Dissecting Shared and Unique Neural Circuitry Underlying Negative Symptoms, Social Cognition, and Functional Outcome in Schizophrenia

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science

Institute of Medical Science
University of Toronto

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Master of Science
Institute of Medical Science
University of Toronto
2015

Abstract

Schizophrenia is a devastating illness with significant disability and poor long-term clinical and functional outcome. Negative symptoms and social cognitive impairments are two key symptom domains that affect functional outcome in schizophrenia. This thesis explores the shared and unique neural circuitry related to negative symptoms, social cognition, and functional outcome in schizophrenia. In study one, the relationship between white matter fractional anisotropy, negative symptoms, and functional outcome in schizophrenia participants was investigated. Study two includes a broad sample of patient and healthy control populations, which is in line with the RDoC methodology. In this study, the relationship between white matter tracts implicated in functional outcome and social cognitive domains was investigated in a sample of schizophrenia, bipolar disorder, and healthy control participants on a continuum of social cognitive performance. Taken together, these studies elucidate circuitry that may be impaired in schizophrenia, and may represent neurobiological correlates of negative symptoms, social cognition, and functional outcome.
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And thank you to our research participants and others who make this work possible. To all who struggle with mental illness, service users, and consumer/survivors, I hope you find your recovery, however you choose to define it.
Contributors

Tina Behdinan wrote the manuscripts and performed majority of the image processing and statistical analysis for studies one and two.

George Foussias, Gary Remington, Tarek Rajji, and Laura Stefanik recruited participants and conducted clinical and neuropsychological assessments for study one participants. Judy Kwan and Mikko Mason recruited and conducted clinical and neuropsychological assessments for study two participants.

Daniel Felsky contributed to image analysis (specifically tractography for study one).

Anne Wheeler was instrumental in conducting the cortical coupling analysis in study one.

Jon Pipitone and Joseph Viviano are part of the technical support team in the Kimel Family TIGR Lab. They manage the computing cluster and were helpful in debugging scripts for image processing and data organization. Arash Nazeri was also helpful in debugging scripts for data organization.

Mallar Chakravarty supervised image processing.

Aristotle Voineskos is the principal investigator, and contributed to manuscript writing, image processing, and statistical analysis.
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<tbody>
<tr>
<td>AIMS</td>
<td>Abnormal Involuntary Movement Scale</td>
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<tr>
<td>BACS</td>
<td>Brief Assessment of Cognition in Schizophrenia</td>
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<tr>
<td>BAS</td>
<td>Barnes Akithisia Scale</td>
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<tr>
<td>C/S</td>
<td>consumer/survivor</td>
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<tr>
<td>CIRS-G</td>
<td>Cumulative Illness Rating Scale for Geriatrics</td>
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<td>CDSS</td>
<td>Calgary Depression Scale for Schizophrenia</td>
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<tr>
<td>DS</td>
<td>Deficit Syndrome</td>
</tr>
<tr>
<td>DSM-5</td>
<td>Diagnostic and Statistical Manual of Mental Disorders - 5</td>
</tr>
<tr>
<td>DT</td>
<td>Diffusion Tensor</td>
</tr>
<tr>
<td>DTI</td>
<td>Diffusion Tensor Imaging</td>
</tr>
<tr>
<td>FA</td>
<td>Fractional Anisotropy</td>
</tr>
<tr>
<td>IFO</td>
<td>Inferior Fronto-Occipital Fasciculus</td>
</tr>
<tr>
<td>MATRICS</td>
<td>Measurement and Treatment Research to Improve Cognition in Schizophrenia</td>
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<tr>
<td>MCCB</td>
<td>MATRICS Consensus Cognitive Battery</td>
</tr>
<tr>
<td>MD</td>
<td>Mean Diffusivity</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini Mental State Examination</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>MSCEIT</td>
<td>Mayer-Salovey-Caruso Emotional Intelligence Test</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>NDS</td>
<td>Non-Deficit Syndrome</td>
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<tr>
<td>NIMH</td>
<td>National Institute of Mental Health</td>
</tr>
<tr>
<td>PANSS</td>
<td>Positive and Negative Symptom Scale</td>
</tr>
<tr>
<td>PLS</td>
<td>Partial Least Squares</td>
</tr>
<tr>
<td>PLSPM</td>
<td>Partial Least Squares Path Model(ing)</td>
</tr>
<tr>
<td>QLS</td>
<td>Quality of Life Scale</td>
</tr>
<tr>
<td>RBANS</td>
<td>Repeatable Battery for the Assessment of Neuropsychological Status</td>
</tr>
<tr>
<td>RDoC</td>
<td>Research Domain Criteria</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>SANS</td>
<td>Scale for the Assessment of Negative Symptoms</td>
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<tr>
<td>SAS</td>
<td>Symptom Angus Scale</td>
</tr>
<tr>
<td>SLF</td>
<td>Superior Longitudinal Fasciculus</td>
</tr>
<tr>
<td>SS</td>
<td>Sagittal Stratum</td>
</tr>
<tr>
<td>TASIT</td>
<td>The Awareness of Social Inference Test</td>
</tr>
<tr>
<td>TBSS</td>
<td>Tract-Based Spatial Statistics</td>
</tr>
<tr>
<td>UF</td>
<td>Uncinate Fasciculus</td>
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<tr>
<td>WTAR</td>
<td>Wechsler Test for Adult Reading</td>
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Chapter 1

1 Introduction

1.1 Schizophrenia

1.1.1 Epidemiology & Diagnosis

Originally termed “dementia praecox” by Emil Kraepelin (Kraepelin, 1971), schizophrenia was believed to be a form of early dementia, characterized by mental deterioration and poor longitudinal course and outcome (Tandon, Nasrallah, & Keshavan, 2009). It was later renamed by Eugen Bleuler (Bleuler, 1950), whose description of schizophrenia focused on negative symptoms and suggested variability in outcomes. In contrast, Schneider’s first rank symptoms of schizophrenia describe the positive symptoms (hallucinations, delusions) associated with the illness (Schneider, 1959). Today, diagnosis of schizophrenia hinges on the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), which incorporate chronicity of illness (signs of disturbance must persist for at least 6 months with at least 1 month of positive/negative/disorganized symptoms), negative symptoms, positive symptoms, and social or occupational dysfunction (Tandon et al., 2013). In general, schizophrenia is more accurately described as a syndrome, with considerable heterogeneity in symptom presentation, course of illness, and outcome (Carpenter & Kirkpatrick, 1988; Heinrichs & Zakzanis, 1998).

The lifetime risk of developing schizophrenia ranges from 0.3 – 2.0%, with similar prevalence in males and females (Saha, Chant, Welham, & McGrath, 2005). Increased risk of developing schizophrenia is associated with urbanicity, male gender, history of migration, and higher paternal age (Malaspina et al., 2001). Though schizophrenia is known to run in families
(having an affected family member substantially increases the risk of developing schizophrenia) 
(Kendler et al., 1993), the nature of genetic contribution to disease liability is still being 
investigated. Another active area of schizophrenia research involves interactions between genetic 
and environmental factors and their relationships to neurobiological mechanisms of disease.

Earlier onset of schizophrenia is associated with poorer prognosis (DeLisi, 1992). Schizophrenia usually develops between late adolescence and early adulthood, with males presenting with psychotic symptoms at an earlier age than females. In addition, the distribution of age at onset is bimodal for females, with a second peak later in life. Females generally tend to have better premorbid functioning, more severe affective symptoms, less severe negative symptoms and cognitive impairment, and better overall prognosis (Leung & Chue, 2000).

1.1.2 Symptomology, Neurocognition, and Social Cognition

Positive symptoms of schizophrenia include hallucinations, which can occur in any sense (auditory hallucinations are the most common), delusions, disorganization (poverty of content of speech, attentional impairment, and inappropriate affect), and a lack of appreciation that symptoms are caused by illness (Foussias, Agid, & Remington, 2011; Picchioni & Murray, 2007). Positive symptoms are not specific to schizophrenia and follow an independent course from negative symptoms over time (Eaton, Thara, Federman, Melton, & Liang, 1995).

Interest in negative symptoms has grown with evidence that they substantially affect functional outcome, with some claiming that they are the best predictor of functional recovery in schizophrenia (Blanchard, Horan, & Collins, 2005; Bowie, Reichenberg, Patterson, Heaton, & Harvey, 2006; Ho, Nopoulos, Flaum, Arndt, & Andreasen, 1998; Milev, Ho, Arndt, & Andreasen, 2005; Rosenheck et al., 2006). Negative symptoms are refractory to conventional
treatments (Stahl & Buckley, 2007) and have been categorized into two domains: 1. Diminished expression, including affective flattening and poverty of speech; and 2. Amotivation, including avolition/apathy, anhedonia (more accurately, anticipatory pleasure deficit as hedonic capacity is preserved in schizophrenia), and asociality (Foussias et al., 2011). Affective flattening and poverty of speech refer to reduced emotional expression and the lack of additional unprompted speech observed in schizophrenia, respectively. Avolition is the primary symptom domain of emphasis by Kraepelin, indicating a lack of motivation in schizophrenia. Avolition presents as apathy and asociality and may be linked to anticipatory pleasure deficits in schizophrenia. In the past, negative symptoms were thought to include inattention, inappropriate affect, and poverty of content of speech; however, these symptoms have been appropriately reclassified into the disorganization symptom domain (Foussias et al., 2011). Primary negative symptoms are a direct expression of schizophrenia psychopathology, while secondary negative symptoms are a consequence of medication effects, depressive anhedonia, paranoid social withdrawal, or preoccupation with psychotic symptoms (Carpenter, Heinrichs, & Wagman, 1988).

It has been claimed that all persons with schizophrenia have some form of neurocognitive deficit (Kremen, Seidman, Faraone, Toomey, & Tsuang, 2000; Palmer et al., 1997). Schizophrenia is associated with widespread neurocognitive deficits, including impairments in attention, verbal memory, executive function (higher order cognitive functions that control decision making), verbal fluency (semantic and phonemic fluency, related to language abilities), motor speed, and processing speed (the ability to process new information rapidly and efficiently) (Harvey, Green, Keefe, & Velligan, 2004; Swerdlow, 2010). The National Institute of Mental Health (NIMH) Measurement and Treatment Research Initiative to Improve Cognition in Schizophrenia (MATRICS) substantiates the importance of neurocognition in achieving functional recovery for individuals with schizophrenia.
Although negative symptoms are moderately correlated with several domains of cognition, they only explain 10% of the variance in cognitive impairment in schizophrenia (Harvey, Koren, Reichenberg, & Bowie, 2006). A recent longitudinal study showed that these symptom domains do not change in parallel over time, allowing them to be classified as semiautonomous disease processes (Bell & Mishara, 2006). Thus, negative symptoms have been validated as a separate domain of psychopathology of schizophrenia (Kirkpatrick, Fenton, Carpenter, & Marder, 2006).

Social cognition is defined as the mental operations that underlie social interactions, including perception, interpretation, and response generation to the intentions, dispositions, and behaviours of others (Kunda, 1999) and is significantly impaired in people with schizophrenia. Social cognitive impairment is thought to be a trait feature of schizophrenia, as it is stable in first episode patients over a 12-month follow-up period and is also comparable across phase of illness (prodromal, first episode, and chronic schizophrenia patients) (Green et al., 2012; Horan et al., 2012). Social cognitive processes are essential for the successful execution of complex social behaviours necessary in daily life. As such, social cognition is a key determinant of functional outcome in schizophrenia (Couture, Penn, & Roberts, 2006; Horan et al., 2012).

Although social cognition and neurocognition are highly related constructs, sophisticated statistical analyses have shown that these domains are distinct and therefore not redundant (Sergi et al., 2007). The relationship between these domains is evident as they rely on shared cognitive processes, such as working memory and perception. However, their distinction is based on the type of stimulus and judgments being made in response to the stimulus (Green & Horan, 2010). Similarly, social cognition is distinct from negative symptoms and further analysis has revealed
that the relationship between these two symptom domains is weaker than the relationship between social cognition and neurocognition (Sergi et al., 2007).

### 1.1.3 Functional Outcome

As suggested by Bleuler, individual outcomes are variable in those diagnosed with schizophrenia. Although some individuals experience extended periods of recovery, long-term disability is common for people with schizophrenia due to impairments in social and occupational functioning (Jobe & Harrow, 2005).

A recent review concluded that schizophrenia is consistently associated with poorer course of illness and outcome compared to other psychiatric disorders (Jobe & Harrow, 2005). Substantial functional impairment has also been reported in schizophrenia (Breier, Schreiber, Dyer, & Pickar, 1991). Functional recovery, or functional outcome, includes social behaviours (such as communicating with others and engaging in the community), as well as maintaining employment and caring for oneself.

Historically, outcomes were assessed in accordance with the medical model, with a greater focus on the effects of pharmacotherapy and (positive) symptom resolution rather than social, work, or community functioning (Remington, Foussias, & Agid, 2010). This was based on the expectation that antipsychotic medication would help to control symptoms and allow for functional recovery in schizophrenia. In a sense, antipsychotics have met expectations by reducing the impact of positive symptoms, thereby improving clinical outcomes. However, reduction of positive symptoms has not been shown to be sufficient for attaining functional recovery (San, Ciudad, Álvarez, Bobes, & Gilaberte, 2007).
Over time, the definition of “outcome” has expanded to address other symptom clusters, such as neurocognition, social cognition, and negative symptoms, which are critical for functional recovery. Due to the limited efficacy of current treatments in addressing these symptoms, there has been increased interest in the neurobiological underpinnings of these symptom domains and functional outcome in schizophrenia. The relationships between these symptom domains and functional outcome, as well as associated neural circuitry, will be explored in the following sections. Briefly, the effect of neurocognitive impairment on functional outcome is mediated by social cognition and functional capacity (the ability to perform everyday tasks in a structured environment) (Bowie et al., 2006; Galderisi et al., 2014). In addition, negative symptoms, particularly amotivation (Foussias et al., 2011; Foussias, Mann, Zakzanis, van Reekum, & Remington, 2009), have been associated with poorer social and work functioning, as well as overall functional outcome (Breier et al., 1991).

1.1.3.1 Negative Symptoms and Functional Outcome

A recent meta-analysis of 73 studies concluded that negative symptoms mediate the relationship between neurocognition and functional outcome (Ventura, Hellemann, Thames, Koellner, & Nuechterlein, 2009). Negative symptoms, particularly amotivation, have also been shown to account for majority of the variance in longitudinal functional outcome (Foussias et al., 2011, 2009). In these studies, cognitive function did not offer any additional contribution to the prediction of functional outcome in schizophrenia. Amotivation may also affect the relationship between neurocognition and functional outcome by contributing to insufficient effort of schizophrenia participants during neuropsychological testing (Foussias & Remington, 2010). Lack of effort during neuropsychological testing is correlated with negative symptom severity in schizophrenia. Although there is a complex relationship between negative symptoms,
neurocognition, and functional outcome, it appears that neurocognition is related to functional capacity, while negative symptoms are related to the likelihood of implementation of abilities in real world scenarios (Bowie et al., 2006; Foussias & Remington, 2010).

1.1.3.2 Neurocognition and Functional Outcome

Green et al (Green, 1996) first demonstrated the relationship of neurocognition, specifically working memory, to functional outcome in schizophrenia patients. Since then, more complex models have shown that the relationship between neurocognition and functional outcome is mediated by functional capacity (Bowie et al., 2006; Galderisi et al., 2014). As such, neurocognitive performance is strongly associated with functional capacity, which is related to multiple domains of real-world functioning (social, occupational, and community functioning). In addition, neurocognitive performance contributes little to the prediction of real-world performance after accounting for functional capacity (Bowie et al., 2006). Therefore, it appears that neurocognitive performance is more closely related to a person’s ability to navigate the real world, rather than the actual implementation of these abilities.

1.1.3.3 Social Cognition and Functional Outcome

The role of social cognition as a mediator between neurocognition and functional outcome in schizophrenia is well supported (Galderisi et al., 2014; Green & Horan, 2010; Schmidt, Mueller, & Roder, 2011). In a recent review of the literature, this finding was replicated by several studies, both in cross-sectional and longitudinal designs (Green & Horan, 2010). As such, the strength of the relationship between neurocognition and functional outcome is reduced when social cognition is included in the model. Other variables such as social competence (analogous to social cognition as functional capacity is to neurocognition) and motivation
mediate the relationship between social cognition and functional outcome (Gard, Fisher, Garrett, Genevsky, & Vinogradov, 2009; Schmidt et al., 2011).

