and bipolar disorder using the same experimental protocol. Despite a correlation between mu suppression and motor facilitation, there was no significant difference between any of the groups on motor facilitation, indicating that in our study, mu suppression may have been a more sensitive measure of mirror systems.

Additional Analyses: Comparing social cognition across the three groups

Only two studies to date have directly compared individuals with schizophrenia and euthymic bipolar disorder on any aspects of social cognition (Addington & Addington, 1998; Donohoe et al., 2012). Comparisons across the three groups (Additional Analyses) indicate that individuals with euthymic bipolar disorder and those with schizophrenia have similar reductions in ToM compared to healthy controls, but that individuals with schizophrenia have additional selective affect recognition deficits. We also found differences between schizophrenia and bipolar disorder on self-reported empathy: while schizophrenia participants reported more personal distress in response to others' anguish, bipolar disorder participants reported more empathic concern for others. Our affect recognition findings support the results of Addington and Addington (1998), who also found reduced facial affect recognition.

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Our ToM findings across the three groups differ slightly from those of Donohoe et al. (2012). While we found that individuals with bipolar disorder and schizophrenia performed similarly across the cognitive and affective ToM tasks, Donohoe et al. found evidence for comparable deficits only in one of the two ToM tasks included. In their study, both clinical groups showed deficits compared to controls on mental state decoding ("eyes task"), but only the schizophrenia group was reduced on mental state reasoning ("hinting task"). Mental state decoding has been related to affective ToM, and mental state reasoning has been related to cognitive ToM. While our study used a cognitive ToM task that attempted to minimise language and executive demands, the hinting task requires good language skills. Given that individuals with schizophrenia tend to have more difficulties with language tasks than individuals with bipolar disorder, this could account for the poor performance observed in this task in schizophrenia but not bipolar disorder. In addition, the hinting task has been labelled as a "basic ToM" task (Samamé et al., 2012), and may not have been difficult enough to detect more subtle cognitive ToM difficulties in bipolar disorder participants. While Donohoe et al. found significant deficits in both clinical groups in the "eyes" task, we only found a trend on the second order affective ToM task for both groups. Our sample size was significantly smaller than that of Donohoe et al., however, and it is possible that our sample was underpowered to detect subtle affective ToM deficits in both clinical groups. Nevertheless, in this thesis, the clear deficit shared by both clinical groups was in second order cognitive ToM, with additional deficits in affect recognition, particularly anger, in schizophrenia.

These three studies and additional analyses, when taken together make a significant contribution to our understanding of the nature of social cognitive deficits in schizophrenia and bipolar disorder, and the possible role of mirror systems.

General Discussion and Implications

1. Social cognition in schizophrenia and bipolar disorder

1.1.   Clinical implications

A key finding in the current thesis was that there are similarities but also differences in social cognitive functioning in bipolar disorder and schizophrenia. In recent years large scale genetic and family studies, as well as evidence from neuroimaging, have revealed some shared genetic susceptibility, and therefore likely share some underlying pathophysiology in these disorders (Craddock & Owen, 2010; Prossin et al., 2010). Our findings support the view that there is likely some overlap in dysfunctional neural circuitry in schizophrenia and bipolar disorder but that there are networks that may be selectively impaired only in schizophrenia, or differentially altered in each disorder. While it is not yet clear whether the same brain dysfunction is underlying the behavioural impairments in these disorders, or even across patients with the same diagnosis, knowledge about deficits at a behavioural level has implications for health care providers. Two individuals with the same psychiatric diagnosis can present with very different levels of functioning, and it could be that differences in social cognition might be contributing to this disparity. Although we did not find a relationship between social cognition and quality of life in this thesis, social cognition has been shown to be important for every day functioning, and therefore reduced social cognition in these disorders could have a negative impact on many aspects of the individual's life

and response to treatment. For example, social cognitive deficits could affect a patient's relationships with family and friends and therefore the level of support they receive, as well as employers, case workers and even their relationship with mental health professionals. Since our findings support the notion that social cognition is not a unitary structure and that individuals with bipolar disorder and schizophrenia can be impaired on some aspects of social cognition and not others, screening for a range of social cognitive deficits would assist clinicians in both understanding which aspects might be contributing to poor function, and also devising an approach to treatment which take these deficits into account.

