

ABNORMAL STRUCTURAL CONNECTIVITY PATTERNS IN LARGE-SCALE  
BRAIN NETWORKS IN SCHIZOPHRENIA

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A DISSERTATION SUBMITTED TO  
THE FACULTY OF GRADUATE STUDIES  
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS  
FOR THE DEGREE OF  
DOCTOR PHILOSOPHY

GRADUATE PROGRAM IN PSYCHOLOGY  
YORK UNIVERSITY  
TORONTO, ONTARIO  
SEPTEMBER 2019

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## Abstract

**Background:** While cognitive impairment is a core feature of schizophrenia, a minority of patients demonstrate average to superior ability on many standard cognitive measures with no attenuation of the psychotic disease process (Heinrichs et al. 2008; Muharib et al., 2014). The data imply a dissociation of cognitive and psychosis-generating neural mechanisms whereby patients share a disease process that leads to psychosis but vary in terms of the pathophysiology that causes cognitive impairment. Furthermore, current views hold that schizophrenia involves abnormalities in the connectivity of large-scale brain networks [default mode (DMN), salience (SN), central executive (CEN), and social brain (SBN)]. However, these findings may reflect pathophysiology related to both the cognitive and psychotic features of schizophrenia. Therefore, we asked: Are aberrations in cortical thickness and/or structural connectivity within and between networks associated with cognitive impairment and/or the severity of psychotic psychopathology? **Method:** Structural magnetic resonance (MRI) and diffusion tensor imaging (DTI), cognitive, and clinical data were collected from 121 participants, which include 16 cognitively-intact and 48 cognitively-impaired schizophrenia patients as well as 36 cognitively normal and 21 below-normal controls. Between-group comparisons and region-of-interest analyses of cortical thickness and structural integrity in the DMN, SN, CEN, and SBN were performed on MRI and DTI data. **Results:** Cognitively normal controls had greater DMN and SN cortical thickness than both cognitively normal and below-normal patients. Structural integrity of the genu of the corpus callosum was significantly different between cognitively normal controls and both patient groups. Superior longitudinal fasciculus connectivity patterns differed between cognitively normal controls and below-normal patients. Lastly, the inferior longitudinal and inferior fronto-occipital fasciculi combined were significantly different between

cognitively normal controls and patients. **Conclusions:** The results suggest that cortical thinning may represent the presence of psychotic psychopathology independent of cognitive impairment. However, tract integrity may index cognitive status, the psychotic disease process, or both. The similarities in white matter integrity associations with cognition among cognitively normal patients and controls suggest shared neurocognitive processes, and the dissimilarities may point to cortical structure aberrations that give rise to psychotic psychopathology. Taken together, this study contributes to the advancement of the literature by providing evidence for dissociable or partially dissociable disease processes in psychotic illness.

## Acknowledgements

First and foremost, I give thanks to the Most High always for strengthening, guiding, and carrying me through this chapter of my life. I am grateful that He has entrusted me with such an important work and career path.

Thank you to my supervisor, Dr. Walter Heinrichs, for his tremendous support, guidance, and expertise throughout my training. I could not have asked for a better mentor. I would also like to thank my committee members. I am truly grateful for your thoughtful contributions to this work.

Thank you to my fellow lab members and cohort for their support; my experience was more pleasant having you all on this journey alongside me. To the most amazing administrative staff (Lori, Freda, Barb, and Sabrina), I am very appreciative of your dedication and assistance, as well as your cheerful countenances that seem to lighten the mood of any situation. Thank you!

A special thank you to the volunteers who not only made my research possible, but also added to my understanding of an illness that drove my passion for a career in clinical neuropsychology.

To my dearest family, I love you beyond words. We always say that we are blessed to have each other in our lives, and I can honestly say that I would not have gotten this far academically or personally without your love, honesty, strength, counsel, and encouragement. I may ask you to quiet down the cheers, but I am so very grateful to have you in my corner. You know what a large family we have so to thank you each by name would be impossible. Thus, in no order of importance, thank you to the Pinnocks, Walters, Garricks, Beaudins, Momens, Mitchells, Allinieces, Somers, Fullingtons, Moodies, Noesgaards, Brown-Scotts, Adamsons, and Chaggers.

To my confidants, Keweda, Sheena, Marvet, Katarzyna, and Tianna thank you for the much-needed laughs, conversations, and comfort – they kept me well-grounded!

~

I dedicate this dissertation to Oswald St. John George Gordon – you have inspired in me a great work.

## Table of Contents

Abstract.....	ii
Acknowledgements.....	iv
List of Tables .....	viii
List of Figures.....	ix
Introduction.....	1
Considering Biological Factors.....	3
Neurodevelopmental Hypothesis .....	3
Dysconnectivity Hypothesis .....	7
Psychological Factors: Cognition as a key disease feature.....	11
Towards a Network-Approach.....	15
Large-Scale Brain Networks.....	16
The Relationship between the Default Mode and Central Executive Networks .....	16
The Salience Network.....	17
The Social Brain Network .....	18
The Evidence on Structural Aberrations.....	18
Study Aim .....	21
Key Functions of each Tract.....	23
Hypotheses.....	24
Methods.....	28
Participants.....	28
Clinical Measures.....	29
Neurocognitive Measures .....	29
Group Assignment .....	32
Scan Acquisition .....	32
Preprocessing .....	33
Statistical Analyses .....	34
Results.....	36

Demographic Characteristics .....	36
Clinical Characteristics .....	38
Neurocognitive Performance .....	39
Adjunct Specialized Cognitive Measures .....	42
Cortical Thickness .....	44
Tract Based Spatial Statistics: Group by Tract Analysis .....	45
Summary of Findings.....	51
 Discussion .....	 53
Hypothesis 1.....	53
Hypothesis 2.....	54
Hypothesis 3.....	58
Hypothesis 4.....	60
Limitations .....	64
 Conclusions.....	 66
 References.....	 71