Social cognition can be broken down into four main domains (Green, Olivier, Crawley, Penn, & Silverstein, 2005; Penn, Addington, & Pinkham, 2006): 1. Theory of mind, which is the ability to attribute mental states (beliefs, feelings, perspectives) to oneself and to others, as well as recognizing that others’ mental states may not be the same as our own. This allows one to understand and predict the behaviour of others. 2. Emotion processing, which refers to the ability to understand and identify different emotions, as well as manage one’s own emotions. 3. Social perception, which is the ability to use verbal and nonverbal cues to understand a social situation based on context. 4. Attributional bias, which depends on whether a person typically attributes the causes of an event to internal, external, or situational factors (Green & Horan, 2010).

Exploratory factor analysis has revealed that social cognitive domains in schizophrenia patients load onto three separate factors, two of which influence functional outcomes. In this study, attributional bias was not related to functional outcome and loaded on one factor. Emotion recognition and social perception loaded onto a second factor representing lower level social cognitive processes, necessary for understanding the emotions and actions of others, while theory of mind loaded onto a third factor representing higher level social cognitive processes, necessary for understanding the mental states of others (Mancuso, Horan, Kern, & Green, 2011). Emotion recognition and social perception are considered to be lower level processes as they correspond to the experiential properties of a stimulus, whereas higher level symbolic interpretations of a stimulus are more accurately conceptualized as theory of mind (Ochsner, 2008). Both these lower and higher level processes were found to influence functional outcome (Mancuso et al., 2011) and are believed to correspond to separate neural networks: 1. An “embodied simulation or low-level mental state inference construct” involving the mirror neuron system and limbic
system and 2. A “high-level mental state/trait inference construct” involving cortical midline and lateral temporal structures (Ochsner, 2008).

1.1.4 Treatment

Up until the de-institutionalization movement after World War II (Novella, 2010), care for schizophrenia patients was mainly custodial and involved long-term inpatient admission to psychiatric hospitals. Effective pharmacotherapies were first introduced in the 1950s, known as first generation antipsychotics, followed by the production of second generation antipsychotics in the late 1960s. Antipsychotic medications have robust efficacy against positive and disorganization symptom domains (Leucht et al., 2009; Mazure, Nelson, Jatlow, & Bowers, 1992). However, they are not effective in reducing primary negative symptoms (Kirkpatrick et al., 2006; Leucht et al., 2009) or most neurocognitive deficits (Mishara & Goldberg, 2004; Mortimer, 1997). They are also not shown to improve lifespan or social functioning in schizophrenia (Lehman et al., 2004; Wunderink, Nieboer, Wiersma, Sytema, & Nienhuis, 2013) and are associated with severe adverse effects, including metabolic syndrome, extrapyramidal symptoms, and tardive dyskinesia (Tandon, Nasrallah, & Keshavan, 2010).

In order to target the broad symptom profile of schizophrenia, multimodal care is required (Kern, Glynn, Horan, & Marder, 2009). Psychosocial treatments recommended by the Patient Outcomes Research Team include Assertive Community Treatment to prevent hospitalization and homelessness, supported employment, skills training to improve community functioning, Cognitive Behavioural Therapy, and family based services, amongst others (Dixon et al., 2010). In addressing neurocognitive impairment of persons with schizophrenia, cognitive remediation has proved to be effective (McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007), while pharmacological augmentation using glycine is being investigated in the treatment of
negative symptoms (Coyle & Tsai, 2003; Heresco-Levy et al., 1999). Intranasal administration of oxytocin is also being explored as a possible therapy for social cognitive impairment in schizophrenia as well as in other psychiatric disorders (Davis et al., 2013). The NIMH Recovery After an Initial Schizophrenia Episode project combines medication management with psychosocial treatments to decrease the likelihood of long-term disability experienced by many people with schizophrenia.

In the future, personalized care will hopefully be available for people with schizophrenia, in order to address the variability in symptom presentation, course of illness, outcome, and response to treatments. To this end, neurobiological markers of various domains of emotion, cognition, and behaviour can be assessed on the macroscopic scale with diagnostic imaging techniques and can lead to more targeted treatments (Morris & Cuthbert, 2012).
1.2 Brain Morphology and Schizophrenia

1.2.1 Grey Matter Volume and Cortical Thickness Changes in Schizophrenia

Schizophrenia has been associated with ventricular enlargement, as well as increased grey matter volume of the basal ganglia and reduced grey matter volume of medial temporal lobe structures (amygdala, hippocampus, parahippocampal gyrus), the superior temporal gyrus, frontal lobe, thalamus, and inferior parietal lobule. It is believed that increased grey matter volume of the basal ganglia is a consequence of antipsychotic treatment (Shenton, Dickey, Frumin, & McCarley, 2001); however, antipsychotic treatment has been associated with smaller grey matter volumes as well (Ho, Andreasen, Ziebell, Pierson, & Magnotta, 2011). Enlargement of the lateral ventricles is one of the most robust findings in schizophrenia, and may be an indicator of neurodegeneration or neurodevelopmental pathology of adjacent structures, such as the amygdala and hippocampus (Shenton et al., 2001). Similarly, enlargement of the third ventricle may correspond to reduced thalamic volume.

In schizophrenia there are often differences in bilateral symmetry, with findings mainly lateralized to the left hemisphere of the brain. There is also greater leftward thalamic asymmetry (Csernansky et al., 2004), reduced laterality of the planum temporale (Ratnanather et al., 2013) and hippocampus (Kim et al., 2005), and reversal of asymmetry of the inferior parietal lobule (Buchanan et al., 2004). Overall, structural imaging has revealed abnormalities in multiple brain regions in schizophrenia (Shenton, Whitford, & Kubicki, 2010; Shenton et al., 2001).

The temporal lobe is the site of the superior temporal gyrus, which is the primary auditory cortex of the brain and is specialized for language and speech in the left hemisphere.
(Howard et al., 2000). Therefore, abnormalities in temporal lobe structures may correspond to auditory hallucinations and impairments in language processing (Barta, Pearlson, Powers, Richards, & Tune, 1990). The temporal pole, also affected in schizophrenia, is connected to the inferior frontal lobe (via the uncinate fasciculus), both of which are important for emotion recognition and processing (Frith & Frith, 2003; Iacoboni et al., 1999). Reversal of asymmetry of the inferior parietal lobule may result in similar emotion recognition impairments in schizophrenia, as well as impairments in neurocognition as it is a key region for integrating sensory information for perception and language processes (Catani, Jones, & Ffytche, 2005; Eidelberg & Galaburda, 1984). The frontal lobe serves a diverse set of higher order behavioural, cognitive, and emotional functions, and is involved in the complex clinical presentation of schizophrenia (Miyake et al., 2000). Medial temporal lobe structures such as the amygdala and hippocampus are part of the limbic system, which is important for emotion processing and memory, both of which are affected in schizophrenia (Holt et al., 2006; Squire, Stark, & Clark, 2004). Alterations in medial temporal and prefrontal cortical areas has also been consistently related to functional outcome in schizophrenia (Dazzan et al., 2015).

More recently, correlations of interregional grey matter volume or cortical thickness are being investigated in schizophrenia. It is suggested that these correlations represent anatomical connectivity or coupling between brain regions, as anatomically connected regions share trophic factors and correlate in size (Alexander-Bloch, Giedd, & Bullmore, 2013). Increased correlations may be indicative of overconnectivity, coordinated grey matter loss, or a lack of developmental specificity, while reduced correlations may be due to dysconnectivity or degeneration of brain regions. In schizophrenia, stronger frontoparietal relationships have been demonstrated in comparison to healthy control participants, which may correspond to deficits in social cognitive
processes and social function (Abbs et al., 2011; Buchanan & Pearson, 2004; Niznikiewicz et al., 2000).

1.2.2 White Matter Microstructural Changes in Schizophrenia

Schizophrenia was first theorized to be a product of alterations in cerebral connectivity by Friston and Frith (Friston & Frith, 1995). One way of assessing connectivity is to compute interregional correlations of grey matter morphology, as explained in section 1.2.1. While grey matter consists of cell bodies and dendrites, white matter consists of axonal projections and forms the basis for structural connectivity in the brain. White matter microstructure can be assessed via diffusion metrics, most commonly fractional anisotropy (FA), calculated from diffusion-weighted images.

White matter tracts most frequently identified as disrupted in schizophrenia include the uncinate fasciculus, cingulum bundle, corpus callosum, and internal capsule (Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011; Wheeler & Voineskos, 2014). These findings, coupled with decreased FA in the prefrontal and temporal lobes in schizophrenia (Kubicki et al., 2007), point towards frontotemporal dysconnectivity in schizophrenia. A recent meta-analysis reported that decreased FA was lateralized to the left hemisphere, which is consistent with the laterality observed in grey matter volumes in schizophrenia (Ellison-Wright & Bullmore, 2009). Another meta-analysis concluded that decreased FA was specific to interhemispheric fibers, including the anterior thalamic radiation, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, cingulum bundle, and fornix (Bora et al., 2011).

The uncinate fasciculus connects the temporal pole and amygdala to the inferior frontal lobe, and is therefore a key connection for intact social cognition (both mentalizing and emotion
processing) (Heide, Skipper, Klobusicky, & Olson, 2013). The cingulum bundle connects cortical midline structures, such as the medial prefrontal cortex and the posterior cingulate cortex, which are important for higher level social cognitive function, to be described in more detail in the following sections. The corpus callosum is a large interhemispheric connection, allowing for communication between the left and right hemispheres of the brain, and has been identified as important for social cognitive performance (Ingalhalikar et al., 2014). The inferior longitudinal fasciculus connects the occipital cortex to the fusiform gyrus, parahippocampal gyrus, and amygdala, and is therefore important for visuoemotional processing (Gur et al., 2007). Finally, the arcuate fasciculus, which connects the inferior frontal lobe to the inferior parietal lobule, is another disrupted circuit in schizophrenia, associated with auditory hallucinations in the left hemisphere and impaired emotion processing in the right hemisphere (de Weijer et al., 2011; Iacoboni et al., 1999).

There are considerable differences in findings across studies, which may be due to methodological differences, variability in symptom presentation of schizophrenia participants, and variation in confounding variables (Fitzsimmons, Kubicki, & Shenton, 2013; Melonakos et al., 2011). One such confounding variable may be antipsychotic treatment, which has been associated with decreased white matter volumes (Ho et al., 2011) and reductions in parietal and occipital white matter FA (Szeszko et al., 2014).

1.2.3 Neuroimaging Findings and Schizophrenia Symptomatology

Studies investigating negative symptoms and neural circuitry in schizophrenia report associations between negative symptom severity and frontotemporal white matter. Decreases in both volume (Sigmundsson et al., 2001) and FA (Szeszko et al., 2008) of the uncinate fasciculus have been associated with negative symptoms. Other regions have also been associated with
negative symptoms, including inferior frontal white matter, the inferior longitudinal fasciculus, internal capsule, and corpus callosum (Nakamura et al., 2012; Sigmundsson et al., 2001; Wolkin et al., 2003). Uncinate fasciculus and inferior longitudinal fasciculus impairment have also been implicated in deficit syndrome (DS) schizophrenia (Kitis et al., 2012; Rowland et al., 2009; Voineskos et al., 2013), which is characterized by prominent negative symptoms, thereby lending further support to the potential identification of these tracts as biomarkers for negative symptoms.

The neural underpinnings of neurocognitive performance in schizophrenia are still under investigation. Early studies assessing white matter microstructure-cognition relationships focused on a limited number of tracts, such as the cingulum bundle (Kubicki et al., 2003; Nestor et al., 2013; Takei et al., 2009) or the uncinate fasciculus (Kubicki et al., 2002; Nestor et al., 2013). Other implicated tracts include the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and superior longitudinal fasciculus (Karlsgodt et al., 2008; Liu et al., 2013). More recently however, neurocognitive deficits have been associated with subtle, widespread tract impairment in schizophrenia (Lim et al., 2006; Spoletini et al., 2009; Voineskos, Felsky, et al., 2013).

1.2.4 Neuropathology of the Deficit Syndrome

Schizophrenia was described by Kraepelin in 1919 as a disorder of volition (Kraepelin, 1971). The ‘deficit syndrome’ is a subtype of schizophrenia characterized by primary, enduring negative symptoms for which no effective treatment exists, as well as poor functional outcomes (Kirkpatrick, Buchanan, Ross, & Carpenter, 2001). This subtype of schizophrenia was originally described in 1988, and its construct has been shown to be valid and stable over time (Amador et al., 1999). Several studies have shown altered white matter connectivity in DS compared to
nondeficit syndrome (NDS) schizophrenia. Rowland et al (Rowland et al., 2009) reported altered frontoparietal connectivity in the DS, with reduced FA in the right superior longitudinal fasciculus (which includes the arcuate fasciculus) compared to NDS schizophrenia. Kitis et al (Kitis et al., 2012) demonstrated altered frontotemporal connectivity in the DS, specifically reduced FA in the left uncinate fasciculus, compared to NDS schizophrenia. Our group’s findings are in line with these studies as DS participants had altered connectivity in the left uncinate fasciculus, right arcuate fasciculus, and right inferior longitudinal fasciculus compared to NDS participants (Voineskos et al., 2013). These findings are further supported by structural correlation analysis, showing stronger coupling of frontoparietal and frontotemporal regions in DS participants (Wheeler et al., 2015). Interestingly, these tracts are associated with social cognitive processes, and so impairments in these tracts may correspond to poor social function in the DS. Overall, it appears that frontotemporal and frontoparietal connectivity may distinguish the neuropathology of the DS from NDS schizophrenia.

1.2.5 Neural Circuitry and Functional Outcome

Although there are several studies examining altered connectivity of white matter tracts in the DS, which is associated with particularly poor functional outcome, there are very few studies examining the direct relationship between neural circuitry and functional outcome. Karlsgodt et al (Karlsgodt, Niendam, Bearden, & Cannon, 2009) reported decreased FA in the left hippocampus and bilateral inferior longitudinal fasciculus as predictors of poor role functioning in individuals at ultra-high risk for psychosis, while decreased FA in the right inferior longitudinal fasciculus also predicted poor social functioning in ultra-high risk subjects. More recently, Kumar et al (Kumar et al., 2014) reported that white matter tract microstructure of the right inferior fronto-occipital fasciculus, corpus callosum, corona radiata, left cingulate
gyrus, and left posterior thalamic radiation predicted social and occupational performance in individuals with psychosis. However, neither study’s sample was specific to schizophrenia, with the former focusing on ultra-high risk for psychosis participants and the latter including people with bipolar disorder (who typically do not have negative symptom burden) with a history of psychosis.

More recently, macroscale wiring architecture of the human connectome has been studied in relation to general functioning in schizophrenia (Collin, de Nijs, Hulshoff Pol, Cahn, & van den Heuvel, 2015). However, in this study, symptom remission was included in assessments of general functioning in schizophrenia, thereby limiting the extent to which clinical and functional recovery can be studied as distinct constructs. Furthermore, the interpretation of the results their imaging analysis is limited to local and hub connectivity or organization of the connectome, rather than identifying specific white matter tracts as potential biomarkers of functional outcome. Therefore, the direct relationship between neural circuitry and functional outcome in schizophrenia is a novel and important area of exploration.
1.3 Neural Circuitry of Social Cognition

1.3.1 Neuroimaging Evidence for Lower Level Social Cognitive Circuitry

There is considerable evidence supporting the role of the human mirror neuron system in simulation (Iacoboni et al., 1999; Iacoboni et al., 2005) i.e. observation/imitation of action and emotion. Mirror neurons are named to reflect their defining property, which is that they fire during the execution of an action (including facial/bodily expressions of emotion) as well as during observation of the action/emotion when performed by another individual. Specifically, the mirror neuron system is activated not only during action recognition but also during intention understanding i.e. understanding the goal of the action in a given context (Iacoboni et al., 2005). It is important to emphasize that identifying goal-oriented actions is a lower level social cognitive process, while inference of mental states is a higher level process (Ochsner, 2008).

The mirror neuron system is lateralized to the right cerebral hemisphere and includes the inferior frontal gyrus and inferior parietal lobule (Iacoboni et al., 1999). These regions, along with the right superior temporal sulcus, form a right frontoparietal circuit connected by the right arcuate fasciculus. Neurons in the superior temporal sulcus respond to body movements engaged in goal-oriented actions, which includes dynamic facial expressions. Within the right frontoparietal circuit, the superior temporal sulcus provides a visual representation of observed actions, which is propagated to the inferior parietal mirror neurons. The inferior parietal mirror neurons code the kinesthetic details of the movement and send this information to the inferior frontal mirror neurons. These neurons code the goal of the action and send efferent copies of motor plans back to the superior temporal sulcus. Once the visual description of the observed action and predicted sensory consequences of the planned imitative action are matched, imitation
can be initiated (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003). The arcuate fasciculus is the white matter tract responsible for structural connectivity of these regions, and so dysconnectivity of this tract may result in impairments in simulation.