1.2. Treatment Implications

Considering social cognitive deficits in treatment planning is crucial for improved management of individuals with bipolar disorder and schizophrenia. From a psycho-education perspective, helping the patient and those around them understand that their social difficulties are a part of their illness and not within their control might help prevent relationship breakdowns. With regard to treatment, social cognitive remediation is a new and emerging field, and considerable headway has been made in developing these programs, most often for people with autism (Gantman, Kapp, Orenski, & Laugeson, 2012; Hopkins et al., 2011; Laugeson, Frankel, Gantman, Dillon, & Mogil, 2012). While some social cognitive remediation programs - such as practicing facial affect recognition and strategies for successful social interactions - have been trialled in schizophrenia with positive results (Kurtz & Nichols, 2007; Veltro et al., 2011), these programs are still in their infancy, and absent in bipolar disorder. Most social cognitive remediation programs in schizophrenia have been as part of a general cognitive remediation program, but given

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the largely independent nature of neurocognitive and social cognitive deficits in schizophrenia, it might be more appropriate to separate these programs, and provide more individually targeted treatments. In bipolar disorder, neurocognitive deficits may be contributing to deficits in social cognition; therefore, it might be effective for social cognitive remediation programs to include a general cognitive element in this patient group. Given that there is variation in the social cognitive deficits displayed in each of the disorders, and likely also between individuals with the same diagnosis, future social cognitive remediation programs should be tailored to individual needs.

2. Mirror systems

2.1.Implications for theories of mirror systems

Overall across the three groups, there was no compelling evidence of a relationship between social cognition and mirror system function. Proponents of the mirror system theory of social cognition have suggested that mirror systems in humans may underlie action understanding, imitation, communication, and ToM (Gallese & Goldman, 1998; Gallese, Keysers, & Rizzolatti, 2004). This thesis included measures of a range of social cognitive processes and two putative measures of mirror system function, and yet despite larger sample sizes than many previous studies examining these relationships, no significant associations were detected. These findings challenge the theory that mirror systems are responsible for social cognition. Indeed, if mirror systems do play a role in social cognition, it may be a minor one, with other networks known to impact on social cognition (such as fronto-limbic circuits) playing a more crucial role.

One view of mirror systems is that rather than being an evolutionary adaption *for* cooperative behaviour, they are a by-product *of* cooperative behaviour, via associative

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learning: that is, when sensory input is continually paired with motor output those neurons in the motor system begin to develop mirror properties (Heyes, 2010). For example, when an adult imitates a young child, the child's visual sensory and motor neurons fire simultaneously, and eventually the sensory neurons trigger the motor neurons even in the absence of movement (i.e., Hebbian association). As such, the mirror system would be associated with aspects of social cognition by default, and though it may enhance aspects of social cognition, it is neither necessary nor sufficient. According to this theory, reductions in mirror neuron activity could arise from a lack of social interaction, or impairments in the quality of the social interaction, rather than the reverse. The associative hypothesis might still predict an association between mirror systems and social cognition; however, it would not be a strong one.

Another possibility is that the types of social cognition measures used in the current study were not at the right level for capturing relationships with mirror system function. There has been a suggestion that given the identification of mirror neurons in other species, the mirror system is phylogenetically older than other neural systems that appear to be unique to humans, such as the mentalising system. It is possible then that mirror systems play a stronger role in lower-level aspects of social cognition, and that the lack of relationship between mirror system and social cognition is due to the higher-level and abstract nature of many of the social cognitive measures currently used in this area of research. Some recent neuroimaging studies support this proposition, as brain regions involved in mirroring seem to be more active when predicting immediate goals from behaviour, while brain regions involved in mentalising become more active when integrating social information at an abstract level (Becchio et al., 2012; Ma,

Vandekerckhove, Van Hoeck, & Van Overwalle, 2012; Van Overwalle, 2009). Finally,

there may be mediating factors which may be influencing the relationship between mirror

systems and social cognition which are yet to be uncovered. There is a clear need for a

better understanding of the role mirror systems play in brain function. It is clear that

social cognition involves the integration of a number of distinct brain networks: Future

research will need to focus on better understanding how these networks work together

and what unique role mirror systems might play.