## List of Tables

Table 1:	Demographic Characteristics for Cognitively Normal Range (CNR) and Below-Normal Range (BNR) Patients and Controls .....	37
Table 2:	Clinical Profiles for Cognitively Normal Range (CNR) and Below-Normal Range (BNR) Patients .....	39
Table 3:	Adjunct Cognitive Performance across Cognitively Normal Range (CNR) and Below-Normal Range (BNR) Patients and Controls .....	42
Table 4:	Average Whole-Brain Fractional Anisotropy (mm), Mean Diffusivity, Radial Diffusivity, and Cortical Thickness in Cognitively Normal Range (CNR) and Below-Normal Range (BNR) Patients and Controls .....	44
Table 5:	Fractional Anisotropy (mm), Mean Diffusivity, and Radial Diffusivity of Key Tracts in Cognitively Normal Range (CNR) and Below-Normal Range (BNR) Patients and Controls .....	45
Table 6:	A Summary of the Study's Predictions, Neuroimaging Results and whether the Hypotheses were Supported, as well as Supportive Evidence from the Cognitive Data .....	48



## List of Figures

Figure 1A:	Cortical thickness and white matter connectivity in cognitively normal schizophrenia patients .....	27
Figure 1A Revised:	Cortical thickness and white matter connectivity in cognitively normal schizophrenia patients .....	65
Figure 1B:	Cortical thickness and white matter connectivity in cognitively below-average schizophrenia patients .....	27
Figure 1B Revised:	Cortical thickness and white matter connectivity in cognitively below-average schizophrenia patients .....	65
Figure 2:	Performance profiles for patients and comparison controls across the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) domains .....	41

# **Abnormal Structural Connectivity Patterns in Large-Scale Brain Networks in Schizophrenia**

## **Introduction**

Schizophrenia is a chronic debilitating disorder characterized by positive and negative symptoms as well as disruptions in social and occupational functioning. Positive symptoms refer to psychotic behaviour that is not typically found in the general population. Negative symptoms, on the other hand, represent the absence of or disruption in normal functioning. Disease onset typically begins in late adolescence to early adulthood. Symptoms may include implausible beliefs (delusions), distorted sensory perceptions (hallucinations), thought disorder (disorganized speech), abnormal psychomotor behaviour, loss of interest and motivation, social withdrawal, apathy, and impoverished emotional expression. Cognitive impairment is a correlate of the disorder, and frequently found in patients. The heterogeneity in clinical presentation is reflected in the interindividual variability of symptom expression, presence and/or severity of cognitive impairment, illness onset and course, clinical and functional outcome/recovery pattern, and treatment-response; heterogeneity is also observed in neurobiological findings (including genetic and cortical structural differences) (Brugger & Howes, 2017). The heterogeneous clinical presentations have contributed to the conceptualization of schizophrenia as a clinical syndrome with various symptoms, rather than a single disease (Insel, 2010).

The chronicity and disabling course of the illness are highlighted in the relapses of psychotic symptoms that are more the norm than the exception and linked to functional deterioration and poorer prognosis (Kessler & Lev-Ran, 2019). Only approximately 14% achieve clinical remission (i.e., loss of symptoms combined with return to premorbid functioning) and social recovery (i.e., minimal social dysfunction with independent economic and residential

functioning) with a 2-year maintenance of improvements in one or both domains (see Jääskeläinen et al., 2013 for a review). The additional presence of common comorbid conditions of substance use, depression, and anxiety further contribute to the complexity of the disorder (Tsai & Rosenheck, 2013; Kessler & Lev-Ran, 2019).

Given the chronicity and complexity of the disease that significantly impacts functioning, this disorder is considered one of the most disabling illnesses worldwide (World Health Organization, 2008). It is known as the “cancer of mental illness” due to its significant morbidity and mortality rates, through its elevation of suicide risk and poor physical health, causing both domestic and international economic burden (Birnbaum & Weinberger, 2017). Individuals with the disorder tend to be repeat users of psychiatric emergency services (Kessler & Lev-Ran, 2019). Indeed, schizophrenia remains one of the greatest challenges for neuroscience, psychiatry, and health care systems as well as for patients and their families (Nutt & Need, 2014). Specifically, the etiology and pathophysiology of schizophrenia remain elusive and as such clinical diagnosis relies solely on subjective reports with no objective measures (e.g., biomarkers/laboratory tests) available to confirm or support diagnosis; nonetheless, objective measures are helpful in ruling out other possible causes (e.g., substance-induced psychosis or medical conditions).

Furthermore, although the illness is considered to be largely genetic, more than 100 loci on different chromosomes have been identified, making the identification of specific disease-causing pathways extremely complex. The absence of definite underlying causes prevents advancements in treatment. There have been limited improvements in pharmacological treatment since the development of second-generation antipsychotics in the 1980’s. Thus far, psychotropic medications are specifically aimed at symptom management and are not a cure. While symptoms

respond moderately to antipsychotic medications, pharmacological intervention can cause unwanted side effects and approximately 30% of patients are treatment-resistant (defined as being nonresponsive to two or more trials of antipsychotic medications despite adequate dose and duration; Vita et al.; 2019).

For this reason, there continues to be an abundance of research aimed at understanding the neuropathophysiology of the disorder to better develop targeted treatment(s) to improve clinical symptoms and functional outcome. It is understood that schizophrenia, like other neurological disorders, is a result of abnormalities that subsequently cause disruptions in psychological (including cognitive) and social functioning. Several hypotheses have attempted to explain the underlying brain pathology. Here, we begin with an exploration of two of these hypotheses (neurodevelopmental and dysconnectivity) and the corresponding evidence to-date, paying specific attention to biological and psychological (particularly neuropsychological) factors. Consequently, the current study's hypotheses and research aim are outlined; the goal is to assist in identifying the neuropathophysiological anomalies of this debilitating illness. An investigation of social factors is beyond the scope of this paper and is thus not addressed here.