The neuronal network for these bottom-up stimulus-driven processes is critical for a person to be able to have shared emotional experiences and therefore empathize with others. Together with the limbic system, which is critical for emotion processing, the right frontoparietal circuit forms the neuronal basis for empathy. Empathic individuals demonstrate unconscious mimicry of postures, mannerisms, and facial expressions of conspecifics more so than others. This supports the notion that engagement of the right frontoparietal circuit through the imitation of facial emotions is a precursor to empathy and shared emotional experience (Tangney, Stuewig, & Mashek, 2007).

In a recent study (Carr et al., 2003), functional magnetic resonance imaging was used to compare activation in the inferior frontal cortex, superior temporal cortex, and amygdala when subjects were either observing or imitating emotional facial expressions. Results showed increased activity of these regions during imitation compared with observation, indicating functional connectivity of frontoparietal and limbic regions during simulation. Structurally, the amygdala and fusiform gyrus are connected to the visual cortex by the inferior longitudinal fasciculus. This tract has been implicated in facial recognition and visuoemotional processing (Crespi et al., 2014; Philippi, Mehta, Grabowski, Adolphs, & Rudrauf, 2009). Thus, the inferior longitudinal fasciculus not only facilitates structural connectivity of limbic regions to other structures, but is also important for emotion recognition and processing. Together, the inferior longitudinal and arcuate fasciculi subserve the lower level simulation network and may be implicated in deficits in corresponding social cognitive processes in schizophrenia.
1.3.2 Neuroimaging Evidence for Higher Level Social Cognitive Circuitry

The simulation network is insufficient for representing complex mental states, which requires the interpretation of contextual information that can drastically affect the meaning of social actions (e.g. sincerity vs. sarcasm or lying). It has been proposed that a separate network of cortical midline and lateral temporal structures is responsible for theory of mind, also called mentalizing. Several studies have concluded that the mirror neuron system and the mentalizing network are distinct from one another (Van Overwalle & Baetens, 2009; Wheatley, Milleville, & Martin, 2007).

Meta-analytic data of studies investigating the neural correlates of higher level social cognitive processes in healthy individuals show that cortical midline structures (the medial prefrontal cortex, posterior cingulate cortex, and precuneus) and lateral temporal structures (the temporoparietal junction and temporal pole) are nodes of the mentalizing network (Mar, 2011). However, impairments in these regions has not been directly associated with social cognitive performance in schizophrenia (Holt et al., 2011). It is likely that different regions support different subprocesses required for mentalizing and it would be interesting to explore whether dysconnectivity between these regions prevents the integration of these subprocesses, resulting in impaired social cognition.

The medial prefrontal cortex is believed to support several social cognitive processes including mentalizing, as well as non-social processes such as attention (Amodio & Frith, 2006). Functional neuroimaging studies consistently point to activation of this region during mentalizing (Frith & Frith, 2003), as well as when reflecting on one’s own emotional states (Gusnard, Akbudak, Shulman, & Raichle, 2001; Lane, Fink, Chau, & Dolan, 1997) and character
traits (Johnson et al., 2002; Macrae, Moran, Heatherton, Banfield, & Kelley, 2004). Thus, this region is important for attributing mental states to oneself and to others.

The posterior cingulate cortex is associated with a range of functions, including attention and mentalizing (Laird et al., 2011; Leech & Sharp, 2014; Mar, 2011). It is closely interconnected with the precuneus, which is also associated with theory of mind tasks (Laird et al., 2011). The precuneus is considered to have an anterior region associated with mental imagery involving the self and a posterior region associated with episodic memory retrieval (Cavanna & Trimble, 2006). Thus, the anterior precuneus supports imagery or imagination processes that may be required to infer the mental states of others.

Activation of the temporoparietal junction is associated with and specific to tasks regarding reasoning about the content of another’s mental states (Saxe & Kanwisher, 2003). Together with the temporal pole, the temporoparietal junction has been implicated in mentalizing (Frith & Frith, 2003; Völlm et al., 2006). The temporal pole is part of the limbic system (Heimer & Van Hoesen, 2006) and has been linked to a variety of social cognitive processes, including face recognition and theory of mind, along with semantic memory (Olson, Plotzker, & Ezzyat, 2007).

These neural circuits overlap with the default mode network, which is active when humans are not engaged in any specific task and is associated with processes reliant on internally focused attention, such as self-reflection and mentalizing (Corbetta, Patel, & Shulman, 2008; Mars et al., 2012; Schilbach, Eickhoff, Rotarska-Jagiela, Fink, & Vogeley, 2008). It has been proposed that this is because humans have a predisposition for social cognition as the default mode of thought (Schilbach et al., 2008), as well as because of the unconstrained nature of higher order social cognitive processes (Mars et al., 2012). Therefore, structural connectivity of
the cortical midline and lateral temporal circuits may be linked to functional connectivity within the default mode network.

Structurally, the cingulum bundle connects the posterior cingulate cortex to the medial prefrontal cortex, while the genu of the corpus callosum connects the left and right medial prefrontal cortex. This is supported by studies showing a direct association between microstructural organization of the cingulum and the strength of default mode functional connectivity (Greicius, Supekar, Menon, & Dougherty, 2009; van den Heuvel, Mandl, Luigjes, & Hulshoff Pol, 2008). The uncinate fasciculus is another white matter tract of interest in higher level social cognitive processes, as it connects the medial prefrontal cortex to the temporal pole and amygdala. This is supported by studies combining structural and functional neuroimaging to show that increased structural connectivity of the uncinate fasciculus is associated with greater coupling of the amygdala and temporal regions involved in higher order social cognition (Carlson, Cha, & Mujica-Parodi, 2013).
1.4 Imaging Modalities and Analysis

1.4.1 Cortical Thickness Analysis Using Magnetic Resonance Imaging

Cortical thickness has been a measure of cortical neuroanatomy since the early work by Brodmann (Brodmann, 1909). Neuroimaging studies have provided substantial evidence for widespread cortical and subcortical grey matter abnormalities in schizophrenia (Shenton et al., 2010; Shenton et al., 2001), while postmortem studies have revealed abnormalities in cortical cytoarchitecture in schizophrenia (Rajkowska, Selemon, & Goldman-Rakic, 1998; Selemon, Mrzljak, Kleinman, Herman, & Goldman-Rakic, 2003). In contrast to volumetric studies, cortical thickness findings are among the most replicable patterns of results in studies of brain morphology in schizophrenia. Therefore, investigating regional cortical thickness in schizophrenia may provide valuable insight into the neurobiological markers and pathophysiology of this disorder.

Cortical thickness may represent cell density and arrangement, with changes in thickness reflecting atypical neurogenesis, neuronal migration, differentiation, synaptogenesis, and synaptic pruning, all of which have been implicated in schizophrenia (Jakob & Beckmann, 1986). As such, magnetic resonance imaging (MRI) and cortical thickness analysis can allow us to model changes in neural processes in the cerebral cortex with regional specificity.

Manual delineation of cortical thickness has been replaced by more reliable and automated techniques. Specifically, the CIVET pipeline was used to acquire cortical thickness measures in the experiments detailed in the following sections. Cortical thickness is measured as the distance between the grey matter/white matter boundary and pial surface of the brain, each of
which is modeled by a three-dimensional polygonal mesh with 40,962 vertices per hemisphere (Lerch & Evans, 2005). Vertex-wise statistical analysis can then be used to visualize group differences of cortical thickness across the entire cortex. The images can also be segmented to calculate the average thickness of each cortical region per subject (Shattuck et al., 2008).

Segmenting the cortex using the LONI Probabilistic Brain Atlas allows for the calculation of average thickness values for 52 cortical regions (Shattuck et al., 2008). It has been previously demonstrated that the thickness of one region influences the thickness of other structurally and functionally connected regions (Alexander-Bloch et al., 2013). Therefore, average cortical thickness values can be used in structural covariance analysis, a measure of cortical connectivity, to complement white matter findings.

1.4.2 Measuring White Matter Microstructure Using Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) was developed relatively recently, making it possible for in vivo visualization and analysis of white matter in the brain. In 1996, Pierpaoli acquired the first DTI of the human brain, and in 1998 Buchsbaum conducted the first DTI study of schizophrenia (Buchsbaum et al., 1998; Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996). Diffusion weighted images are acquired by applying diffusion-sensitizing gradients in multiple directions to measure the diffusion of water and infer tissue structure and orientation (Jones, 2008).

The degree of anisotropy depends on how restricted the diffusion of water is in different directions. In cerebrospinal fluid, water is unrestricted in all directions and diffusion is said to be isotropic. On the other hand, in white matter, the diffusion of water is restricted along the fiber
and so diffusion is anisotropic. Once diffusion weighted images are acquired, a tensor (i.e. an ellipsoid) can be fitted at each voxel to represent the distance of water diffusion in all directions at that voxel, thereby providing information about the orientation of the tract as well as the underlying tissue structure. From this tensor, diffusion metrics can be calculated, with fractional anisotropy and mean diffusivity (MD) being most commonly used in neuroimaging studies (Jones, 2008).

FA provides information about the shape of the diffusion tensor and is independent of fiber orientation, with values ranging from 0 (isotropic diffusion) to 1 (maximum anisotropic diffusion). MD on the other hand, provides information on the size of the diffusion tensor, or the average displacement of water molecules within the voxel. Therefore, as MD increases in value, diffusion of water is less restricted, as in cerebrospinal fluid, as opposed to white matter. Although a change in these diffusion metrics is not specific to a single biological interpretation, decreases in FA and increases in MD are associated with axonal damage, reductions in the number/density/coherence of axons, and demyelination (Mori & Zhang, 2006). Decreased FA and increased MD have been consistently reported in schizophrenia, supporting the dysconnectivity hypothesis of schizophrenia (Frith & Frith, 2003). Furthermore, changes in these measures of white matter microstructure have been associated with various behavioural measures, reviewed by Johansen-Berg (Johansen-Berg, 2010).

DTI analysis involves preprocessing steps to register the diffusion-weighted images and correct for distortions due to eddy currents and motion artifacts. This is followed by fitting the tensor, which can then be used either to calculate diffusion metrics or as the input for tractography (Soares, Marques, Alves, & Sousa, 2013). Tractography is a method for modeling the trajectory of white matter tracts in order to assess structural connectivity in the brain (Mori &
van Zijl, 2002). It is achieved by constructing streamlines from local estimates of fiber orientation (i.e. the tensor). Diffusion metrics can then be calculated and averaged along each white matter tract.

Here, the first experiment makes use of a reliable automated clustering tractography pipeline (O’Donnell et al., 2006; Voineskos et al., 2009). Rather than rely on manual placement of regions of interest (ROI) to delineate tracts of interest, white matter fibers are grouped together based on shape and similarity. White matter tracts can then be visualized and diffusion metrics can be calculated along each tract. This method has been shown to be reliable and in high agreement with other tractography methods in both healthy control and schizophrenia populations (O’Donnell et al., 2006; Voineskos et al., 2009). One of the advantages of this method over manual ROI placement is reduced possibility for human error, as well as less opportunity for user bias since the user cannot visualize the diffusion tensors when assigning fiber clusters to a tract.

Another method for DTI analysis is called Tract-Based Spatial Statistics (TBSS), which addresses the limitations of traditional voxelwise approaches by: 1. Aligning FA images from multiple subjects using carefully tuned non-linear registration; and 2. Introducing an alignment-invariant tract representation so as to avoid the arbitrariness of spatial smoothing (Smith et al., 2006). Similar to our automated clustering tractography pipeline, the TBSS pipeline can be combined with ROI placements to calculate average FA values along tracts of interest in each subject, for use in group comparisons or more sophisticated statistical modeling or regression analyses (Jahanshad et al., 2013).
1.4.3 Partial Least Squares Path Modeling

Partial least squares (PLS) path modeling is a multivariate statistical method that allows for multiple relationships between blocks of variables to be analyzed in a prespecified model, thereby taking into account background information on the phenomenon of interest. It exists at the intersection of regression analysis, structural equation modeling, and multiple table analysis (Sanchez, 2013). More detailed explanations of PLS and PLS path modeling have been published (McIntosh & Lobaugh, 2004; McIntosh, Bookstein, Haxby, & Grady, 1996; Sanchez, 2013). PLS has several advantages over univariate statistical methods: 1. It has increased power to detect relationships between sets of variables in a sample; 2. It can be used to analyze data where variables in a single block are highly correlated; 3. It uses resampling algorithms to validate findings (resulting in increased certainty in findings compared to univariate tests of significance) (McIntosh & Lobaugh, 2004).

In PLS path modeling, each block of variables is reduced to a latent variable representing a theoretical concept (e.g. several white matter tract FA values can be reduced to a ‘neural circuitry’ latent variable), which is analogous to a factor in principal component analysis. PLS path modeling is robust to small sample sizes and does not impose any assumptions with respect to the distribution of data. In order to maximize the explained variance of the dependent variables, PLS path modeling looks for a linear combination of independent variables in such a way that the obtained latent variables take into account the relationships in the outer model (model of latent variables) and inner models (loadings of manifest variables onto latent variables). It also allows for causal relationships to be explored.
1.4.4 Clinical and Cognitive Measures of Interest

The heterogeneity of methods used to assess social cognition in schizophrenia populations has been shown to contribute to inconsistencies in findings across studies (Bora, Yucel, & Pantelis, 2009). As such, the Social Cognition Psychometric Evaluation study aims to achieve consensus of social cognitive domains in schizophrenia and to evaluate psychometric properties of existing scales (Pinkham et al., 2013). The Awareness of Social Inference Test (TASIT) is one such measure of social cognition and was originally developed for assessing theory of mind after traumatic brain injury (McDonald, Flanagan, Rollins, & Kinch, 2003). The TASIT uses video vignettes to allow for recognition of complex and spontaneous emotional displays, akin to those encountered in daily life (as opposed to static displays in the form of photographs). Consistent with this goal, the actors in the vignettes were trained in the “method” style so as to produce as natural a stimulus as possible. The TASIT has been shown to be suitable for use in both healthy and schizophrenia populations (Kern et al., 2009) and includes three subtests. Part 1 of the TASIT is the Emotion Evaluation test, and involves identifying six basic emotions from 28 short vignettes, with a maximum score of 28. Part 2 of the TASIT is the Social Inference-Minimal test, which includes 15 vignettes, 5 of which display sincere exchanges while 10 display sarcastic exchanges. To identify the sarcastic exchanges correctly, paralinguistic cues need to be recognized and interpreted. Part 3 of the TASIT is the Social Inference-Enriched test, which includes 16 vignettes, half of which display sarcastic exchanges, while the other half display white lies. In addition to paralinguistic cues, enriched contextual cues are given, usually via additional scenes showing the true state of affairs. Each vignette in the Social Inference tests is scored out of 4, with higher scores indicating greater social cognitive performance.
The Quality of Life Scale (QLS) is a 21 item semistructured interview, intended for outpatients and designed with the deficit syndrome in mind (Heinrichs, Hanlon, & Carpenter, 1984). It was the highest rated scale by the Validation of Everyday Real-World Outcomes study (Leifker, Patterson, Heaton, & Harvey, 2011) and is used to assess functioning in schizophrenia in four domains: 1. Intrapsychic foundations, which includes a sense of purpose, motivation, curiosity, empathy, ability to experience pleasure, and emotional interaction. As such, this domain overlaps with measurements of negative symptoms and is excluded from the QLS total score in our analysis. 2. Interpersonal relations, including the capacity for intimacy, active/passive participation in relationships, avoidance and withdrawal tendencies, and frequency of social contact. 3. Instrumental role i.e. assuming the role of a worker/student/parent/etc. and judging levels of accomplishment in these roles, degree of underemployment, and satisfaction derived from these roles. 4. Common objects and activities, such as participation in the community, which is assumed to be reflected in the possession of common objects and engagement in a range of regular activities in modern society. Each item is rated from 0 – 6, with the maximum score indicating unimpaired functioning.

The Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983) involves multiple symptom domains (attention, avolition/apathy, anhedonia/asociality, alogia, affective flattening) and multiple items per domain, which improves its psychometric properties compared to other measurements of negative symptoms, such as the Positive and Negative Symptom Scale (PANSS). Thus, the SANS is preferred to the PANSS by the NIMH MATRICS Consensus Statement on Negative Symptoms (Kirkpatrick et al., 2006). In the following studies, the attentional impairment subscale is excluded from our analysis since it more closely aligns with the disorganization symptom domain in schizophrenia (Foussias et al., 2011). Each item in
the SANS is scored from 0 – 5, which a higher score indicating greater negative symptom burden.