2.1.1. *Mirror systems in schizophrenia and bipolar disorder*

The finding in the current thesis of reduced mirror system activity on one measure of

mirror systems in bipolar disorder but not another, and no evidence for reduced mirror

system activity in schizophrenia could have a number of interpretations. Firstly, the

reliability of the current mirror system measures available must be questioned. Previous

results of mirror system studies in schizophrenia have been mixed, with under-activity,

over-activity and no difference from healthy comparison groups reported. Findings from

mirror system studies in other clinical groups, such as autism, have also been mixed

(Southgate & de C. Hamilton, 2008). Certainly there are no direct non-invasive methods

for detecting mirror neuron activity in humans, and there has been criticism from

researchers that the current methods for detecting mirror system activity are not adequate.

Given that our mirror system measures did show correlation, however, it is likely that

they are both tapping into a common underlying brain process. Assuming our findings do

indicate reduced mirror system activity in bipolar disorder but not schizophrenia, what

might this mean for each disorder?

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In schizophrenia, one possibility for the null finding with regard to mirror system activity is that mirror systems might be intact in this disorder. Schizophrenia is known to be associated with a number of other brain changes, including disruption to fronto-limbic circuits, reduced connectivity, and reduced volumes in a number of brain areas (Benedetti et al., 2009; Daskalakis, Fitzgerald, & Christensen, 2007; Frith, 1997; Hirao et al., 2008). These changes might be causing the social cognitive difficulties, rather than mirror systems. Further, the previous studies that reported reduced or increased mirror system activation might have detected downstream changes from other brain processes, such as changes to visual processing or attention, or reduced connectivity between frontal and parietal areas, which impacted on mirror system reactivity. Another possibility is that due to the heterogeneous nature of schizophrenia, mirror systems might be reduced in one group of individuals with schizophrenia but not another. Schizophrenia has been referred to as a "group of disorders" rather than a single disorder, due to variations on a genetic, neural and clinical level. It has been suggested that some clinical presentations of schizophrenia, such as those with predominantly negative symptoms, might preferentially involve reduced mirror system function.

Mirror system dysfunction in bipolar disorder could be caused by a number of mechanisms. Firstly, mirror systems could be reduced in bipolar disorder as a trait deficit. The current thesis examined mirror systems in euthymic bipolar disorder so that acute mood symptoms would not confound the results. There has been some speculation that a serotonin transporter gene associated with mood disorders might be associated with mirror system dysfunction (Canli & Lesch, 2007); however, there is no research directly testing this hypothesis. It could be that individuals with bipolar disorder who have this

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gene might experience changes to the mirror system at the onset of mood symptoms, which are maintained during euthymia. This, however, is highly speculative, and research exploring mood disorders and mirror systems specifically is needed to examine this possibility.

Alternatively, reductions in mirror systems in bipolar disorder could be caused by dysfunction in other areas of the brain. Alteration of activity in the dorsolateral prefrontal cortex, which is associated with a number of key cognitive functions, has been shown to alter mirror system reactivity in healthy individuals (Gangitano, Mottaghy, & Pascual-Leone, 2008), due to inputs to the mirror system from frontal regions. Given that individuals with euthymic bipolar disorder show changes in prefrontal regions, it is possible that these changes are having an impact on mirror system activity. Another possibility is that altered connectivity between brain regions might be having an impact on the system. White matter is known to be abnormal in bipolar disorder, and could be contributing to reduced activity in mirror systems (Mahon, Burdick, & Szeszko, 2010).

Overall, there is too much that is still unknown about mirror systems, including their function, interaction with other brain processes, or what their significance might be, to form any strong conclusions at this stage regarding mirror systems in schizophrenia or bipolar disorder. Regardless, our findings do indicate a possible reduction in mirror system function in bipolar disorder, indicating that further research is imperative.