### **Considering Biological Factors**

#### *Neurodevelopmental Hypothesis*

Evidence for understanding schizophrenia as a neurodevelopmental disorder emerges from both genetic and neuroimaging studies that suggest that early abnormal brain development may in part predispose individuals to developing the illness (Birnbaum & Weinberger, 2017). It is held that the genetic abnormalities in conjunction with prenatal and perinatal environment (such as maternal nutrition, gestational insults, and/or infection) impact brain development and mediate the clinical expression of schizophrenia in early adulthood. Current investigations

suggest that schizophrenia is a polygenic disorder and cannot be reduced to one gene. The most compelling genetic evidence comes from monozygotic and dizygotic twin studies (and other family studies) that show that genetic relatedness is the highest predictor of the illness, with estimated heritability rates up to 80% (Birnbaum & Weinberger, 2017). Furthermore, genetic linkage studies identified numerous putative genetic variants in susceptibility loci that influence risk (Birnbaum & Weinberger, 2017; Murray, Bhavasar, Tripoli, & Howes, 2017).

Further genetic evidence that points towards a neurodevelopmental understanding of schizophrenia includes findings that similar genomic variations seen in known neurodevelopmental disorders (e.g., autism and mental retardation) are also observed in individuals with schizophrenia, though at a later developmental stage (i.e., at 3 years of age versus 18 years, respectively). During prenatal life, cell proliferation and migration occur as part of the normal development of the cortex while ongoing arborization and myelination occur postnatally throughout the first two decades of life. There is some evidence of arrested cell distribution in schizophrenia, suggestive of changes in density and distribution in different regions rather than fewer neurons (Insel, 2010). Thus, schizophrenia may result from excessive pruning of excitatory synapses, reduced inhibitory synapses, and reduced myelination. As a result, these early brain developmental abnormalities may disrupt the postnatal development of the neural circuitry of brain regions that reach maturity in early adulthood (e.g., the prefrontal cortex; Birnbaum & Weinberger, 2017).

Supporters of the neurodevelopmental model argue that, in the context of earlier brain abnormalities, a confluence of maturational and environmental factors most likely contribute to the clinical expression of the disorder during the period of adolescence (Birnbaum & Weinberger, 2017). Findings from animal studies support the neurodevelopmental hypothesis in

that prenatal cortical lesions can cause behavioural and neurobiological abnormalities in late adolescence to early adulthood (Birnbaum & Weinberger, 2017). In late adolescence, myelination and other late maturational processes co-occur at the time of stress hormone changes and environmental stressors. The illness onset occurs between 18-25 years of age at a time period marked by significant physical and behavioural changes that are typically linked to underlying changes in the brain (including aberrant synaptic pruning and cortical thinning; Insel, 2010; Murray et al., 2017).

Supporters of the neurodevelopmental model acknowledge that abnormalities occur during several developmental stages (i.e., fetal life, childhood, and adolescence) and interact with other risk factors (Murray et al., 2017). The presence of and possible interaction between the physical, behavioural, and neurobiological changes points to potential biopsychosocial influences that give rise to the expression of the illness during a particular developmental stage. The evidence suggests that these psychosocial influences can double or triple the risk of developing schizophrenia; these influences include being born and/or raised in urban settings, ethnic minority status (not dependent on recent migration), social exclusion/adversity, and/or cannabis use (Os, Kenis, & Rutten, 2010; Vassos, Pederson, Murray, Collier, & Lewis, 2012). A dose-response relationship exists between urbanicity (as measured by population size or density) and risk of developing schizophrenia (van Os et al., 2010). Thus, while heritability continues to be the strongest illness predictor, individual genetic variants have small effect sizes suggestive of a minor role for gene variants in susceptibility (Birnbaum & Weinberger, 2017), and growing evidence supports the interaction between genes and chronic psychosocial stressors that contribute to the manifestation of psychotic symptoms. It may be that genes mediate the risk of the illness by increasing the sensitivity to environmental factors (Misiak et al., 2019).

Additional genetic evidence comes from longitudinal studies (e.g., Copenhagen and Dunedin birth cohorts) which revealed that the developmental history of individuals who later progress to schizophrenia frequently include delays in achieving motor, language, and social developmental milestones during the first year of life as well as lower IQ scores during childhood (Murray et al., 2017; Ordóñez, Luscher, & Gogtay, 2016). Neuroimaging investigations reveal evidence of cortical thinning as well as significant progressive gray matter loss in childhood-onset schizophrenia and adolescence suggestive of a neurodevelopmental process specific to the illness that occurs even prior to medication exposure (see Ordóñez, Luscher, & Gogtay, 2016 for a review). Of note, while subtle cortical thinning may be observed in nonschizophrenic psychotic disorders, excessive gray matter loss seems to be associated with schizophrenia illness in particular and not due to IQ- or medication effects.

The neurodevelopmental model of schizophrenia therefore purports that the observed symptoms of the illness during adolescence mark a late stage of the disorder rather than true onset per se. It has been previously proposed that there are 4 disease stages secondary to changes that occur in prenatal or perinatal life. Stages 1 to 4 mark a transition from *risk* (genomics, environmental factors, epigenetics) to *prodrome* (ultra-high risk or pre-psychosis phase typically remarkable for attenuated symptoms such as mild delusional thoughts or suspiciousness and impaired social and academic functioning) to *psychosis* (symptoms) to *chronic disability* (Insel, 2010). However, research is needed to find more compelling evidence for the earliest stage (e.g., genetic and epigenetic biomarkers, cognitive predictors, etc.). While prodromal symptoms increase the predictive power of future development of schizophrenia, prodrome is a poor illness predictor overall because it is nonspecific (Insel, 2010; Woodberry, Shapiro, Bryant, & Seidman,

2016). In fact, many adolescents with similar symptoms either do not develop schizophrenia or develop other psychological illnesses.