Neurocognition was assessed using the MATRICS Consensus Cognitive Battery (MCCB), excluding the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT), which is a measure of social cognition (Nuechterlein et al., 2004). Within the MCCB, speed of processing is measured using the Brief Assessment of Cognition in Schizophrenia: Symbol Coding, Category Fluency: Animal Naming, and Trail Making Test: Part A. The Brief Assessment of Cognition in Schizophrenia: Symbol Coding test is a paper and pencil test in which participants match symbols to numerals 1-9 in 90 seconds, with the measure of interest being the number of correct numerals allowing for a maximum score of 110 (Keefe et al., 2004). Category Fluency: Animal Naming is an oral test in which the participant names as many animals as possible in 60 seconds. Part A of the Trail Making Test involves connecting dots irregularly spaced on a sheet of paper in ascending numerical order, with scores corresponding to the time taken to complete the test (in seconds) (Reitan, 1979). Attention is measured using the Continuous Performance Test-Identical Pairs, which involves responding to consecutive matching numbers as they are presented in succession (Cornblatt & Keilp, 1994). Scoring involves calculating a manipulated ratio (d’) of the number of correct and incorrect responses. Working memory is measured using the Wechsler Memory Scale 3rd Ed.: Spatial Span and Letter Number Sequencing (Wechsler, 1979). The former involves a board with 10 irregularly spaced cubes and the participant taps cubes in the same or reverse sequence as the administrator, while the latter is an orally administered test in which the participant repeats strings of numbers and letters after mentally reordering them. Verbal learning is measured using the Hopkins Verbal Learning Test-Revised, which involves recall of 12 words from 3 taxonomic categories and is scored up to 36 (with a maximum score of 12 per trial) (Brandt, 1991). Visual learning is measured using the Brief
Visuospatial Memory Test-Revised, which involves reproducing six geometric shapes from memory and is also scored up to 36 (Benedict, Schretlen, Groninger, Dobraski, & Shpritz, 1996). Reasoning and problem solving are measured using the Neuropsychological Assessment Battery: Mazes, which involves completing seven mazes of gradually increasing difficulty, each of which is scored out of five, for a total of 35 (Stern & White, 2003).
2 Overview of Experiments and Hypothesis

This thesis aims to elucidate the relationship between neural circuitry of schizophrenia and functional outcome, as well as identifying the shared and unique neural circuitry underlying negative symptoms, neurocognition, and domains of social cognition, all of which have been shown to be correlated with functional outcome.

2.1 Study One: Neuroimaging Predictors of Functional Outcome in Schizophrenia at Baseline and 6-month Follow-up

2.1.1 Background

The uncinate fasciculus, inferior longitudinal fasciculus, and arcuate fasciculus have shown greater impairment in the deficit (compared to the nondeficit) syndrome of schizophrenia, which is characterized by primary enduring negative symptoms and poor functional outcome. This study aims to directly relate these white matter tracts to functional outcome across a broad heterogeneous sample of schizophrenia participants, as well as to examine the effects of negative symptoms and neurocognition on this relationship.

2.1.2 Hypothesis

We hypothesized that the uncinate fasciculus, inferior longitudinal fasciculus, and arcuate fasciculus would be correlated with baseline and 6-month follow-up functional outcome measures in schizophrenia participants. In addition, we hypothesized that negative symptom severity would mediate the relationship between neural circuitry and functional outcome.
2.2 Study Two: Social Cognition-Circuitry Relationships in Schizophrenia, Bipolar Disorder, and Healthy Individuals: A Pilot Study

2.2.1 Background

Structural equation models have shown that social cognition is a significant predictor of functional outcome in schizophrenia. This study aims to elucidate the underlying neural circuitry of higher level and lower level social cognitive processes in schizophrenia, bipolar disorder, and healthy control participants. By directly assessing brain-behaviour relationships across healthy and patient populations along a continuum of social cognitive performance, this study aligns with the NIMH Research Domain Criteria (RDoC) initiative, which emphasizes a dimensional approach to studying behavioural and neural features of mental illness.

2.2.2 Hypothesis

We hypothesize that structural connectivity of the arcuate fasciculus and inferior longitudinal fasciculus will be associated with lower level social cognitive performance in schizophrenia, bipolar disorder, and healthy control participants. Similarly, we hypothesize that structural connectivity of the uncinate fasciculus will be associated with higher level social cognitive performance across all participants.
3 Neuroimaging Predictors of Functional Outcome in Schizophrenia at Baseline and 6-month Follow-up

3.1 Abstract

Purpose: Studies show that deficit syndrome schizophrenia patients, characterized by primary negative symptoms and poor functional outcome, have impairment in specific neural circuits. We assessed whether these same neural circuits are directly linked to functional outcomes across schizophrenia patients.

Methods: T1- and diffusion-weighted MR images were obtained for schizophrenia (n=30) and matched healthy control participants (n=30). Negative symptoms and functional outcome were assessed at baseline and 6-month follow-up. Cortical thickness and tract-wise fractional anisotropy (FA) were compared between groups. To assess relationships of neuroimaging measures with functional outcome, principal component analysis (PCA) was performed on tract-wise FA values and components were entered into a multiple regression model for schizophrenia participants.

Results: Consistent with the literature, schizophrenia participants showed frontotemporal reductions in cortical thickness and tract-wise FA compared to controls. The top two components from PCA explained 71% of the variance in tract-wise FA values. The second component (associated with inferior longitudinal and arcuate fasciculus FA) significantly predicted functional outcome (baseline: \( \beta=0.54, p=0.03 \); follow-up: \( \beta=0.74, p=0.047 \)), and further analysis
revealed this effect was mediated by negative symptoms. Post-hoc network analysis revealed increased cortical coupling between right inferior frontal and supramarginal gyri (connected by the arcuate fasciculus) in schizophrenia participants with poorer functional outcome.

**Conclusions:** Our findings indicate that impairment in the same neural circuitry identified as susceptible in deficit syndrome schizophrenia predicts functional outcome in a continuous manner in schizophrenia participants. This relationship was mediated by negative symptom burden. Our findings provide novel evidence for brain-based biomarkers of longitudinal functional outcome in people with schizophrenia.

### 3.2 Introduction

Schizophrenia is almost certainly a heterogeneous group of disorders for which specific and reliable neurobiological correlates have yet to be identified (Breier et al., 1991; Milev et al., 2005). Schizophrenia is associated with a high risk of long-term disability and poor functional outcome (Breier et al., 1991). In people with schizophrenia, more severe negative symptoms and cognitive deficits have independently been associated with poorer functional outcome (Blanchard et al., 2005; Green, Kern, Braff, & Mintz, 2000; Ho et al., 1998; Milev et al., 2005; Rosenheck et al., 2006). However, negative symptoms may mediate the relationship between neurocognition and functioning in schizophrenia (Ventura et al., 2009). Furthermore, negative symptoms predict variance in functional outcome in community dwelling outpatients above and beyond neurocognitive impairment (Foussias et al., 2011, 2009).

Inter-regional dysconnectivity and white matter impairment in schizophrenia has been well-established through diffusion tensor imaging (DTI) studies (Kubicki et al., 2007; Wheeler & Voineskos, 2014). In deficit syndrome schizophrenia, characterized by prominent negative
symptoms and poor functional outcome (Carpenter et al., 1988; Kirkpatrick et al., 2001), specific impairments in white matter tract circuitry have been found in the uncinate fasciculus (Kitis et al., 2012; Voineskos et al., 2013), inferior longitudinal fasciculus, and arcuate fasciculus (Voineskos et al., 2013), compared to non-deficit syndrome schizophrenia and healthy control participants. Early studies assessing white matter microstructure-cognition relationships focused on a limited number of tracts, such as the cingulum bundle (Kubicki et al., 2003; Nestor et al., 2013; Takei et al., 2009) or the uncinate fasciculus (Kubicki et al., 2002; Nestor et al., 2013). More recently, neurocognitive deficits have been associated with subtle, widespread tract impairment in schizophrenia (Lim et al., 2006; Spoletini et al., 2009; Voineskos et al., 2013).

Despite the large number of DTI studies examining negative symptoms and neurocognitive performance, a direct link between white matter tract microstructure and functional outcome in schizophrenia patients is less well-established, particularly over a period of time.

Using fractional anisotropy (FA) as a measure of white matter tract microstructure (Jones, 2008), our objective was to identify the neural circuitry that is related to baseline and longitudinal functional outcomes in people with schizophrenia. We have previously demonstrated that deficit syndrome patients differ from non-deficit syndrome patients in white matter microstructure in the arcuate, inferior longitudinal, and uncinate fasciculi (Voineskos et al., 2013), as well as in network-level properties of cortical regions connected by these tracts (Wheeler et al., 2015). Our main hypotheses were: At baseline and 6-month follow-up, 1. FA of these three tracts in people with schizophrenia would be a significant predictor of functional outcome; 2. FA of these same tracts would be inversely correlated with negative symptom burden; and 3. Negative symptom burden would mediate the relationship between white matter tract FA and functional outcome in schizophrenia.
3.3 Methods

3.3.1 Participants

Participants were recruited and underwent clinical assessments at the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada. After receiving a complete description of the study, approved by the CAMH ethics review board, participants provided written, informed consent. Participants with a DSM-IV diagnosis of schizophrenia and schizoaffective disorder, following administration of the Structured Clinical Interview for DSM-IV TR Axis I Disorders and diagnostic confirmation by a trained psychiatrist (GF or ANV), comprised the schizophrenia sample. Schizophrenia (n=30) and healthy control (n=30) participants were individually matched on sex and handedness (categorized as left or right-handed based on the Edinburgh handedness inventory), and group-matched on age and parental level of education. Exclusion criteria for all subjects in this study included current substance use (verified by urine toxicology screen), history of substance dependence, head trauma with loss of consciousness, and neurological disorders. Healthy control subjects were also excluded if there was a history of primary psychotic disorder in a first-degree relative.

The Positive and Negative Symptom Scale (PANSS) (Kay, Flszbein, & Opfer, 1987) was administered to further characterize illness symptoms in the schizophrenia group. Negative symptoms of schizophrenia participants were assessed using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983), cognitive function using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph, Tierney, Mohr, & Chase, 1998), and functional outcome using the Quality of Life Scale (QLS) (Heinrichs et al., 1984). The SANS score was calculated excluding the Attention subscale from the total and inappropriate affect from the Affective Flattening subscale, as these symptoms are more closely
associated with the disorganized symptom domain in schizophrenia (Foussias et al., 2011). Similarly, the QLS total score excluded the Intrapsychic Foundations subscale, to eliminate overlap in item content of this subscale with measures of negative symptoms (Foussias et al., 2011, 2009). A number of other measures were administered to participants to further characterize the sample and to account for secondary negative symptoms. N=24 individuals also returned to repeat a number of assessments at 6-month follow-up, including the SANS and QLS (see Appendix and Table 1).

3.3.2 Image Acquisition

Participants underwent magnetic resonance and diffusion tensor imaging at Toronto General Hospital. Diffusion images were acquired with a single-shot spin echo planar sequence with diffusion gradients applied in 23 noncollinear directions (b=1000s/mm²). Diffusion images, including two baseline (b=0) images, were obtained with the following scan parameters: echo time=85.5 milliseconds, repetition time=15 000 milliseconds, field of view=330 mm, acquisition matrix=128 mm x 128 mm. Fifty-seven axial slices were acquired, with a 2.6 mm slice thickness and isotropic voxels. The entire sequence was repeated 3 times to improve the signal to noise ratio. Magnetic resonance images were acquired using an 8-channel head coil on a 1.5-Tesla GE Echospeed System (General Electric Medical Systems) with the following acquisition parameters: echo time=5.3 ms, repetition time=12.3 ms, time to inversion=300 ms, flip angle=20°, number of excitations=124 contiguous images with 1.5 mm thickness.
3.3.3 Image Processing

3.3.3.1 Tractography

For DTI analysis, the 3 repetitions were coregistered to the first b=0 image in the first repetition, using the FSL FMRIB Linear Image Registration Tool to concatenate the motion corrected images. Gradients were reoriented using a weighted least squares approach. Registration corrected eddy current distortions and subject motion while averaging the three repetitions to improve the signal to noise ratio. A brain mask was then generated and deterministic whole brain tractography (Runge-Kutta second order tractography with a fixed step size of 0.5 mm) was performed at seed points in each voxel of the brain. Threshold parameters for tractography were based on the linear anisotropy measure \( C_L \): \( T_{\text{seed}}=0.3 \) mm, \( T_{\text{stop}}=0.15 \) mm, \( T_{\text{length}}=20 \) mm (Westin et al., 2002). Tractography, creation of white matter fiber tracts, and clustering segmentation were performed using 3D Slicer (version 2) and Matlab (version 7.0) as previously described (Voineskos et al., 2009). Clusters were then identified to comprise each fiber tract of interest: bilateral uncinate fasciculus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, arcuate fasciculus, cingulum bundle, and the genu and splenium of the corpus callosum. For each white matter tract, mean measures of fractional anisotropy were calculated using Matlab.

3.3.3.2 Cortical thickness

All T1-weighted MR images were submitted to the CIVET pipeline (version 1.1.10; Montreal Neurological Institute at McGill University) (Lerch & Evans, 2005). T1 images were linearly registered to the ICBM152 nonlinear sixth-generation template, intensity inhomogeneity corrected (Sled, Zijdenbos, & Evans, 1998), and tissue classified into gray matter, white matter,
cerebrospinal fluid, and background (Tohka, Zijdenbos, & Evans, 2004; Zijdenbos, Forghani, & Evans, 2002). A surface deformation algorithm was applied to create white and gray matter surfaces for each hemisphere, resulting in 4 surfaces of 40,962 vertices each (Kim et al., 2005). Cortical thickness can therefore be defined as the distance between the linked vertices of the two surfaces within each hemisphere. The \( t_{\text{link}} \) metric was derived from each surface to determine the distance between the white and gray matter surfaces (Lerch & Evans, 2005). Thickness data were blurred using a 20-mm surface-based diffusion blurring kernel and unnormalized, native-space thickness values were used in the analysis, due to the weak correlation between cortical thickness and brain volume (Ad-Dab’bagh, Singh, & Robbins, 2005). The software package mni.cortical.statistics (Brain Imaging Centre, Montreal Neurological Institute) was used for vertex-wise cortical thickness analysis in R (version 2.15.1). Vertex-wise cortical thickness maps were also segmented using the LONI Probabilistic Brain Atlas and average regional thickness values were calculated (http://www.loni.usc.edu/atlas/) (Shattuck et al., 2008).

3.3.4 Statistical Analysis

3.3.4.1 Between-group differences in brain structure

Although not a primary aim of our study, we compared schizophrenia and healthy control groups on DTI-based FA measures and cortical thickness to further characterize our sample. For DTI-based mean FA values of each tract, the general linear model was used with age as a covariate. All twelve tracts listed above were compared between groups. CIVET outputs for cortical thickness for each group were also compared using the general linear model, with “group” as the between-group factor and age as a covariate.
3.3.4.2 Principal component analysis of 12 white matter tracts

In the baseline and follow-up schizophrenia samples, dimension reduction of FA values from the 12 frontotemporal and interhemispheric white matter tracts was performed using a principal component analysis (PCA) with varimax rotation in SPSS (version 20.0.0, SPSS Inc.). The threshold for retaining components within each principal component was $\lambda > 1$. This PCA was performed in preparation for examination of the relationship between white matter tract FA and QLS total scores, since there is well-established correlation of FA values among white matter tracts within each individual, and such dimension reduction reduces the number of comparisons in our main analyses.

3.3.4.3 Multiple Linear Regression Models

Using R (version 3.0.2), a regression model was investigated with principal component scores as predictors; age, parental level of education, chlorpromazine equivalent dose, and duration of illness as covariates; and QLS total score as the outcome variable to test our primary hypothesis. Chlorpromazine equivalent dose and duration of illness were included as covariates to evaluate the effect of medication and chronic illness on brain structure. Regression models were similarly built with the SANS total score and RBANS total score as outcome variables to test whether to proceed with mediation. Principal component scores calculated using data from the individuals with 6-month follow-up data (n=24) were entered into similar regression models with follow-up QLS total score or SANS total score as the outcome variable. Age was not included as a covariate for the RBANS model, as the total score used was age-normed.
Where relationships were found with either the baseline SANS or RBANS total scores, exploratory analyses were then conducted with subscores. These analyses were not corrected for multiple comparisons.

### 3.3.4.4 Mediation Analysis

Mediation models were built, initially with baseline and subsequently with 6-month follow-up data, using the following specifications: independent variable = the second principal component; outcome variable = QLS total score; mediator = SANS total score; covariates = age, parental level of education, chlorpromazine equivalent dose, and duration of illness. The model was tested in the R program as outlined by Baron and Kenny’s protocol (Baron & Kenny, 1986). The effect size (ab) of the mediator was calculated from the product of the partial correlations of each coefficient (a and b). The Sobel test was conducted to test for significance of this effect. To further substantiate the model, reverse causal effects were assessed by testing a feedback model (switching the outcome and mediator variables). Moderation was also assessed by including an interaction term of the independent and mediator variables in the model and re-running the analysis.