2.1.2. Treatment implications

If future research confirms reduced mirror system activity in bipolar disorder, and clarifies a negative impact on the individual, then this could be a potential target for treatment. Sensorimotor learning has been shown to alter the activity of the mirror

system, suggesting that the mirror system is impacted by the experience of the individual (Catmur, Walsh, & Heyes, 2007). Further, non-invasive brain stimulation techniques such as repetitive TMS (rTMS), deep TMS and transcranial direct current stimulation can be used to modulate the excitability of a particular region of the brain, and via neuronal plasticity ultimately altering the function of brain networks. These techniques have been used to improve symptoms in psychiatric disorders, particularly depressive symptoms and cognitive impairment (Bersani et al., 2013; Demirtas-Tatlidede, Vahabzadeh-Hagh, & Pascual-Leone, 2013). Indeed, in one study of healthy individuals, rTMS targeted at the prefrontal cortex resulted in increased motor resonance, possibly via a reduction in the influence of prefrontal inhibitory mechanisms (Gangitano et al., 2008). Although more research is needed, these findings imply that social cognition might be improved by directly targeting relevant areas of the brain. Recently, a case study reported improvement in social functioning in a patient with Asperger's disorder, following deep rTMS targeting the mPFC (Enticott, Kennedy, Zangen, & Fitzgerald, 2011). Because some preliminary evidence suggests that brain stimulation effects can be enhanced by simultaneous cognitive activity (Andrews, Hoy, Enticott, Daskalakis, & Fitzgerald, 2011), one exciting possibility for future treatment might be the combination of social cognitive remediation techniques with brain stimulation to relevant brain areas, for enhanced effect.

3.   Limitations

3.1. Clinical samples

One key limitation of the current research was the sample size, which meant that some analyses might have been underpowered to detect subtle differences between

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groups, while others (such as regression or subgroup analyses) could not be undertaken at all. Recruiting sufficient numbers in clinical research is always a challenge in this type of neurophysiological research, because of the more involved methodology. Although the sample sizes in the current thesis were similar to other similar studies, the lack of consistency of findings in this area indicates that larger sample sizes are needed. In psychiatric research this is particularly important, given the heterogeneity of individuals in these groups, who can vary on attention, cognitive ability, mood and other clinical feature, all of which can affect the reliability of the results.

3.2.Social cognition measures

There were some limitations to the social cognition measures used in the current research. Our ToM task, the Yoni task, discriminated between cognitive and affective ToM but did not discriminate between ToM errors due to under- verus over-mentalising. This limited our ability to test the hypotheses that we generated following our unexpected mirror system results. Further, the Yoni task, while not overly reliant on language or executive function, is static and has an abstract component to it. Given that the mirror system seems to be most strongly activated when viewing movement and concrete goals, the use of this task somewhat limits any conclusions that can be drawn regarding a lack of correlation between the mirror system measures and ToM. Other ToM tasks, such as those which utilise video-based vignettes, or geometric moving shapes which are ascribed intentions, might be better measures to employ in future studies exploring mirror systems and social cognition. However, given that some studies have identified the engagement of mirror system areas to static face and hand stimuli (Enticott, Johnston, et al., 2008;

Montgomery & Haxby, 2008), future research should also focus on understanding what activates the mirror system and how it might interact with other networks.

In the current thesis, self-report empathy measures were used. While the IRI has been commonly used in empathy research, self-report is limited by the level of insight and honesty of participants, which might be impacted by impressions of social desirability. While objective behavioural measures of empathy are not currently feasible, given the inherently subjective nature of empathy, the combination of empathy with imaging studies might allow for the detection of absence or alteration of brain activity during empathy tasks. Indeed, studies exploring other social cognitive abilities in euthymic bipolar disorder discovered altered brain activity in the context of relatively intact accuracy (Malhi et al., 2008; Malhi et al., 2007) indicating that combining imaging with behavioural measures might be beneficial for understanding a range of social cognitive processes in clinical disorders.

A final broader limitation, common to most social cognition research, is the lack of properly validated and normed social cognitive measures (Harrington et al., 2005; Samamé et al., 2012). While many measures have face validity, and may discriminate between clinical groups, their level of construct and concurrent validity has not always been established. In order to reach any firm conclusions about social cognitive deficits in different clinical groups, researchers need to develop well-validated consensus measures, which can be used across studies, allowing for proper comparisons across research.