The neurodevelopmental model takes into account that events during adolescence may also increase the risk of schizophrenia. Nonetheless, current views support a Developmental Risk Factor Model rather than the neurodevelopmental model's reductionistic approach in attributing the illness to disruptions in neurodevelopment. The Developmental Risk Factor Model purports that an increase in adverse life events (including victimization and trauma) as well as excessive drug use during adolescence are contributory to psychotic symptoms, especially delusional thinking (Murray et al., 2017). This more recent model also better accounts for evidence of neurodegeneration in schizophrenia.

#### *Dysconnectivity Hypothesis*

Another supported hypothesis is that schizophrenia is a dysconnectivity syndrome whereby symptoms emerge from abnormal connections between brain regions rather than region-specific abnormalities (Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011). Brain networks make up not only the brain regions involved in a particular function, but also the connections (or "edges") that make synchronized activity between isolated regions (or "nodes") possible (van den Heuvel & Fornito, 2014; Sporns, 2011). It has been suggested that aberrant connections exist between schizophrenia brain regions causing functional disintegration that underlies the psychopathological symptoms (Brandl et al., 2019). Since the early 1990's, functional neuroimaging data continue to provide evidence for dysconnectivity between and within key brain regions among individuals with schizophrenia irrespective of chronicity and diagnostic subgroups (Pettersson-Yeo et al., 2011).



Within the last decade, a growing number of investigators have been attempting to find psychosis-specific structural correlates of functional dysconnectivity and/or distinct white matter abnormalities (Pettersson-Yeo et al., 2011). Advances in magnetic resonance imaging (MRI) techniques provide non-invasive ways to investigate the structural anatomical changes underlying brain diseases like schizophrenia, to further the understanding of pathological processes. Two structural imaging analyses often used in schizophrenia research are diffusion tensor imaging (DTI) and measures of cortical thickness. DTI allows for the investigation of structural connectivity by examining commonly reported measures such as fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD). These three measures provide complementary information on the integrity of overall white matter microstructure.

Fractional anisotropy is considered the most sensitive measure of the underlying microstructure and provides information on the degree to which the diffusion of water molecules is constrained. Thus, myelinated axons (white matter) with good structural integrity have high FA values, reflective of their ability to permit one-directional water diffusion along cells, while restricting movement across cells. FA values are indicative of relative axonal size, myelination, axon connections, and orientation or direction of fibres such that lower regional FA values are suggestive of reduced axonal connectivity and white matter structural integrity due to lower axial (parallel) and/or higher radial (perpendicular) diffusivity (Alexander, Lee, Lazar, & Field, 2007). Given that axonal connectivity and myelination independently contribute to anisotropy, FA is sensitive, but nonspecific to the type of microstructural pathological changes (e.g., radial or axial; Alba-Ferrara & Eraudquin, 2013). Specifically, radial diffusivity indexes myelin damage (i.e., increase RD reflects demyelination), while axial diffusivity indexes axonal injury. For this

reason, incorporating several diffusion measures may help to provide greater specificity or characterization of tissue structure/neuropathology (Alexander et al., 2007).

MD and FA typically have an inverse relationship. MD is a measure of the mean diffusion of water in all directions, and thus higher values are found in regions with unconstrained motion (e.g., cerebrospinal fluid and in neurons with compromised myelination). MD is particularly sensitive to edema, necrosis, and cellularity. RD is considered an indirect measure of overall myelin integrity as it reflects the diffusion of water molecules perpendicular to the primary axis of the diffusion ellipsoid. RD increases with reduced myelination and can also be affected by the density or diameter of axons. The evidence thus far suggests that reduced structural network connectivity of large-scale white matter tracts may be implicated in the development of schizophrenia illness, particularly those projections between frontal, temporal, and parietal brain areas (van den Heuvel & Fornito, 2014).

Functional connectivity and structural (i.e. white matter) integrity are closely related (Hermundstad et al., 2013). In fact, either structural or functional connectivity is used to measure hypo- or hyperconnectivity. The integrity of brain regions and networks provides a good estimate of the quality of functional integration between networks, suggesting that anatomical patterns underlie functional connectivity (Nelson, Bassett, Camchong, Bullmore, & Lim, 2017). Of note, the anatomical integrity of one region directly influences regions with which it is structurally and functionally connected (Wheeler & Voineskos, 2014).

Cortical thickness is a sensitive imaging measure used to detect alterations in brain structure that may give rise to psychotic illness and cognitive impairment. The thickness of the cerebral cortex is dependent on the density, structure, and arrangement of neurons and glial cells (Garey, 2010). Current views hold that schizophrenia involves reductions in whole-brain volume

and cortical thickness most consistently in the prefrontal, temporal, and parietal regions (Menon, 2011; Olabi et al., 2011; Woodward et al., 2015). A recent meta-analytic study supports previous findings of widespread cortical thinning in individuals with schizophrenia in comparison to control volunteers, though there were some brain regions with relatively thicker cortex (van Erp et al., 2018). It is noteworthy that thicker cortex is not always indicative of better functioning; indeed, thinner cortex may be suggestive of “efficient neural organization and learning-dependent plasticity” (Meyer, Liem, Hirsiger, Jäncke, & Hänggi, 2014).

Abnormal structural (and functional) network connectivity has also been shown in individuals with schizophrenia in the fronto-temporal, fronto-parietal and fronto-striatal networks (Nelson, Bassett, Camchong, Bullmore, & Lim, 2017). These abnormalities may partially explain why those with the illness and comparison controls have been found to use dissimilar brain regions to complete the same cognitive task (e.g., executive functioning tasks; Tan et al., 2006). Currently, a meta-analytic study conducted by Brandl and colleagues provides cutting-edge evidence of substantial dysconnectivity as a result of both alterations in functional connectivity and brain structure (Brandl et al, 2019). Specifically, the presence of functional dysconnectivity combined with diminished gray matter volume (GMV) in particular brain regions (i.e., insula, lateral postcentral cortex, striatum, and thalamus) among individuals with schizophrenia is suggestive of dysfunctional brain regions that can be targeted for pharmacological and behavioural treatment. Thus, GMV and functional dysconnectivity (hyper- or hypoconnectivity) overlap in a bi-directional way at least in particular brain areas. Nonetheless, these imaging findings may reflect pathophysiology related to both the cognitive and psychotic features of schizophrenia (i.e., positive and negative symptoms).