### 3.3.4.5 Structural Correlation Analysis

Based on the results of the principal component and multiple regression analysis, cortical regions connected by tracts of interest were selected for post-hoc cortical thickness correlation analysis, as previous data supports associations between structural correlations and white matter tracts (Gong, He, Chen, & Evans, 2012; Lerch et al., 2006; Raznahan et al., 2011). A linear regression was performed for each region to remove the effects of age, parental level of education, chlorpromazine equivalent dose, and duration of illness on cortical thickness.
Schizophrenia subjects were assigned to good vs. poor functional outcome groups via median split of QLS total scores and correlations in cortical thickness were examined in each group. Significant differences in individual correlations were determined with permutation testing using Matlab. Permutation testing involved shuffling subject labels to produce several permuted combinations of the original two groups of data. Following each permutation, the test statistic (correlation coefficient difference) was recalculated. The number of events that exceeded the observed test statistic was determined and a probability of the number of observed events being greater than expected was assigned.

3.4 Results

3.4.1 Brain structure and circuitry differences in schizophrenia

Schizophrenia participants showed modest reductions in white matter tract FA compared to healthy controls in the left uncinate fasciculus, left arcuate fasciculus, bilateral cingulum bundle, and genu of the corpus callosum. Similarly, schizophrenia participants were characterized by reductions in cortical thickness in a number of frontal and temporal regions (Supplementary Materials Figure 1A and 1B).

3.4.2 Data Reduction and Prediction of Functional Outcome

The PCA generated two components with $\lambda>1$ in both the baseline (n=30) and follow-up (n=24) samples (in both samples 61% and 11% of the variance was explained by the first and second principal component, respectively). FA of a number of white matter tracts loaded on the first component (Supplementary Materials Table 1A and 1B), except for that of the inferior longitudinal and arcuate fasciculus (Figure 1), which loaded prominently on the second component (data reported for baseline and follow-up samples, respectively: left inferior
longitudinal fasciculus loading=0.81 and 0.78, right inferior longitudinal fasciculus loading=0.85 and 0.82, left arcuate fasciculus loading=0.79 and 0.85, and right arcuate fasciculus loading=0.82 and 0.84). The first principal component was not a significant predictor of the QLS total (baseline $\beta=-0.25$, $p=0.3$; follow-up $\beta=-0.15$, $p=0.6$) or SANS total score (baseline $\beta=1.78$, $p=0.62$; follow-up $\beta=5.64$, $p=0.2$, uncorrected). The second principal component was a significant predictor of the QLS total (baseline $\beta=0.54$, $p=0.03$; follow-up $\beta=0.74$, $p=0.047$) and SANS total scores (baseline $\beta=-8.38$, $p=0.03$; follow-up $\beta=-11.3$, $p=0.01$, uncorrected). There was no significant relationship between either principal component and the RBANS total score. Within the baseline sample, exploratory analyses showed that the second principal component was related to the SANS Avolition/Apathy ($\beta=-2.05$, $p=0.05$, uncorrected), and SANS Anhedonia/Asociality subscale scores ($\beta=-2.61$, $p=0.04$, uncorrected) in the baseline sample (Table 2).

3.4.3 Negative symptoms mediate the relationship between tract FA and longitudinal functional outcomes

As $c' < c$, partial mediation of the relationship between baseline tract FA and functional outcome was observed ($c$, the total effect=0.59; $c'$, the direct effect=0.25). Similarly, mediation of the relationship between baseline tract FA and functional outcome in the follow-up sample was also observed ($c=0.75$, $c'=0.11$). The SANS total score had an effect on the relationship between the second principal component and the QLS total score (effect size $ab=0.3$). This effect was found to be significant by the Sobel test ($z=2.0$, $p=0.046$). No reverse causal effects were seen in the feedback model ($b=-8.25$, $c'=-3.89$). The SANS total score was not found to be a moderator of the relationship between the second principal component and the QLS total score.
(second principal component and SANS total score interaction term $\beta=-0.007$, $p=0.65$) (Figure 2).

3.4.4 Inter-regional cortical coupling is associated with baseline functional outcome

Results from the principal component and multiple regression analyses were used to guide post-hoc analyses of cortical coupling. Correlations in cortical thickness among regions connected by the arcuate fasciculus (inferior frontal gyrus, angular gyrus, supramarginal gyrus) and the inferior longitudinal fasciculus (inferior temporal gyrus and fusiform gyrus) were compared between the good and poor-outcome groups. Of these eight comparisons, one was significantly different between the two groups; there was increased coupling of the right inferior frontal gyrus and right supramarginal gyrus in poor ($r=0.81$) vs. good functional outcome schizophrenia participants ($r=0.37$, $p=0.024$, uncorrected) (Figure 3).

3.5 Discussion

In this study, we evaluated the relationship between white matter tract microstructure and baseline and 6-month functional outcomes in people with schizophrenia. Our main finding was that inferior longitudinal fasciculus and arcuate fasciculus FA (represented together as a principal component) were associated with functional outcome at both baseline and 6-month follow-up. This relationship was mediated by negative symptom burden. In the context of recent findings of inferior longitudinal and arcuate fasciculus impairment in deficit syndrome patients, who exhibit severe functional impairment, our present findings extend our previous work to a clinically heterogeneous group of schizophrenia participants that may be more representative of neuroimaging schizophrenia studies. Supporting this contention, comparisons between
schizophrenia participants and healthy controls showed differences in brain structure and neural circuitry reflecting those previously reported (Crespo-Facorro et al., 2000; Kubicki et al., 2007; Onitsuka, Shenton, Kasai, & et al., 2003; Shenton et al., 2001; Wheeler & Voineskos, 2014). Therefore, on a preliminary basis, we can conclude that impairment in the inferior longitudinal and arcuate fasciculus may serve as a biomarker of functional outcome in people with schizophrenia that is stable over time.

Our study is one of the first to directly examine the relationship between white matter tract microstructure and functional outcome in a sample of schizophrenia participants. Supporting evidence for our findings come from an earlier study in prodromal patients. Karlsgodt et al (Karlsgodt et al., 2009) reported decreased FA in the left hippocampus and bilateral inferior longitudinal fasciculus as predictors of poor role functioning in individuals at ultra-high risk for psychosis, while decreased FA in the right inferior longitudinal fasciculus also predicted poor social functioning in ultra-high risk subjects. This was an important finding as it demonstrated the association between the functional decline seen in antipsychotic naïve prodromal patients and FA of the inferior longitudinal fasciculus early in the course of illness. More recently, Kumar et al (Kumar et al., 2014) reported that white matter tract microstructure of the right inferior fronto-occipital fasciculus, corpus callosum, corona radiata, left cingulate gyrus, and left posterior thalamic radiation predicted social and occupational performance in patients with psychosis. It is likely that these results differ from our findings due to the inclusion of both bipolar disorder patients (who typically do not have negative symptom burden) and schizophrenia patients.

To date, the link between white matter tract impairment and poor functional outcome in schizophrenia has primarily been supported indirectly through findings in deficit syndrome
patients (Kitis et al., 2012; Rowland et al., 2009; Voineskos et al., 2013), who are known to have enduring primary negative symptoms and particularly poor long-term outcomes (Strauss, Harrow, Grossman, & Rosen, 2010). Neural circuitry of deficit syndrome patients has also been explored using network analysis of cortical properties in schizophrenia (Wheeler et al., 2015). Wheeler et al (Wheeler et al., 2015) reported stronger frontoparietal and frontotemporal coupling in deficit syndrome patients compared to non-deficit syndrome patients and healthy control subjects. Our study results are consistent with this recent work, since stronger frontoparietal coupling was found in participants with poorer functional outcome.

Analysis of our mediation model demonstrated that the relationship between white matter tract FA and functional outcome is mediated by negative symptoms. In schizophrenia, negative symptoms have been previously correlated with white matter tract impairment (Asami et al., 2014; Kitis et al., 2012; Lee et al., 2013; Mitelman et al., 2009; Nakamura et al., 2012; Rowland et al., 2009; Sigmundsson et al., 2001; Szieszko et al., 2008; Voineskos et al., 2013; Wolkin et al., 2003) and with functional outcome (Foussias et al., 2011) As such, based on our previous findings in community-dwelling outpatients, we predicted that negative symptoms would mediate the effect of white matter tract FA on functional outcome. Wolkin et al (Wolkin et al., 2003) reported that inferior frontal white matter tract FA was negatively correlated with SANS total, Anhedonia/Asociality subscale, and Affective Flattening subscale scores in schizophrenia. Sigmundsson et al (Sigmundsson et al., 2001) also reported lower white matter volumes in the inferior longitudinal fasciculus in schizophrenia patients with enduring negative symptoms, while Rowland et al (Rowland et al., 2009) reported reduced FA values in the right superior longitudinal fasciculus (which includes the arcuate fasciculus) of deficit syndrome patients compared to healthy controls. Studies have also reported that other tracts may be related to negative symptom severity in schizophrenia, including the uncinate fasciculus. Sigmundsson et
al (Sigmundsson et al., 2001) showed reduced volumes of the uncinate fasciculus, internal capsule, and corpus callosum in schizophrenia patients with enduring negative symptoms, while Szaszko et al (Szaszko et al., 2008) demonstrated that uncinate fasciculus FA was negatively correlated with SANS Affective Flattening and Alogia subscale scores. In the present study, the uncinate fasciculus did not load very heavily on the second principal component, although we did previously find impairment of this tract in deficit syndrome patients, along with that of the inferior longitudinal and arcuate fasciculi (Voineskos et al., 2013). Another study by Nakamura et al (Nakamura et al., 2012) reported that the FA of the anterior corpus callosum was negatively correlated with the SANS Avolition/Apathy subscale score in schizophrenia.

It is likely that differences in methodologies and sample populations resulted in different patterns of results in these studies. Our statistical analysis features a dimension reduction method in order to explore the contribution of all white matter tracts, since there is well-established correlation of FA values among white matter tracts within each individual. We also used our group’s validated tractography pipeline (Voineskos et al., 2009), whereas other studies have used voxel-based DTI, focused on a single tract of interest, or used Tract-Based Spatial Statistics and correlation analyses in their experimental design. Our study also presents data on an outpatient sample, while some studies include both inpatients and outpatients (Nakamura et al., 2012) or solely inpatients (Szaszko et al., 2008), which could account for differences in results.

There was no relationship between either principal component and neurocognitive impairment, as measured by the RBANS total score, in this schizophrenia sample. We had hypothesized that negative symptoms, not neurocognitive deficits, would mediate the relationship between white matter tract FA and functional outcome. Our group has previously built on existing evidence for the relationship between neurocognition and neural circuitry by
demonstrating that widespread impairment of white matter tracts is associated with cognitive performance in schizophrenia (Voineskos et al., 2013). Structural and functional studies show similar results, where cognitive performance is associated with a larger compensatory network of cortical (particularly frontal and temporal) brain regions in schizophrenia participants (Ehrlich et al., 2012; Tan et al., 2006). It is possible that in the current study we were underpowered to detect these relationships or that the use of a composite score to represent neurocognitive impairment resulted in a loss of information that may be necessary to identify the complex associations between neural circuitry and neurocognition.

There are a number of limitations that should be considered in this study. These include the effects of medication on white matter tracts in the schizophrenia sample, as cumulative effects of medication is shown to cause reductions in white matter volumes (Ho et al., 2011) and decreased white matter FA in the parietal and occipital lobe (Szeszko et al., 2014). However, in an effort to account for this confounding variable, we included chlorpromazine equivalent dose as a covariate in our statistical analysis. Antipsychotic medication and duration of illness concerns are further mitigated given a previous similar finding in a prodromal sample (Karlsgodt et al., 2009). On another note, it has been shown that experiential circumstances can influence brain structural measures, including FA (Scholz, Klein, Behrens, & Johansen-Berg, 2009). Though we limited the effects of substance use in our sample by including participants who met our strict inclusion criteria, other experiences may still have had an effect on brain structure. Finally, a future study with a larger sample size may enhance confidence in our findings and provide further clarification regarding the absence of a relationship with neurocognitive deficits in the present study.
In summary, we found that impairment in the inferior longitudinal and arcuate fasciculus, both of which were identified as being implicated in deficit syndrome schizophrenia, are associated with functional outcomes across a more heterogeneous group of schizophrenia participants. The results of our study provide preliminary evidence for brain-based biomarkers of functional outcome in people with schizophrenia. If confirmed, our findings may assist in neuroimaging-guided early detection efforts and in determining long-term prognosis. Targeting the identified brain circuitry in treatment studies may improve negative symptoms and functional outcome in people with schizophrenia.
<table>
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<td>-</td>
</tr>
</tbody>
</table>

HC=healthy controls; WTAR=Wechsler Test for Adult Reading; MMSE=Mini-Mental State Examination; CIRS-G=Cumulative Illness Rating Scale for Geriatrics; CDSS=Calgary Depression Scale for Schizophrenia; AIMS=Abnormal Involuntary Movement Scale; SAS=Symptom Angus Scale; BAS=Barnes Akathisia Scale

*p < 0.05
Figure 3-1: Right inferior longitudinal fasciculus and arcuate fasciculus. Sagittal view of the right inferior longitudinal fasciculus and right arcuate fasciculus as modeled by the tractography pipeline used in this study.

![Figure 3-1: Right inferior longitudinal fasciculus and arcuate fasciculus](image)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PC 1 β</th>
<th>p</th>
<th>PC 2 β</th>
<th>p</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>QLS Total excl. IF</td>
<td>-0.2539</td>
<td>0.2952</td>
<td>0.5366</td>
<td>0.0336*</td>
<td>0.144</td>
</tr>
<tr>
<td>SANS Total excl. Att.</td>
<td>1.775</td>
<td>0.6229</td>
<td>-8.3775</td>
<td>0.0278**</td>
<td>0.148</td>
</tr>
<tr>
<td>RBANS Total¹</td>
<td>-2.3459</td>
<td>0.4832</td>
<td>-0.2046</td>
<td>0.9481</td>
<td>0.076</td>
</tr>
<tr>
<td>SANS Affective Flattening</td>
<td>-0.1798</td>
<td>0.9165</td>
<td>-2.613</td>
<td>0.1379</td>
<td>-0.013</td>
</tr>
<tr>
<td>SANS Alogia</td>
<td>0.7868</td>
<td>0.3456</td>
<td>-1.2752</td>
<td>0.1329</td>
<td>0.012</td>
</tr>
<tr>
<td>SANS Avolition/Apathy</td>
<td>0.1135</td>
<td>0.9092</td>
<td>-2.0455</td>
<td>0.0493**</td>
<td>0.148</td>
</tr>
<tr>
<td>SANS Anhedonia/Asociality</td>
<td>1.0317</td>
<td>0.3953</td>
<td>-2.6068</td>
<td>0.0393**</td>
<td>0.078</td>
</tr>
</tbody>
</table>

PC=principal component of 12 white matter tract mean FA values, QLS Total excl. IF=Quality of Life Scale total score excluding Intrapsychic Foundations subscale, SANS Total excl. Att.=Scale for the Assessment of Negative Symptoms total score excluding Attention subscale, RBANS Total=Repeatable Battery for the Assessment of Neuropsychological Status

Covariates: Age, Parental Level of Education, Chlorpromazine Equivalent Dose, Duration of Illness

¹Covariates: Parental Level of Education, Chlorpromazine Equivalent Dose, Duration of Illness

*p < 0.05

#p < 0.05, uncorrected
Figure 3-2: Mediation Model. Model showing the relationship between the second principal component and functional outcome in schizophrenia participants, which was mediated by negative symptoms. The direct effect (c’=0.25, p=0.26) was less than the total effect (c=0.59, p=0.02). Mediation was validated by the Sobel test, demonstrating a significant effect (ab=0.3, p=0.05) of negative symptoms on the relationship between neural circuitry and functional outcome. Similarly, mediation of the relationship between baseline tract FA and functional outcome in the follow-up sample was also observed (c=0.75, p=0.04; c’=0.11, p=0.71).
**Figure 3-3: Inter-regional Cortical Coupling.** Increased cortical coupling of the right inferior frontal gyrus and right supramarginal gyrus (connected by the arcuate fasciculus) was observed in schizophrenia participants with poorer functional outcome (low QLS total score, $r=0.81$ vs. high QLS total score, $r=0.37$, $p=0.024$, uncorrected).
3.6 Appendix

Participants’ blood pressure, weight (in kg), and height (in m) were measured. In both the schizophrenia and healthy control samples, IQ was assessed using the Wechsler Test for Adult Reading (WTAR) (Wechsler, 2001), global cognitive impairment using the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975), and chronic medical illness burden using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (Miller et al., 1992). The Calgary Depression Scale for Schizophrenia (CDSS) (Addington, Addington, & Maticka-Tyndale, 1993) was used to measure depression, a potential source of secondary negative symptoms. The Abnormal Involuntary Movement Scale (AIMS) (Lane, Glazer, Hansen, Berman, & Kramer, 1985), Symptom Angus Scale (SAS) (Simpson et al., 1970), and Barnes Akathisia Scale (BAS) (Barnes, 1989) were administered to assess extrapyramidal symptoms in schizophrenia participants. Chlorpromazine equivalent dose was calculated for schizophrenia participants taking antipsychotic medication, according to Andreasen et al (Andreasen, Pressler, Nopoulos, Miller, & Ho, 2010).