3.3.Mirror system measures

Studies of mirror systems in humans are limited by the necessarily non-invasive and indirect nature of the measures employed (Heyes, 2010). Putative measures of the mirror

system assess activity in whole brain areas, rather than at the level of the individual

mirror neuron. Because of this, some researchers have expressed doubt of the accuracy of

the measures, and research that examines the concurrent validity of mirror system

measures is important. Other than the current thesis, the only study to date that has

included both measures of EEG and TMS did not find a correlation between mu

suppression and motor resonance (Lepage et al., 2008). The authors theorised that mu

suppression and motor resonance might each reflect different aspects of the mirroring

process (sensory and motor aspects, respectively). While our study, with a larger sample

size, found a significant relationship between these two measures across the three groups,

this correlation was only in the moderate range, and the results of our between group

analyses were not consistent across the measures. This indicates that there is a significant

amount of variance currently unaccounted for in these measures. Current TMS and EEG

procedures are prone to human error. For example, with TMS, there is always the

possibility that the coil may inadvertently slip from the target location or be placed at an

incorrect angle, which can impact on the effectiveness of eliciting the desired response.

Further, other aspects, such as attention and anxiety, can impact on level of corticospinal

excitability. Learning what contributions other cognitive domains, such as attention,

might have on mirror system function, would allow for this to be accounted for in future

research. A limitation of the EEG methodology in the current thesis stemmed from the

inclusion of TMS and EEG in the same study. For participant comfort, the number of

TMS trials included in a mirror system study must be limited. In order to have enough

trials to run the EEG analysis in our study, all conditions that included biological

movement were combined, and so it was not possible to compare the different types of

movement for differences in mu suppression response. Further, the TMS pulse can also reduce the amount of useable EEG data. There is a clear need for future research aimed at improving the sensitivity and specificity of mirror system measures in humans, and ensuring they work well together, so that findings in this area can be interpreted with more confidence.

4.   *Future Directions*

In order to make headway in understanding the neurobiological contributors to reduced social cognition in schizophrenia and bipolar disorder, it is imperative that much larger samples be recruited. Large samples would allow for sufficient power and more confidence in any results, as well as allow for more advanced statistical techniques and subgroup analysis. Given the challenges in assembling sufficiently large samples from individual research centres, collaboration across research groups would be a practical way to allow for these kinds of studies.

Given that relationships between social cognition and impact on quality of life are unlikely to be direct in schizophrenia or bipolar disorder, future research should explore potential mediating factors in these relationships. Further, understanding the role of mirror systems, as well as a possible role in psychiatric disorders, will rely on understanding how the mirror system interacts with other neural circuits. Functional and structural imaging studies will assist in this revealing these interactions.

Finally, the findings from the current thesis indicate the importance of using multiple measures of both brain function and behaviour, in order to verify the validity of measures used, and to better understand the interaction between brain and behaviour on a number of different levels. Our findings reiterate the importance of moving beyond research

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within diagnostic groups, instead focusing on understanding what similarities and differences in clinical presentation and neuropathology exist across psychiatric disorders. Insights into these shared mechanisms might ultimately guide treatments that target underlying causes of poor functional outcome regardless of diagnosis, to improve quality of life in these disorders.

5. Conclusion

Schizophrenia and bipolar disorder share genetic markers, as well as some clinical signs and symptoms. Despite improvement in acute clinical symptoms, quality of life as well as social function often remains reduced in both disorders during remission, and the reasons for this remain unknown, although the contribution of social cognitive deficits have been suggested. The overall aim of the current thesis was to assess mirror systems as a possible contributor to the social cognitive deficits often observed in schizophrenia and euthymic bipolar disorder. We comprehensively assessed social cognition and mirror system function, as well as other cognitive, clinical and quality of life variables across a schizophrenia, euthymic bipolar disorder, and healthy control group. We found clear evidence for cognitive ToM deficits in both disorders, and the addition of impairment in the recognition of anger in the schizophrenia group, indicating some likely shared underlying neuropathology, but also disorder-specific differences. There was some evidence for reduced mirror systems in euthymic bipolar disorder but not in schizophrenia, and mirror system function was not strongly related to any of the social cognitive measures included in this study. This thesis provides valuable insights into social cognition in schizophrenia and bipolar disorder, as well as calling into question the proposed important role of mirror systems in social cognition. These findings further

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support the importance of considering social cognitive dysfunction in assessment and treatment planning in schizophrenia and bipolar disorder, as well as further research aimed at understanding the neurobiology of social cognition so that future treatments can target social cognitive deficits at both a neurobiological and behavioural level, with an aim to significantly improve outcomes for patients.

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