### **Psychological Factors: Cognition as a key disease feature**

Although cognitive impairment is not included in the diagnostic criteria of schizophrenia, it is a core feature of the disorder affecting approximately 75% of patients. Research studies have highlighted the importance of cognition (including social cognition) in not only separating individuals with schizophrenia from controls (Heinrichs, 2005), but also in its influence on community functioning (see Fett, Viechtbauer, Dominguez, Penn, van Os, & Krabbendam, 2011 for a meta-analytic review). Previous evidence suggested that neurocognitive functioning accounted for approximately 60% of functional outcome variance (defined as community outcome, social problem-solving, and psychosocial skill acquisition; Green, Kern, Braff, & Mintz, 2000); though recent findings suggest more modest effects (i.e., 4-23%; Fett et al., 2011).

Nonetheless, cognitive impairment is typically observed in the domains of attention, processing speed, learning and memory, problem-solving, and social cognition (e.g., perspective-taking, emotion recognition and management; Wei, Wang, Yan, Li, Pan, Cui, Su, Liu & Tang, 2015). On average, patients perform approximately one standard deviation below control groups on cognitive measures (Heinrichs, 2005). Meta-analytic findings suggest that the most common neuropsychological abilities affected include attention and working memory, phonemic word fluency, verbal learning and memory, and aspects of executive functioning (i.e., abstract reasoning and mental flexibility), which have the largest effect sizes ( $d \geq 1$ ; see Heinrichs, 2005 for review). Evidence from systematic reviews and a meta-analytic study suggest that attention and vigilance, verbal fluency, verbal learning and memory, and executive functioning, as well as processing speed and visual learning and memory are linked to functional outcome (Fett et al., 2011; Green, 1996; Green et al., 2004). However, the utility of examining domain-specific relationships to functional outcome is questionable given that the difference between these effect

sizes tend to be relatively small with overlapping confidence intervals (Fett et al., 2011). Specifically, given that there is generalized cognitive impairment in schizophrenia, selective deficits are influenced by this broad background impairment and may be difficult to observe.

While the majority of individuals with schizophrenia are cognitively impaired, there is no biological abnormality that occurs consistently in a majority of patients (Birnbaum & Weinberger, 2017). Additionally, there is no unique neuropsychological profile that defines schizophrenia or that has been definitively linked to a specific concomitant biological abnormality. Nonetheless, cognition is very sensitive to the presence of the illness; indeed, distribution overlap is greater with neuroimaging than with neurocognitive performance (Heinrichs, 2005). Of note, medications typically attenuate positive symptoms but do little for cognitive and negative symptoms (Fusar-Poli et al., 2014; Nielsen et al., 2015); and both cognitive and negative symptoms contribute to significantly poor functional outcome (Fusar-Poli et al., 2014).

However, a minority of patients (15-25%) demonstrate average to superior ability on many standard cognitive measures with no attenuation of the severity of psychotic symptoms (Ammari, Heinrichs, & Miles, 2010; Heinrichs et al. 2008; Muharib, Heinrichs, Miles, Pinnock, McDermid Vaz, & Ammari, 2014; Palmer et al., 1997) and little or no functional advantage in the community even with supports (Ammari, Heinrichs, Pinnock, Miles, Muharib, & McDermid Vaz, 2014; Muharib et al., 2014). The data imply a dissociation of cognitive and psychosis-generating neural mechanisms. It may be that these patients share a disease process that leads to psychosis but vary in terms of the pathophysiology that causes cognitive impairment. If this conjecture holds true, the inclusion of patients with relatively intact cognitive functioning in

research studies provides a unique opportunity to investigate the possible origins of psychosis in the brain, without the obscuring influence of cognitive pathology.

It is known that a subset of community-dwelling neurologically normal individuals performs below average limits on neurocognitive measures (Schretlen, Testa, Winicki, Pearlson, Gordon, 2008), but they are seldom included in schizophrenia research. Schretlen and colleagues found that 13-19% of control participants obtained demographically and estimated premorbid IQ-adjusted T-scores below 40 (1 *SD* below the mean), and up to 6% approximately had scores 2 *SDs* below the mean across 43 cognitive measures. Cognitive performance among the patient population, akin to the control population, may be on a continuum. In this respect, the presence of cognitive impairment is not a pathognomonic sign of schizophrenia illness. However, the majority of research findings to-date are obscured by data typically collected from and comparing cognitively impaired patients with cognitively normal nonpsychiatric controls. A meta-analysis of functional imaging studies conducted by Minzenberg and colleagues revealed that only 8 of the 41 studies matched controls and individuals with schizophrenia on cognition (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). The problem is, if cognition and psychosis reflect different effects on brain processes and structure, the failure to include both patients and controls with and without cognitive impairment precludes the investigation of these differential effects. Thus, the inclusion of both cognitively normal patients and below-average controls in schizophrenia research may elucidate the structural brain differences attributable to schizophrenia psychopathology and not due to cognitive impairment.

It is noteworthy, however, that cognitive normality in schizophrenia remains a controversial topic, and some researchers contest its existence. There is evidence to suggest that despite some patients' current average cognitive performance profile, there are at least some

whose level of performance is a reduction from above-average premorbid functioning (Allen et al., 2003). Still others argue against cognitive normality in schizophrenia in light of the existence of performance deficits on some cognitive measures (e.g., psychomotor abilities and executive functioning) as compared to controls (Heinrichs et al., 2015; Wilk et al., 2005). However, patients' and controls' performance are not always discrepant (Heinrichs et al., 2008; Muharib et al., 2014), and it is perhaps reasonable to expect some dissimilarities in performance between patients and controls given the illness burden. The existence of cognitive variability necessitates inquiry as this may contribute to the understanding of the neuropathologic heterogeneity of schizophrenic illness.