A number of measures were also administered at 6-month follow up, including the MINI to re-affirm diagnosis, the CDSS, AIMS, SAS, SANS, and QLS. Neurocognitive performance was measured using the Brief Assessment of Cognition in Schizophrenia (BACS).
**Figure 3-S1: Group-wise differences in cortical thickness and white matter tract FA.**

Comparison of white matter tract FA and cortical thickness in schizophrenia and healthy control participants. *(A)* Decreased white matter FA was seen in schizophrenia participants compared to healthy controls in the left uncinate fasciculus, left arcuate fasciculus, bilateral cingulum bundle, and genu of the corpus callosum (p<0.05, uncorrected). *(B)* Widespread cortical thickness reductions were seen in schizophrenia participants compared to health controls, with greater localization in the left hemisphere (1% FDR correction).
### Table 3-S1A: Principal Component Loadings (Varimax Rotation), baseline sample (n=30)

<table>
<thead>
<tr>
<th></th>
<th>PC 1</th>
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</tr>
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<tbody>
<tr>
<td>Left UF FA</td>
<td>0.847</td>
<td>0.067</td>
</tr>
<tr>
<td>Right UF FA</td>
<td>0.827</td>
<td>0.263</td>
</tr>
<tr>
<td>Left AF FA</td>
<td>0.216</td>
<td>0.789</td>
</tr>
<tr>
<td>Right AF FA</td>
<td>0.369</td>
<td>0.819</td>
</tr>
<tr>
<td>Left ILF FA</td>
<td>0.295</td>
<td>0.806</td>
</tr>
<tr>
<td>Right ILF FA</td>
<td>0.194</td>
<td>0.852</td>
</tr>
<tr>
<td>Left IFOF FA</td>
<td>0.691</td>
<td>0.568</td>
</tr>
<tr>
<td>Right IFOF FA</td>
<td>0.671</td>
<td>0.596</td>
</tr>
<tr>
<td>Left CB FA</td>
<td>0.625</td>
<td>0.482</td>
</tr>
<tr>
<td>Right CB FA</td>
<td>0.699</td>
<td>0.289</td>
</tr>
<tr>
<td>gCC FA</td>
<td>0.754</td>
<td>0.352</td>
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<tr>
<td>sCC FA</td>
<td>0.602</td>
<td>0.560</td>
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### Table 3-S1B: Principal Component Loadings (Varimax Rotation), 6-month follow-up sample (n=24)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Left UF FA</td>
<td>0.826</td>
<td>-0.018</td>
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<td>Right UF FA</td>
<td>0.864</td>
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<td>Left AF FA</td>
<td>0.094</td>
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<tr>
<td>Right AF FA</td>
<td>0.353</td>
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</tr>
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<td>Left ILF FA</td>
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<td>Right ILF FA</td>
<td>0.194</td>
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<td>Left IFOF FA</td>
<td>0.692</td>
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</tr>
<tr>
<td>Right IFOF FA</td>
<td>0.684</td>
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<tr>
<td>Left CB FA</td>
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<tr>
<td>Right CB FA</td>
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<td>gCC FA</td>
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</tr>
<tr>
<td>sCC FA</td>
<td>0.692</td>
<td>0.511</td>
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</table>
Chapter 4

4 Social Cognition-Circuitry Relationships in Schizophrenia, Bipolar Disorder, and Healthy Individuals: A Pilot Study

4.1 Abstract

**Background:** Studies have shown that social cognitive processes are impaired in schizophrenia and significantly affect functional outcomes. Using diffusion tensor imaging (DTI), we previously found specific neural circuits implicated in patients with deficit syndrome schizophrenia, who are socially impaired. In the present pilot study, we assessed whether those same circuits may be related to social cognitive performance (and impairment) cross-diagnostically in healthy individuals, bipolar disorder participants, and schizophrenia participants.

**Methods:** Diffusion-weighted magnetic resonance images were acquired for schizophrenia (n=15), bipolar disorder (n=15), and healthy control participants (n=22) 18-39 years of age on a 3T GE MR750 scanner at CAMH. Average fractional anisotropy (FA) values were calculated for white matter tracts of interest using Tract-Based Spatial Statistics and the ENIGMA-DTI ROI extraction protocol. Neurocognitive and social cognitive performance were measured using the MATRICS Consensus Cognitive Battery and The Awareness of Social Inference Test, respectively. A prespecified model was built and tested using partial least squares path modeling.
(PLSPM) to explore relationships between social cognition and neural circuitry across all participants and within diagnostic subgroups.

**Results:** Neurocognition was significantly correlated with social cognition across all subjects. The relationship between FA of the uncinate fasciculus and higher level social cognition was observed across all participants as well as in the bipolar disorder and schizophrenia subgroups, while FA of the arcuate and inferior longitudinal fasciculus was associated with moderate to higher level social cognition in healthy control participants.

**Conclusion:** By directly assessing brain-behaviour relationships across several patient populations, our approach is consistent with the NIMH Research Domain Criteria initiative. Our results provide further insight into the behavioural correlates of white matter tracts previously implicated in functional outcome, and on a preliminary basis, the complex relationships between neural circuitry and social cognition.

### 4.2 Introduction

Social cognitive impairment is believed to be a trait feature of schizophrenia, as it is stable in first episode patients over a 12-month follow-up period and is also comparable across phase of illness (Green et al., 2012; Horan et al., 2012). There are four main domains of social cognition (Green et al., 2005; Penn et al., 2006): theory of mind, emotion processing, social perception, and attributional bias (Green & Horan, 2010). Social cognition significantly contributes to poor functional outcome in schizophrenia (Couture et al., 2006; Horan et al., 2012) and is related to but distinct from neurocognition (Sergi et al., 2007). Social cognition is consistently shown to be a mediator between neurocognition and functional outcome in schizophrenia (Galderisi et al., 2014; Green & Horan, 2010; Schmidt et al., 2011).
Along with schizophrenia, bipolar disorder is recognized as a major psychotic disorder with shared genetic vulnerability (Cardno et al., 2012; Cardno, Rijsdijk, Sham, Murray, & McGuffin, 2002), similar brain morphological abnormalities (Rimol et al., 2010), and symptom overlap (Curtis, van Os, & Murray, 2000). Individuals with bipolar disorder appear to have less neurocognitive and social cognitive impairment compared to individuals with schizophrenia (Lee et al., 2013), which makes this group interesting for investigation in a study designed with the NIMH Research Domain Criteria principles in mind.

Exploratory factor analysis of social cognition in schizophrenia has shown that social cognitive domains load onto three factors, two of which are related to functional outcome in schizophrenia. Specifically, emotion recognition and social perception load onto one factor representing lower level social cognitive processes, necessary for understanding the emotions and actions of others, while theory of mind loads onto its own factor representing higher level social cognitive processes, necessary for understanding the mental states of others. Both lower and higher level processes were found to influence functional outcome in schizophrenia (Mancuso et al., 2011).

These social cognitive processes are believed to correspond to separate neural networks: 1. An “embodied simulation or low-level mental state inference construct” involving the mirror neuron system and limbic system and 2. A “high-level mental state/trait inference construct” involving cortical midline and lateral temporal structures (Ochsner, 2008). Our group has previously shown altered connectivity of the inferior longitudinal fasciculus, arcuate fasciculus, and uncinate fasciculus in patients with deficit syndrome schizophrenia (Voineskos et al., 2013). These patients are known to have considerable social impairment. We subsequently demonstrated that fractional anisotropy (FA) of the inferior longitudinal fasciculus and arcuate fasciculus is directly related to functional outcome in schizophrenia. The inferior longitudinal
fasciculus connects limbic structures (fusiform gyrus, parahippocampal gyrus, and amygdala) to the occipital cortex, and is therefore important for visuoemotional processing, while the arcuate fasciculus connects the inferior frontal lobe to the inferior parietal lobule, which are key nodes of the human mirror neuron system (Gur et al., 2007; Iacoboni et al., 1999). These tracts are believed to comprise the lower level simulation network, while the uncinate fasciculus connects cortical midline structures (such as the medial prefrontal cortex) to the temporal pole and amygdala and is believed to be one important white matter tract that subserves the higher level mentalizing network (Heide et al., 2013).

Using FA as a measure of white matter tract microstructure, our objective was to assess the relationship among FA of these three tracts, neurocognitive performance (which has been shown to covary with social cognitive performance (Sergi et al., 2007)), and social cognitive performance across schizophrenia, bipolar disorder, and healthy control participants. Social cognitive performance is impaired in schizophrenia subjects and slightly impaired in bipolar disorder (though not to a significant degree) but comparable to performance in healthy control individuals (Lee et al., 2013). In this way, we will be able to capture brain-behaviour relationships of participants on a continuum of social cognitive performance. We hypothesize that structural connectivity of the arcuate fasciculus and inferior longitudinal fasciculus (measured with FA) will be associated with lower level social cognitive processes across all participants. Similarly, we hypothesize that structural connectivity of the uncinate fasciculus will be associated with higher level social cognitive processes across all participants.
4.3 Methods

4.3.1 Participants

Participants were recruited and underwent clinical assessments at the Centre for Addiction and Mental Health (CAMH) in Toronto, Canada. After receiving a complete description of the study, approved by the CAMH ethics review board, participants provided written, informed consent. Participants with a DSM-IV diagnosis of schizophrenia and schizoaffective disorder, following administration of the Structured Clinical Interview for DSM-IV-TR Axis I Disorders and diagnostic confirmation by a trained psychiatrist, comprised the schizophrenia sample, while those with a DSM-IV diagnosis of bipolar disorder who were also euthymic comprised the bipolar disorder sample. Schizophrenia (n=15), bipolar disorder (n=15), and healthy control (n=22) participants between the ages of 18 and 39 were included in the study. This younger age range mitigates (to some effect) duration of illness and long-term medication exposure confounds, as well as the effect of age on social cognition (Kern et al., 2008). Exclusion criteria for all subjects in this study included current substance use (verified by urine toxicology screen), history of substance dependence, head trauma with loss of consciousness, and neurological disorders. Healthy control participants were also excluded if there was a history of primary psychotic disorder in a first-degree relative.

Social cognitive performance of all participants was assessed using The Awareness of Social Inference Test-Revised (TASIT). Part 1 of the TASIT tests the subject’s ability to recognize six basic emotions after watching a 15-60 second videotaped vignette, and therefore represents the lower level social cognitive process of emotion recognition. In part 2 of the TASIT, participants must distinguish between sincere and sarcastic exchanges. In the sarcastic
scenes, interpretation of paralinguistic cues is required (tone of voice, body language, gestures, and facial expressions). Part 2 of the TASIT is called the Social Inference-Minimal Test, and can be thought of as relying on social cognitive processes of higher order than part 1 of the TASIT, but of lower order than part 3 of the TASIT. Part 3 of the TASIT represents higher level social cognitive processing as it not only requires interpretation of paralinguistic cues in order to distinguish between lies and sarcasm, but also includes additional scenes requiring the observer to interpret information about the true state of affairs (McDonald et al., 2003). Neurocognition was assessed using the MATRICS Consensus Cognitive Battery (MCCB), excluding the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT), which is a measure of social cognition. Within the MCCB, speed of processing is measured using the Brief Assessment of Cognition in Schizophrenia: Symbol Coding, Category Fluency: Animal Naming, and Trail Making Test: Part A; attention is measured using the Continuous Performance Test-Identical Pairs; working memory is measured using the Wechsler Memory Scale 3rd Ed.: Spatial Span and Letter Number Sequencing; verbal learning using the Hopkins Verbal Learning Test-Revised; visual learning using the Brief Visuospatial Memory Test-Revised; and reasoning and problem solving using the Neuropsychological Assessment Battery: Mazes (Nuechterlein et al., 2004). To further characterize the sample, IQ was assessed using the Wechsler Test for Adult Reading (WTAR) (Wechsler, 2001), global cognitive impairment using the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), and chronic medical illness burden using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (Miller et al., 1992). The Abnormal Involuntary Movement Scale (AIMS) (Lane et al., 1985), Symptom Angus Scale (SAS) (Simpson et al., 1970), and Barnes Akathisia Scale (BAS) (Barnes, 1989) were administered to assess extrapyramidal symptoms in schizophrenia participants. The Young Mania Rating Scale (YMRS) and Hamilton
Depression Rating Scale (HDRS) were administered in bipolar disorder participants to assess mood symptoms.

### 4.3.2 Image Acquisition

Participants underwent diffusion imaging at the Centre for Addiction and Mental Health in Toronto, Canada. Diffusion images were acquired using a 3 Tesla Discovery MR750 system (General Electric) equipped with an 8-channel head coil. An echo planar imaging sequence with dual spin echo was applied with diffusion gradients in 60 noncollinear directions \((b=1000 \text{ s/mm}^2)\). Diffusion images, including five baseline \((b=0)\) images, were obtained with the following scan parameters: echo time = 85 ms, repetition time = 8800 ms, field of view= 25.6 cm, acquisition matrix = 128 mm x 128 mm. Axial slices parallel to the AC-PC line were acquired, with 2.0 mm isotropic voxels.

### 4.3.3 Image Processing

Diffusion images were preprocessed to correct eddy current induced distortions and misalignment due to motion using the FMRIB Software Library (FSL, version 5.0.6). Brain extraction was followed by fitting a diffusion tensor model at each voxel, using the `dtifit` function to estimate FA maps.

The Tract-Based Spatial Statistics (TBSS, FSL) pipeline (Smith et al., 2006) was modified slightly to incorporate the ENIGMA-DTI ROI extraction protocol (http://enigma.ini.usc.edu). First, images were aligned using non-linear registration to the ENIGMA-DTI target. They were then averaged to create a mean FA map and skeletonized by projecting the ENIGMA-DTI skeleton onto each image. Regions of interest were then extracted
using the skeletonized image and the JHU-atlas to obtain average FA values (Mori et al., 2008).
Specifically, regions of interest were selected to correspond with the specified white matter tracts under investigation: bilateral superior longitudinal fasciculus (SLF, which includes the arcuate fasciculus), bilateral uncinate fasciculus (UF), bilateral inferior fronto-occipital fasciculus (IFO, including projections from the uncinate and inferior longitudinal fasciculus), and bilateral sagittal stratum (SS, including the inferior fronto-occipital and inferior longitudinal fasciculus).

4.3.4 Statistical Analysis

Before proceeding with partial least squares path modeling (PLSPM) (Sanchez, 2013), data were cleaned by: 1. Removing outliers (values more than 3 standard deviations above or below the mean); 2. Imputation of missing MCCB and TASIT values using the mice package in R (version 3.0.2, http://cran.r-project.org); 3. Regressing out the effects of sex and age on mean FA values, and using residuals in the following analysis.

Partial least square path models were then built, using the plspm package in R, to examine the relationships between social cognition, neurocognition, and neural circuitry in our sample. In each model, the MCCB (excluding the MSCEIT) total scores were manifest variables for the neurocognition latent variable. In model 1, total scores of parts 1, 2, and 3 of the TASIT were treated as manifest variables for the social cognition latent variable, while mean FA values of the white matter regions of interest (SLF, UF, IFO, SS) were manifest variables for the neural circuitry latent variable. In model 2, the total score of part 3 of the TASIT was treated as the social cognition manifest variable, while mean FA values of the UF and IFO were neural circuitry manifest variables. In model 3, the total score of part 1 of the TASIT was treated as the social cognition manifest variable, while mean FA values of the SLF, IFO, and SS were neural circuitry manifest variables. These three models were tested across all participants, and further
exploratory analyses were conducted in diagnostic subgroups. PLSPM allows us to study multivariate relationships among blocks of variables, and does not impose any assumptions with respect to distributions of variables (Tenenhaus, Vinzi, Chatelin, & Lauro, 2005). To test these relationships, path coefficients were calculated and bootstrapping (with 1000 samples) was performed as a reliability estimate of our findings.