Taken together, the study of patients with normatively average-range neuropsychological performance profiles at time of testing, including those with putative deterioration from higher premorbid levels, has implications for understanding the neural mechanisms underlying psychotic disorder and its effects on real-world functioning (Shamsi et al., 2011). One such implication of poor functionality in cognitively normal patients is that perhaps the field is wrong in its emphasis on cognition as the main driver of adjustment. Another explanation is that perhaps the level of cognitive proficiency required for basic daily functioning is not that high. Of course, both cognitive and daily functioning are in part dependent on intact brain systems integral for information processing, and thus impairments in functioning suggests cortical disruptions.

Behavioural data suggest that cognitive impairment and psychosis are largely independent illness processes (de Gracia Dominguez et al., 2009; Heinrichs et al., 2015), while neuroimaging data are inconsistent. For instance, imaging data have shown reduced gray matter volumes in individuals with schizophrenia irrespective of cognitive status (i.e., cognitively

normal and below-normal range patients) indicating that the illness is associated with structural brain changes (Wexler et al., 2009; Heinrichs, Pinnock, Parlar, Hawco, Hanford & Hall, 2017). Other research findings suggest that it is white matter (not gray matter) abnormalities that are a hallmark of schizophrenia, affecting both neuropsychologically normal and impaired patients compared to controls (Woodward et al., 2015). More recent evidence from Czepielewski and colleagues (2017) adds further discrepant findings to the literature. These researchers used structural imaging techniques to examine both whole-brain and regionally specific areas in the frontal and temporal lobes (i.e., anterior cingulate cortex, anterior insula, and hippocampus) known to be affected in schizophrenia compared to comparison controls. The data revealed substantial structural brain abnormalities (including reduced total brain volume, intracranial volume, cortical gray matter volume, and cortical thickness) in cognitively impaired patients with little such structural changes observed in their cognitively normal counterparts (Czepielewski, Wang, Gama, & Barch, 2017).

### **Towards a Network-Approach**

Nonetheless, more compelling evidence for illness-specific brain processes comes from network analyses that examine spatially distinct brain areas that function together (i.e., belong to a given brain network) rather than specific cortical regions. While previous views held that brain networks were disjointed, recent data highlight that the same brain regions may belong to more than one network simultaneously (Najafi, McMenamin, Simon, & Pessoa, 2016). Indeed, there has been an increase in using a network approach as it more appropriately accounts for cognition and behaviour, which depend on the complex exchange between brain regions that are functionally connected. Furthermore, region of interest analyses, avoid the problem of multiple comparisons and allow for greater statistical power (Lindquist & Mejia, 2015). Identifying



aberrant structural changes of key brain networks may pinpoint the pathological processes that give rise to problematic cognitive and psychological functioning. It is more plausible that a complex and debilitating disorder like schizophrenia results from abnormal functioning in interconnected brain regions as opposed to focal lesions in a few cortical areas (van den Heuvel & Fornito, 2014).

## **Large-Scale Brain Networks**

### *The Relationship between the Default Mode and Central Executive Networks*

Key networks include the default mode network (DMN), salience network (SN), and central executive network (CEN). The default mode network (DMN) is active at rest and involved in processing internally-directed thoughts and feelings (Anticevic et al., 2012; Hu et al., 2017). It consists of the posterior cingulate, precuneus, ventromedial prefrontal cortex, medial and lateral temporal lobes, inferior parietal lobule (angular gyrus), posterior extent of the inferior parietal lobule, as well as the superior and inferior frontal gyri (Spreng et al., 2013; Stevens & Spreng, 2013). The DMN is negatively correlated with the central executive network (CEN), which is engaged by goal-directed, externally-directed cognitive effort (i.e., higher-order cognitive and attentional control processes such as working memory, inhibitory control, problem solving, and mental flexibility; Hu et al., 2017; Menon & Uddin, 2010; Metzak et al., 2011). The primary CEN nodes include the dorsolateral prefrontal cortex (dlPFC), intraparietal sulcus (IPS), frontal eye field (FEF), anterior extent of the inferior parietal lobule (aIPL), medial superior prefrontal cortex (msPFC), anterior insular cortex and posterior parietal cortex (Menon, 2015; Spreng et al., 2013).

An over-active DMN may produce psychopathology while also suppressing the CEN, leading to cognitive impairment (Anticevic et al., 2012; Hu et al., 2017). Evidence suggests that

an over-active DMN in schizophrenia patients not only correlates with impaired cognitive performance, but is also linked to greater psychopathology (e.g., positive symptoms such as hallucinations and delusions; Whitfield-Gabrieli & Ford, 2012; see Hu et al., 2017 for a review). However, from this perspective psychosis should associate invariably with cognitive impairment, a prediction contradicted by the discovery of cognitively normal patients. Research has found that there exists an inhibitory connection from the CEN to the DMN such that CEN-activation deactivates the DMN (Chen et al., 2013). The existence of patients with preserved cognition offers a unique opportunity to test the DMN/CEN model and to determine the neural correlates of psychosis as distinct from cognitive impairment in schizophrenia pathophysiology.

### *The Salience Network*

The salience network (SN) is important for detecting salient information from among various competing stimuli to orient resources towards its processing (Bressler & Menon, 2010; Kim, 2014; Vossel, Geng, & Fink, 2014). This network is composed of the anterior insula, the dorsal anterior cingulate cortex, temporo-parietal junction, and subcortical regions including the amygdala, substantia nigra, and thalamus, and has been shown to control switching between the DMN and CEN (Menon, 2015; Menon & Uddin, 2010). Its interconnection with these key networks and role as a high-level multisensory integration system allows for its involvement in complex (social) cognitive functioning and initiation or modification of behaviour (e.g., self-awareness, social interactions; Menon, 2015; Palaniyappan, L & Liddle, P., 2012). Disruptions in saliency can be observed among individuals with schizophrenia who typically misattribute the importance of internal and external sensations (Menon, 2015; Palaniyappan, L & Liddle, P., 2012). Thus, an impaired DMN may lead to psychosis, while impaired DMN and SN lead to impaired cognition as well as psychosis.

### *The Social Brain Network*

Lastly, the social brain network (SBN) involves a number of brain regions important for processing social information (Grossman, 2013) and thus, the social cognitive deficits in schizophrenia. Social cognition includes social perception, emotion processing, attributional bias, and theory of mind (ToM, ability to infer another individual's views or judgments; Green & Horan, 2010). Patients are significantly debilitated by deficits in social functioning, which is a good predictor of illness recovery and functional outcome (job attainment, interpersonal relationships, and managing instrumental activities of daily living; Dodell-Feder, Tully, & Hooker, 2015; Green, Lee, & Ochsner, 2013). Important SBN nodes include the anterior insula, amygdala, dorsomedial prefrontal cortex, temporo-parietal junction, the superior temporal sulcus, posterior cingulate cortex, and parts of the ventromedial prefrontal cortex (Kennedy & Adolphs, 2012). Muharib and colleagues (2014) found that cognitively normal patients outperformed cognitively-impaired patients on all cognitive measures except social cognition and were indistinguishable from cognitively-impaired patients with respect to dependence on social support systems. These findings highlight that preserved cognition may not translate to benefits in functional outcome.

### **The Evidence on Structural Aberrations**

The evidence suggests that large-scale brain networks are disrupted in schizophrenia (See Brandl et al., 2019 for recent meta-analysis). Heinrichs and colleagues (2017) recently published data indicating that cognitively normal controls have greater cortical thickness in key networks (i.e., default mode network (DMN), salience network (SN), but not the central executive network (CEN)) than cognitively normal and below-normal patients. However, there were no differences found between cognitively normal and below-normal controls or between cognitively normal and

below-normal patients (Heinrichs, Pinnock, Parlar, Hawco, Hanford & Hall, 2017). Thus, DMN and SN structural abnormalities may be related to the psychotic disease process and not to cognitive impairment.

The dysconnectivity hypothesis (i.e., aberrant connections between brain regions) is mostly supported by findings of hypoconnectivity within and between key large-scale brain networks (e.g., between SN and DMN, SN and CEN, as well as between SN and key brain areas of the SBN like the amygdala) in patients when compared to control participants (Dong, Wang, Chang, Luo & Yao, 2017; Mukherjee et al., 2013). On the other hand, hyperconnectivity between and within some brain regions and circuits has also been reported (Wheeler & Voineskos, 2014; Mothersill et al., 2017). Hyperconnectivity between the DMN and SBN, for example, could give rise to impairment in social cognition and positive symptoms. Specifically, simultaneous activation of both circuits could cause increased salience of self-referential processes and poor perspective-taking (i.e., poor ToM; see Nekovarova, Fajnerova, Horacek, & Spaniel, 2014 for a review of large-scale network abnormalities related to self and ToM disturbances).

As previously mentioned, neuroimaging findings comparing individuals with schizophrenia and controls have been largely inconsistent, with evidence reported of reduced connectivity particularly in frontal brain regions, as well as hyperconnectivity (e.g., among unmedicated patients at illness onset; Anticevic, 2015), or no difference (see Wheeler & Voineskos, 2014 for a review). A recent meta-analysis of resting-state functional and structural imaging data (fMRI and GMV) revealed more pronounced hypoconnectivity in the salience (SN), default mode (DMN), frontoparietal (FPN) or CEN, and limbic networks in the insula, thalamus, and striatum of individuals with schizophrenia compared to a community sample,

major depressive disorder, bipolar disorder, addiction, and anxiety disorder patient populations (Brandl et al., 2019). Furthermore, this study found hyperconnectivity within regions of the DMN, and between large-scale networks (e.g., limbic network and FPN or CEN) among individuals with schizophrenia in contrast to the same comparison groups. Thus, the study found hypoconnectivity between and across networks in DMN, SN, and CEN, and hyperconnectivity between DMN and the limbic network (Brandl et al., 2019). Of note, clinical or demographic variables (e.g., age, illness duration, symptom severity, medication) did not significantly impact dysconnectivity pattern (Brandl et al., 2019).

The inconsistencies in findings suggest widespread, slight alterations in brain networks rather than obvious lesions in specific tracts (Wheeler & Voineskos, 2014). Tract-based differences are typically more variable between studies. Group differences are likely based in network approaches across the brain which tend to be more replicable (Wheeler & Voineskos, 2014). Thus, the inconsistencies may simply reflect the heterogeneity of the disease within the study sample and/or whether the data were analyzed by particular subgroups. Furthermore, previous studies have focused on functional and/or anatomical connectivity, whole-brain volume or regional cortical thickness between large-scale brain networks in schizophrenia patients and controls. However, the field lacks a comparative investigation of these brain circuits and performance on neurocognitive measures between cognitively normal patients and controls. Such an approach would help clarify whether cognition and psychosis are indeed dissociable.

Of course, an obstacle to identifying the independent contribution of structural abnormalities to cognitive impairment and psychosis is the co-existence of both in typical research samples. For this reason, the current study included patients who performed in the average to above average range, and control participants who performed in the below-average

range. Examination of both cortical thickness and white matter integrity across patient groups and between patients and controls will help to dissociate neurobiological correlates of cognitive impairment and psychosis. To date, no study has investigated the structural integrity of these four large-scale networks in cognitively normal individuals with schizophrenia compared to more typically cognitively impaired patients to take into account cognitive status. This project represents one approach to understanding the correlates of psychotic illness. This study investigated whether psychosis-specific networks are identifiable and dissociable from cognitive pathology and contribute to the understanding of heterogeneity within this complex disorder.