4.4 Results

4.4.1 Participant demographic and clinical data

Participants did not differ in terms of age (F=2.26, p=0.14), sex (F=0.01, p=0.91), education (F=3.21, p=0.08), or handedness (F=2.47, p=0.12). However, there was a difference between healthy control and bipolar disorder participants in CIRS-G scores (t=3.24, p=0.003).

4.4.2 PLS path modeling reliably elucidates social cognition-circuitry relationships

The three prespecified models examine the relationships between neural circuitry, social cognition, and neurocognition across all participants, as well as in diagnostic subgroups [Figure 1]. Loadings of manifest variables listed below exceeded a threshold magnitude of 0.6. PLSPM analysis revealed neurocognitive performance to be a significant predictor of social cognitive performance (β=0.56, p<0.01 for model 1 within all participants) [Table 2]. Across the entire sample, FA of the bilateral UF and IFO were related to performance on part 3 of the TASIT (model 2: β=0.32, p<0.01, validated by bootstrapping). In healthy control participants, FA of the bilateral SLF and SS were related to performance on parts 2 and 3 of the TASIT (model 1: β=0.47, p=0.04). In bipolar disorder participants, FA of the bilateral UF and IFO were related to performance on all three parts of the TASIT (model 1: β=0.64, p=0.03). In schizophrenia
participants, FA of the bilateral UF and IFO were related to performance on all three parts of the TASIT (model 1: $\beta=0.49$, $p<0.01$) and FA of the bilateral UF and IFO were related to performance on part 3 of the TASIT (model 2: $\beta=0.41$, $p=0.03$, validated by bootstrapping). In schizophrenia participants, FA of the left IFO was also related to performance on part 1 of the TASIT (model 3: $\beta=-0.54$, $p<0.01$); however, in this case the loading of left IFO FA onto the neural circuitry latent variable was negative (-0.80) [Figure 2].

4.5 Discussion

The objective of this study was to directly relate neural circuitry (specifically the uncinate, arcuate, and inferior longitudinal fasciculi) to social cognition in participants (schizophrenia, bipolar disorder, and healthy control) on a continuum of social cognitive performance. Due to the relationship of the following tracts with functional outcome in schizophrenia, as well as their role in deficit syndrome schizophrenia, where considerable social impairment is present, and in structural connectivity of regions involved in social cognition, we hypothesized that: 1. Structural connectivity of the uncinate fasciculus, which connects the medial prefrontal cortex to the temporal pole and amygdala, would be correlated with higher level social cognitive performance; 2. Connectivity of the arcuate fasciculus (connecting the inferior frontal gyrus to the inferior parietal lobule) and inferior longitudinal fasciculus (connecting the amygdala and fusiform gyrus to the occipital cortex) would be correlated with lower level social cognitive performance. Using partial least squares path modeling, we were able to elucidate several social cognition-circuitry relationships. We consistently observed association of the uncinate fasciculus (represented by the UF and IFO regions of interest) with overall and higher level social cognition (represented by performance on the overall TASIT and part 3 of the TASIT, respectively) in the entire sample, as well as in the bipolar disorder and
schizophrenia subgroups. In the healthy control subgroup, we observed relationships between the arcuate and inferior longitudinal fasciculus (represented by the SLF and SS regions of interest) and moderate to higher level social cognition (represented by performance on parts 2 and 3 of the TASIT). We also found neurocognition to be a reliable predictor of social cognitive performance, which is in line with results of studies using structural equation modeling and path analysis (Gard et al., 2009; Schmidt et al., 2011).

In this study, we demonstrated the relationship between the arcuate and inferior longitudinal fasciculi and moderate to higher level social cognitive performance in healthy control participants. These data suggest that the putative simulation network is also involved in mentalizing. In order to further investigate this trend, it would be beneficial to combine structural imaging results with functional neuroimaging in order to visualize circuitry engagement during social cognitive tasks and identify whether the simulation and mentalizing networks are dissociated or if there is inclusion of both networks during higher and/or lower level social cognitive processes. Although the relationship between these networks and social cognition has not been directly studied in schizophrenia (Holt et al., 2011), preliminary evidence for impairment in this circuit in schizophrenia has been found during action observation in studies using brain stimulation techniques (Enticott et al., 2008). There is also evidence in healthy control individuals linking the inferior longitudinal fasciculus to interpersonal emotional intelligence (Takeuchi et al., 2013). Our findings are also supported by studies on persons with diffuse low-grade glioma-affecting the arcuate fasciculus (Herbet et al., 2014). Furthermore, in patients with acute ischemic stroke in the right hemisphere, damage to the sagittal stratum was associated with impaired recognition of sarcasm (Davis et al., 2015).
We also consistently demonstrated the relationship between the uncinate fasciculus and overall and higher level social cognition. This may be explained by the use of part 1 of the TASIT as the measure for lower level social cognitive performance, which may require some higher level processing as it involves emotion recognition in complex social situations. It is also possible that the relationship between the uncinate fasciculus and part 3 of the TASIT was driving the relationship between this tract and the complete TASIT. These results are supported by preliminary evidence relating default mode network (which overlaps with the mentalizing network (Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009)) dysfunction to impairments in theory of mind in schizophrenia (Das, Calhoun, & Malhi, 2012). Structural imaging studies have shown associations between decreased grey matter volume of the ventromedial prefrontal cortex and theory of mind deficits (Hooker, Bruce, Lincoln, Fisher, & Vinogradov, 2011). In addition, in healthy control participants, increased structural connectivity of the uncinate fasciculus has been associated with greater coupling of the amygdala with temporal regions involved in higher level social cognition (Carlson et al., 2013).

Although we observed associations between the uncinate fasciculus and social cognition in all participants, it appears that this relationship was driven by the schizophrenia and bipolar disorder subgroups. This may suggest that certain individuals in patient populations rely on different circuitry than healthy control populations during social cognitive performance. Previous studies have shown lack of cortico-limbic coupling in schizophrenia and bipolar disorder compared to healthy control participants during emotion regulation (Morris, Sparks, Mitchell, Weickert, & Green, 2012). Although different activation patterns of these regions is observed in schizophrenia and bipolar disorder, these findings may point to shared differences in structural connectivity of cortical and limbic regions, such as those subserved by the uncinate fasciculus. From a systems neuroscience approach, shared neural abnormalities in the medial prefrontal
cortex during emotion processing are reported in both schizophrenia and bipolar disorder (Frangou, 2014). Furthermore, reduced FA of the uncinate fasciculus is observed in schizophrenia and bipolar disorder compared to healthy control participants (Sussmann et al., 2009).

Limitations of this study include the effects of medication on white matter tracts in the schizophrenia and bipolar disorder sample, as cumulative effects of antipsychotic medication is shown to cause reductions in white matter volumes and decreased white matter FA in the parietal and occipital lobe (Szeszko et al., 2014). In order to avoid including this confounding variable, future studies may consider focusing on first episode or medication naïve participants. Future studies should also consider applying two tensor models to diffusion-weighted images, in order to account for crossing fibers and partial volume effects. However, by using the TBSS algorithm, we were able to avoid issues with spatial smoothing of the FA maps (Jones, Symms, Cercignani, & Howard, 2005). Due to the impact of age on social cognitive performance (Kern et al., 2008), we decided to restrict our sample to participants between the ages of 18 and 39. A larger sample size may provide further clarification regarding the relationships between neural circuitry and social cognitive performance in the present study. A larger sample may also allow for the division of patient groups into subgroups based on severity of impairment in the domain of interest. It has been proposed that severity may be a nonlinear phenomenon with “tipping points” that reflect distinct pathology (Cuthbert & Insel, 2013). Thus, some patients may have considerably greater impairment in circuitry that is intact in other patient subgroups, and may consequently be using compensatory circuits during tasks, which increases heterogeneity of the sample and is less optimal for clearly identifying neurobiological substrates of psychopathology (Dazzan et al., 2015). We believe that the relationship between the IFO and part 1 of the TASIT in schizophrenia participants may be a result of heterogeneity in the sample, which can be further
examined in a larger group of patients.

In conclusion, this study demonstrates the relationship between the uncinate fasciculus and higher level social cognitive performance in all participants along a continuum of social cognitive performance, as well as in the schizophrenia subgroup. We have also shown relationships between the arcuate and inferior longitudinal fasciculus and moderate to higher level social cognitive performance in schizophrenia and bipolar disorder participants. This study therefore highlights and provides preliminary evidence for potential shared and unique neurobiological correlates of social cognitive processes in both healthy and patient populations, consistent with modern conceptualizations of psychiatric research and disorders.
<table>
<thead>
<tr>
<th></th>
<th>Bipolar Disorder</th>
<th>Schizophrenia</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>28.0 (5.4)</td>
<td>31.4 (4.8)</td>
<td>25.6 (6.0)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>8:7</td>
<td>7:8</td>
<td>12:10</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian (n)</td>
<td>15</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Asian (n)</td>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>African American (n)</td>
<td>0</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Other (n)</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Education (years)</td>
<td>14.7 (1.7)</td>
<td>13.8 (2.2)</td>
<td>15.8 (2.1)</td>
</tr>
<tr>
<td>Handedness (R:L)</td>
<td>15:0</td>
<td>14:1</td>
<td>19:3</td>
</tr>
<tr>
<td>IQ (WTAR)</td>
<td>118.0 (7.3)</td>
<td>111.1 (10.9)</td>
<td>116.9 (6.3)</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.3 (1.4)</td>
<td>28.8 (1.3)</td>
<td>29.4 (0.9)</td>
</tr>
<tr>
<td>CIRS-G*</td>
<td>1.1 (0.2)</td>
<td>0.8 (0.6)</td>
<td>0.6 (0.7)</td>
</tr>
<tr>
<td>AIMS</td>
<td>-</td>
<td>0.14 (0.5)</td>
<td>-</td>
</tr>
<tr>
<td>SAS</td>
<td>-</td>
<td>1.3 (2.4)</td>
<td>-</td>
</tr>
<tr>
<td>BAS</td>
<td>-</td>
<td>0.7 (1.1)</td>
<td>-</td>
</tr>
<tr>
<td>YMRS</td>
<td>2.1 (1.9)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HDRS</td>
<td>5.0 (2.7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PANSS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>-</td>
<td>13.4 (5.2)</td>
<td>-</td>
</tr>
<tr>
<td>Negative</td>
<td>-</td>
<td>10.5 (2.7)</td>
<td>-</td>
</tr>
<tr>
<td>General</td>
<td>-</td>
<td>22.7 (4.3)</td>
<td>-</td>
</tr>
</tbody>
</table>

HC=healthy controls; WTAR=Wechsler Test for Adult Reading; MMSE=Mini-Mental State Examination; CIRS-G=Cumulative Illness Rating Scale for Geriatrics; AIMS=Abnormal Involuntary Movement Scale; SAS=Symptom Angus Scale; BAS=Barnes Akathisia Scale; YMRS=Young Mania Rating Scale; HDRS=Hamilton Depression Rating Scale; PANSS=Positive and Negative Symptom Scale

*p < 0.05
Figure 4-1: Partial least squares path models. (A) Model 1, (B) Model 2, and (C) Model 3 were each tested in all participants and within diagnostic subgroups.
C

- Bilateral SLF FA
- Bilateral SS FA
- Bilateral IFO FA

Neural Circuitry

- MCCB excluding MSCEIT

Neurocognition

Social Cognition

TASIT 1
### Table 4-2A: Partial Least Squares Path Model in All Participants

<table>
<thead>
<tr>
<th>Model</th>
<th>Paths</th>
<th>$\beta$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Neural Circuitry $\rightarrow$ Neurocognition</td>
<td>0.27</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td><strong>Neurocognition $\rightarrow$ Social Cognition</strong>*</td>
<td>0.56</td>
<td>0.00001</td>
</tr>
<tr>
<td></td>
<td>Neural Circuitry $\rightarrow$ Social Cognition</td>
<td>0.21</td>
<td>0.08</td>
</tr>
<tr>
<td>Model 2</td>
<td>Neural Circuitry $\rightarrow$ Neurocognition</td>
<td>0.16</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td><strong>Neurocognition $\rightarrow$ Social Cognition</strong>*</td>
<td>0.49</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Neural Circuitry $\rightarrow$ Social Cognition</td>
<td>0.32</td>
<td>0.007</td>
</tr>
<tr>
<td>Model 3</td>
<td>Neural Circuitry $\rightarrow$ Neurocognition</td>
<td>0.27</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td><strong>Neurocognition $\rightarrow$ Social Cognition</strong>*</td>
<td>0.57</td>
<td>0.00002</td>
</tr>
<tr>
<td></td>
<td>Neural Circuitry $\rightarrow$ Social Cognition</td>
<td>0.01</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Cl=Confidence Interval  
Covariates: Age, Sex  
* $p<0.05$, validated by bootstrapping (95% CI does not include 0)  
* * $p<0.05$  
* $^\dagger$ $p<0.05$  

### Table 4-2B: Partial Least Squares Path Model in Bipolar Disorder

<table>
<thead>
<tr>
<th>Model</th>
<th>Paths</th>
<th>$\beta$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Neural Circuitry $\rightarrow$ Neurocognition</td>
<td>0.53</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Neurocognition $\rightarrow$ Social Cognition</td>
<td>0.07</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td><strong>Neural Circuitry $\rightarrow$ Social Cognition</strong>*</td>
<td>0.64</td>
<td>0.03</td>
</tr>
<tr>
<td>Model 2</td>
<td>Neural Circuitry $\rightarrow$ Neurocognition</td>
<td>0.48</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>Neurocognition $\rightarrow$ Social Cognition</td>
<td>0.17</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Neural Circuitry $\rightarrow$ Social Cognition</td>
<td>0.53</td>
<td>0.06</td>
</tr>
<tr>
<td>Model 3</td>
<td>Neural Circuitry $\rightarrow$ Neurocognition</td>
<td>0.71</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Neurocognition $\rightarrow$ Social Cognition</td>
<td>-0.03</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Neural Circuitry $\rightarrow$ Social Cognition</td>
<td>0.59</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Cl=Confidence Interval  
Covariates: Age, Sex  
* $p<0.05$, validated by bootstrapping (95% CI does not include 0)  
* * $p<0.05$  
* $^\dagger$ $p<0.05$
### Table 4-2C: Partial Least Squares Path Model in Schizophrenia

<table>
<thead>
<tr>
<th>Paths</th>
<th>β</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neural Circuitry → Neurocognition</td>
<td>-0.02</td>
<td>0.9</td>
</tr>
<tr>
<td>Neurocognition → Social Cognition*</td>
<td>0.72</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>Neural Circuitry → Social Cognition</strong></td>
<td>0.49</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neural Circuitry → Neurocognition</td>
<td>0.15</td>
<td>0.6</td>
</tr>
<tr>
<td>Neurocognition → Social Cognition*</td>
<td>0.66</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Neural Circuitry → Social Cognition</strong></td>
<td>0.41</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Model 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neural Circuitry → Neurocognition</td>
<td>0.16</td>
<td>0.6</td>
</tr>
<tr>
<td>Neurocognition → Social Cognition*</td>
<td>0.81</td>
<td>0.00004</td>
</tr>
<tr>
<td><strong>Neural Circuitry → Social Cognition</strong></td>
<td>-0.54</td>
<td>0.001</td>
</tr>
</tbody>
</table>

CI=Confidence Interval  
Covariates: Age, Sex  
*p<0.05, validated by bootstrapping (95% CI does not include 0)  
#p<0.05

### Table 4-2D: Partial Least Squares Path Model in Healthy Controls

<table>
<thead>
<tr>
<th>Paths</th>
<th>β</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neural Circuitry → Neurocognition</td>
<td>0.54</td>
<td>0.01</td>
</tr>
<tr>
<td>Neurocognition → Social Cognition</td>
<td>0.18</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Neural Circuitry → Social Cognition</strong></td>
<td>0.47</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Model 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neural Circuitry → Neurocognition</td>
<td>-0.36</td>
<td>0.1</td>
</tr>
<tr>
<td>Neurocognition → Social Cognition</td>
<td>0.57</td>
<td>0.01</td>
</tr>
<tr>
<td>Neural Circuitry → Social Cognition</td>
<td>0.21</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Model 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neural Circuitry → Neurocognition</td>
<td>0.53</td>
<td>0.01</td>
</tr>
<tr>
<td>Neurocognition → Social Cognition</td>
<td>0.18</td>
<td>0.5</td>
</tr>
<tr>
<td>Neural Circuitry → Social Cognition</td>
<td>0.27</td>
<td>0.3</td>
</tr>
</tbody>
</table>

CI=Confidence Interval  
Covariates: Age, Sex  
*p<0.05, validated by bootstrapping (95% CI does not include 0)  
#p<0.05
**Figure 4-2: PLSPM path coefficients and manifest variable loadings.** Models and path coefficients of neural circuitry-social cognition-neurocognition relationships in schizophrenia, bipolar disorder, and healthy control participants. Outlined arrows indicate significance of path coefficients (p<0.05) and loadings of manifest variables onto latent variables is indicated (threshold=0.6) in (A) model 2 in all participants, (B) model 1 in bipolar disorder, (C) model 1 in healthy control participants, (D) model 1 in schizophrenia, (E) model 2 in schizophrenia, and (F) model 3 in schizophrenia.

A

B
E

Bilateral UF FA  Bilateral IFO FA

Neural Circuitry

MCCB excluding MSCEIT

Neurocognition  Social Cognition  TASIT 3

0.41

F

Bilateral SLF FA  Bilateral SS FA  Bilateral IFO FA

Neural Circuitry

MCCB excluding MSCEIT

Neurocognition  Social Cognition  TASIT 1

-0.54

Left IFO: 0.81
Right IFO: 0.73
Left UF: 0.91
Right UF: 0.93

Left IFO: -0.80
Chapter 5

5 General Discussion & Future Directions

5.1 Summary of Results

The first study revealed that impairment in the bilateral arcuate fasciculus and inferior longitudinal fasciculus is correlated with functional outcome in schizophrenia. The results of this study supported our hypothesis and previous findings of altered connectivity in these tracts using diffusion tensor imaging and structural covariance analysis in deficit syndrome schizophrenia (Voineskos et al., 2013; Wheeler et al., 2015), which is characterized by primary negative symptoms and poor functional outcomes. Thus, our findings provide preliminary evidence for brain-based biomarkers of functional outcome in schizophrenia, which, if confirmed, may become treatment targets and aid in early detection/prognostic efforts in the future. Specifically, we believe that these white matter tracts may be neural correlates for social cognitive processes based on their anatomical connectivity to mirror neuron and limbic structures in the brain.

With growing interest in the neural correlates of social cognition, our second study aimed to elucidate relationships between separate circuits and social cognitive processes across a sample of participants along a continuum of social cognitive performance. Based on our group’s previous findings of white matter tracts implicated in deficit syndrome schizophrenia and determining functional outcomes, we hypothesized that the arcuate fasciculus and inferior longitudinal fasciculus would be associated with lower level social cognitive processes, while the uncinate fasciculus would be associated with higher level social cognitive processes. We consistently observed relationships between the uncinate fasciculus and higher level social
cognitive performance. We also observed relationships between the arcuate and inferior longitudinal fasciculus and moderate to higher level social cognitive performance. Although our approach was theoretically sound, as partial least squares analysis is not dependent on sample size or data distribution, our goals would have been better served with a more distributed sample. Due to the impact of age on social cognitive performance (Kern et al., 2008), we decided to include participants between the ages of 18 and 39. It is important that these relationships be examined in a larger sample as well as with different imaging modalities, such as functional neuroimaging, in order to visualize engagement of neural circuits during social cognitive tasks and further dissect the underlying neural correlates of social cognition.
5.2 From DSM to RDoC: Addressing the Heterogeneity in Psychiatric Disorders

Early forms of documentation of psychiatric disorders include Frederick Wines’ “Report on the Defective, Dependent, and Delinquent Classes of the Population of the United States” in 1888 and the American Psychiatric Association’s “Statistical Manual for the Use of Institutions for the Insane” in 1917. The Diagnostic and Statistical Manual of Mental Disorders (DSM), colloquially known as the “bible of psychiatry”, is the first classification system for psychiatric disorders to make an impact on how mental illness is diagnosed, studied, and understood.

The purpose of the DSM was to increase standardization of psychiatric diagnosis and provide a starting point for researching these disorders (Frances, 2013). Despite its many critics, the DSM has important clinical applications, in terms of diagnosis, guiding appropriate treatment, and obtaining social supports and services. However, the conceptualization of diagnostic categories and criteria in the DSM occurred before the age of modern neuroscience, bringing into question their scientific validity (Morris & Cuthbert, 2012). When the DSM-5 was released, it fell short of expectations, as our understanding of psychiatric disorders based on modern neuroscience has not been integrated into their current conceptualization. It is likely that due to the heterogeneity in each diagnostic category and overlap in symptoms across categories, a scientific focus on group differences and diagnosis has hindered our progress toward understanding psychiatric illness. A shift in focus towards the organization of neural circuits and their associated behaviours is therefore required, in order to dissect the individual presentations of psychiatric illness and develop targeted treatments.
The lack of integration of neuroscientific evidence in psychiatric disease classification has sparked an NIMH initiative called the Research Domain Criteria (RDoC) project (Hyman, 2007). It has been proposed that our current classification system has become reified, thereby impeding progress in newer conceptualizations of brain-behaviour relationships that may shed light on etiology and potential treatments (Hyman, 2010). The goal of the RDoC initiative is to develop new ways of classifying psychiatric disorders according to dimensions of behaviour and neurobiology, and studying brain-behaviour relationships independently of current classification systems.

The RDoC is essentially a matrix of functional constructs, grouped into a number of domains (cognition, social processes, arousal systems, and positive and negative valence systems) and studied across units of analysis such as genetics, molecular biology, cell biology, circuitry, physiology, behaviour, and self report (Cuthbert & Insel, 2013; Morris & Cuthbert, 2012). By starting with these basic constructs, the RDoC framework provides a platform for understanding homogeneous symptom sets that cut across disorders and for dissecting the heterogeneity in psychiatric diagnosis.

Although the process of selection of these constructs took into account their relevance to psychopathology, the RDoC framework is sparse so as to allow for a strong focus on these domains, rather than introduce an overwhelming number of constructs with diminishing utility (Morris & Cuthbert, 2012). The goal of modern neuroscience, in concert with the RDoC initiative, is to take a dimensional approach to each construct, studying participants along a continuum of performance.

One of the shortcomings of a categorical approach to psychiatric disorders is the expectation that we are able to draw the line between neurotypical and neuroatypical for any
given diagnosis. It is evident that not all patients with the same diagnosis are impaired to the same degree or have overlapping areas of impairment (Krueger & Markon, 2006). It is important to take a more dimensional approach to the study of psychiatric illness in order to cater to the unique symptom presentations and needs of each patient.

With a focus on neural circuitry, the RDoC will allow for direct assessment of brain-behaviour relationships to explain phenotypic differences observed in typical and atypical neurodevelopment, as many psychiatric disorders are postulated to be neurodevelopmental in origin (Owen, O’Donovan, Thapar, & Craddock, 2011). In this way, we can elucidate the nature and degree of changes in brain morphology and circuitry, as well as how developmental, compensatory, environmental, and epigenetic factors modify them (Owen et al., 2011).

It is important to note that the RDoC is not a comprehensive document, and is still in its early stages of being implemented as a guide for neuroscientific and psychiatric research (Morris & Cuthbert, 2012). Specifically, the role of the RDoC is one of a research framework, and is not intended to displace the DSM. In fact, the RDoC and DSM may be thought of as complimentary to one another. Although the DSM has improved the reliability of classification of psychiatric disorders, the current conceptualization of these disorders has impeded our understanding of their etiologies and potential treatment targets. Current diagnostic categories can be thought of as latent constructs, though they are not necessarily unidimensional (Hartman et al., 2001). Today’s diagnostic categories do not capture the complex relationships between genetic, neurophysiological, and behavioural features of mental illness (Borsboom, 2008). Rather than continue to search for common causes within a heterogeneous group of patients, the RDoC framework will encourage reconceptualization of psychiatric diagnoses as individual, multidimensional, brain-behaviour relationships.
5.3 Recovery in Schizophrenia

The definition of recovery from mental illness varies between the scientific and psychiatric consumer/survivor (C/S) communities. While scientific definitions of recovery focus on outcome, C/S definitions conceptualize recovery as an ongoing process (Remington et al., 2010). The scientific literature has historically considered recovery from a clinical/disease orientation, involving the elimination or reduction of symptoms and return to premorbid levels of function (Bellack, 2006). As neuroscience and psychiatric research continues to make advances, we are getting closer to addressing the heterogeneity in psychiatric illness by identifying symptom-specific biomarkers and developing personalized treatment plans.

C/S definitions of recovery have developed alongside civil rights movements among consumer/survivors and sociopolitical shifts in attitudes towards mental illness (Poole & Durbin, 2012). Rather than focusing on recovering “from” a disease, C/S are more interested in being “in” recovery, which has been supported and described by various mental health consumer advocates, psychiatric rehabilitation practitioners, and researchers. This notion of recovery refers to an individualized process that is self-determined and aimed at building meaning into one’s life. In this way, a person in recovery is able to feel empowered and retain their sense of autonomy. Although we cannot yet guarantee full remission and a return to premorbid functioning for everyone with schizophrenia, taking such a perspective of recovery is crucial to conveying hope and encouraging patients to be an active participant in their own journey towards wellness.

Patricia Deegan’s definition of recovery claims that individuals must be active participants in their recovery journey by making use of resources such as medication and
institutional care (Deegan, 1997). However, this generalization does not account for diversity in identity, accessibility, and culture. For instance, describing mental illness in terms of disability ignores the experiences of those who have found a sense of self and purpose in their lived experience. In addition, suggesting that individuals must be active participants in their recovery journey assumes having access to community and health care services and supports. It also emphasizes Western ideals of individualism and wellbeing, which results in isolation for culturally diverse populations (Poole & Durbin, 2012). Therefore, it is important to take into account each person’s individual conceptualization of distress and wellbeing, as each person’s lived experience will differ.

As shown in a recent comprehensive study of functional outcome in a large cohort of people with schizophrenia, social supports and access to effective interventions are crucial for achieving recovery in schizophrenia (Galderisi et al., 2014). Therefore, treatment models for schizophrenia must incorporate individualized medicine (i.e. brain-based biomarkers) with patient goals and conceptualizations of wellness as well as access to these interventions.
5.4 Limitations

There are a number of limitations to the studies outlined in the chapters above that must be considered. For the first study, though our results were supported by previous findings in deficit syndrome participants, they must be replicated in an independent sample. In addition, since our sample consists of participants with chronic schizophrenia, medication effects on brain structure are a concern. In an effort to mitigate these effects, we included chlorpromazine equivalent dose in our analysis. In addition, our images were acquired using a 1.5 Tesla magnet, which limits the quality of our data. As such, we analyzed images acquired using a 3 Tesla magnet in the subsequent study. Both studies were primarily cross-sectional, as we did not include follow-up image acquisitions in our analysis. However, in study one, we analyzed the effects of brain structure on baseline and 6-month longitudinal functional outcomes. We were also limited in terms of sample size, with a maximum of 52 participants for any given group under analysis. In order to maximize our power, we used multivariate approaches, such as partial least squares path modeling, to allow for more complex relationships in the data to be explored while limiting the number of multiple comparisons.

More generally, there are limitations to single tensor modeling of diffusion-weighted images in order to infer fiber orientation and microstructure (Jones, Knösche, & Turner, 2013). A change in FA may reflect changes in one or more aspects of connectivity (orientational dispersion, myelination, axonal number and density), though we cannot say which. Furthermore, FA is affected by partial volume effects, which occur when 1. The dimensions of a voxel exceed the dimensions of an axonal bundle; or 2. The voxel includes crossing fibers. In these situations, ambiguity in the microstructure of the tract is introduced, since we cannot discern the cause.
behind the change in FA (Jones et al., 2013). Thus, a decrease in FA may be related to reductions in white matter microstructural integrity, or it may be due to limitations in image processing.

### 5.5 Future Directions

With diffusion tensor imaging, rather than directly tracing axonal fibers, white matter tract structure and orientation is computationally modeled and therefore limited by image acquisition and analysis protocols. Therefore, an important issue is the low specificity of current DTI methods when it comes to describing the pathology associated with changes in DTI indexes (Jones et al., 2013). Improvements and innovation in computational methods and technology will significantly increase our ability to identify neural correlates of emotion, cognition, and behaviour. Acquisition techniques incorporating magnetization transfer imaging, which is specific to myelination, may address this issue (van Buchem & Tofts, 2000). Another such technique is Higher Angular Resolution Diffusion Imaging (HARDI), which can be used to infer more complex information from diffusion of water in white matter tracts, allowing for modeling of crossing fibers (Tuch et al., 2002). The issue of partial voluming and crossing fibers is also being addressed with two tensor models of diffusion-weighted images (Peled, Friman, Jolesz, & Westin, 2006). In the future, higher resolution images may allow us to model individual fibers. Furthermore, combining DTI with other imaging modalities, such as functional MRI, magnetic resonance spectroscopy, electroencephalography, magnetoencephalography, and positron emission tomography, will allow for the integration of anatomical and functional data.

A great deal of the literature focuses on individual white matter tracts and grey matter regions in psychiatric disorders. However, this trend is shifting towards a focus on neural networks in the brain. Recent methods such as Brainbow and CLARITY allow researchers to
visualize and examine how individual neurons are connected. However, these methods have not yet been extended to in vivo brain imaging (Chung et al., 2013; Lichtman, Livet, & Sanes, 2008). Ideally, future studies and initiatives will integrate both macro and micro analyses in order to understand both individual and broad connections in the brain. The National Institute of Health BRAIN Initiative is aimed at understanding and mapping neural circuitry, which requires “identifying and characterizing component cells, defining synaptic connections with one another, observing patterns of activity in vivo during behaviour…It also requires an understanding of the algorithms that govern information processing within a circuit and between interacting circuits in the brain as a whole” (Bargmann & Newsome, 2013). The BRAIN initiative signifies a leap not only in terms of the conceptualization and approach towards studying brain-behaviour relationships, but also in terms of developing new methods for analysis and large-scale collaboration across research institutes.

Similarly, the RDoC is another recent shift in the foundation for studying brain-behaviour relationships, with the goal of translating identified neural correlates of emotion, cognition, and behaviour to treatments for psychiatric disorders. Future studies aimed at understanding psychiatric illness would do well to examine neural processes and corresponding biomarkers, rather than focus on group differences. Furthermore, studies on neuroplasticity of identified biomarkers of symptoms (e.g. neurocognition and social cognition) and their response to psychosocial remediation will be key sources of evidence-based practice (Dodell-Feder, Tully, & Hooker, 2015).

The RDoC also addresses several other questions in psychiatric research: “How can we redefine mental illness to capture variability in individual experiences?” and “How do we take into account a person’s unique biology and experiences in order to best care for them?” The
criteria and categories outlined in the current Diagnostic and Statistical Manual are not black and white – what we have is a formula for heterogeneity in groups and shared symptoms across psychiatric disorders. By studying brain-behaviour relationships rather than group differences, we can begin to understand each patient as a unique individual and implement interventions that take into account the variability in disease presentation.

A major confounding variable in studies of chronically ill patients is medication-induced changes in brain structure and function (Ho et al., 2011; Szeszko et al., 2014). It is often difficult to acquire accurate and detailed information on patient medication history, due to errors in reporting bias. Furthermore, many methods of calculating equivalent antipsychotic dose in participants, so as to covary for this variable, do not account for medication history or duration of use. Thus, in order to confirm positive findings in the literature, it is important that studies also be carried out on first episode or medication-naïve participants.

Lastly, there is some debate around whether the clinical and cognitive scales employed in studies are measuring what we believe they are measuring (Hayhurst, Massie, Dunn, Lewis, & Drake, 2014; Khatri, Romney, & Pelletier, 2001). For instance, the Quality of Life Scale, used to measure functional outcome in schizophrenia, was originally designed with the deficit syndrome in mind (Heinrichs et al., 1984). As such, it includes items that overlap with negative symptoms, despite being selected as one of the most representative measures of functional outcome in a recent RAND panel (Harvey, 2013; Leifker et al., 2011). Some scales of social functioning, like the QLS and the Birchwood Social Functioning Scale, need to be updated to reduce focus on activities that are not common in today’s society. Some of the items in these scales also require one to have the financial means to participate in the specified activities, or focus solely on heterosexual relationships, which may bias the results. Newer methods of measuring functional
outcome are being developed, such as virtual reality simulations, which may be more reliable and have greater validity than traditional questionnaires (Zawadzki et al., 2013).
5.6 Conclusion

The aim of the two studies outlined above was to elucidate the relationships between neural circuitry impairments in schizophrenia and functional outcome, as well as identifying shared and unique neural circuitry with negative symptoms and domains of social cognition. We demonstrated that white matter microstructure of major tracts involved in the putative simulation network were correlated with functional outcome in schizophrenia; this relationship was mediated by negative symptom burden. We also demonstrated the relationships of these tracts, along with the uncinate fasciculus, to social cognitive domains in schizophrenia as well as in bipolar disorder and healthy populations. Future studies of structural connectivity using DTI and network analysis can allow us to identify neural circuits involved in different symptom and behavioural domains of schizophrenia, fostering the identification of potential biomarkers for future diagnostic purposes and for developing targeted and effective treatments.
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