### **Study Aim**

The main impetus for this study was to examine whether cognitively normal versus impaired patients have different structural connectivity patterns along tracts connecting core regions within and between four brain networks. Addressing this aim would further the understanding of whether psychotic illness and cognitive impairment represent separable yet comorbid disease processes. To this end, we asked: Are aberrations in cortical thickness and/or structural connectivity within and between networks associated with cognitive impairment and/or the severity of psychotic psychopathology at the time of this study? To answer this, we examined 1) performance on standard consensus as well as adjunct specialized cognitive measures, 2) cortical thickness across the whole brain and within key large-scale brain regions (DMN, CEN, SN, SBN), and 3) the structural integrity of key white matter tracts; specifically the cingulum (CGC), genu of the corpus callosum (GCC), superior longitudinal fasciculus (SLF), sagittal stratum (includes the inferior longitudinal fasciculus and the inferior fronto-occipital fasciculus), and the uncinate fasciculus. Comparisons were made between schizophrenia patients and controls who met or failed to meet a cognitive normality criterion based on a widely used

neuropsychological test battery (Nuechterlein, et al., 2008).

With respect to structural integrity, the white matter tracts studied were chosen on the basis of their connections to two key nodes (or brain regions) for each of the four networks. Specifically, key nodes for the DMN are the ventromedial prefrontal cortex (vmPFC) and the precuneus/posterior cingulate cortex (Uddin, Supekar, Ryali, & Menon, 2011). The cingulum bundle mediates the connection between these nodes (Bonnelle et al., 2012; De Simoni et al. (2016); Leech & Sharp, 2014; Menon 2013). The CEN's core nodes are the posterior parietal cortex and the dorsolateral prefrontal cortex (Bressler & Menon, 2010; Uddin et al., 2011), and they are connected via the superior longitudinal fasciculus and genu of the corpus callosum (Wetherill et al., 2012). The anterior insula (AI) and dorsal anterior cingulate cortex (dACC) are crucial within the SN and communicate via the (ventral) uncinate fasciculus (Menon, 2015; Uddin et al., 2011). Lastly, the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus (IFOF; together called the sagittal stratum (SS)) connects crucial SBN structures (i.e., amygdala, fusiform face area, and superior temporal sulcus; Jou et al., 2011).

We were also interested in examining tracts that connect key nodes across networks. Of note, communication between key hubs across networks often rely on the same fibre tracts as within networks. The cingulum bundle allows key nodes within the CEN and DMN to exchange information as it connects the DLPFC and PCC (Heilbronner, & Haber, 2014). It also links key nodes of the SN (dACC) and DMN (PCC) (Heilbronner, & Haber, 2014). The key nodes of SN and CEN (i.e., AI and DLPFC, respectively) communicate via the fronto-occipital fasciculus (Uddin et al., 2011). The SN and CEN hubs (right AI and right PPC) are also linked through fibres from the superior longitudinal fasciculus (SLF; Supekar & Menon (2012). The SLF also connects the SN to the SBN through their key nodes (ACC and STS, respectively; see Wang,

Metoki, Alm, & Olson, 2018 for review). Lastly, the ventral cingulum bundle and inferior fronto-occipital fasciculus (IFOF) allows communication between the DMN and SBN via their key nodes, the PCC and amygdala (Wang et al., 2018). Taken together, the five tracts (cingulum bundle, superior longitudinal fasciculus, genu of the corpus callosum, uncinate fasciculus, and the sagittal stratum) were selected a priori for study inclusion based on previous research, reviewed below, that has established their role in allowing communication between and within networks.

### **Key Functions of each Tract**

A recent meta-analytic study has confirmed findings of reduced structural integrity in these five tracts in schizophrenia, among others (Kelly et al., 2018). Interhemispheric and fronto-temporal dysconnectivity are among the most consistent findings in schizophrenia research (Kelly et al., 2018). Among these, dysconnectivity of the genu of corpus callosum is an often replicated finding with one of the largest effects (Wheeler & Voineskos, 2014). Perhaps this tract's importance lies in its role in interhemispheric communication in the prefrontal cortex region (typically impacted in schizophrenia). Studies support its reduced structural integrity as an enduring disease feature given its existence among individuals in the chronic or first-episode stage and those at high risk of developing the disease; it is involved in integrating behavioural, emotional, and cognitive information for processing and is linked to schizophrenia symptomatology (Di Biase et al., 2017; Kelly et al., 2018; Mike et al., 2013; Park et al., 2008). Reduced white matter integrity in the uncinate fasciculus has also been linked to social and neurocognitive impairment (e.g., impulsive responding/decision-making, poor long-term memory retrieval (particularly verbal memory), diminished emotional processing) as well as reduced functioning and possibly negative symptoms (Olson, Von Der Heide, Alm, & Vyas,



2015; Seitz et al, 2016). Additionally, given the uncinate's role in allowing communication between the frontal and temporal (limbic) brain regions as well as its late maturation (i.e., into the third decade of life; Olson et al., 2015), it is unsurprising that it is found disrupted in patients.

The superior longitudinal fasciculus is another tract of particular interest given its role in cognitive control and processing speed (Schaeffer et al., 2015; Turken et al., 2008). Studies have found reduced white matter integrity in both patients and comparison controls with poor cognitive control performance such as working memory (Karlsgodt, van Era, Poldrack, Bearden, Neurcheterlein, & Cannon, 2008; Schaeffer et al., 2015). Indeed, the SLF's bidirectional fronto-parietal connections may allow for its role in the top-down regulation needed for cognitive control (e.g., from prefrontal areas such as the dorsolateral prefrontal cortex to parietal regions such as the posterior parietal cortex; Schaeffer et al., 2015). Thus, superior longitudinal fasciculus may be an important tract to demonstrate the impact of cognitive deficit separate from that of psychotic psychopathology. On the other hand, the cingulum was not expected to differentiate cognitively normal and below-normal range patient groups given that this tract is involved in both psychotic symptoms and cognitive functioning (e.g., hallucinations, flat affect and anhedonia/asociality, emotional regulation, processing speed, and executive functions such as cognitive control; Bubb, Metzler-Baddeley, & Aggleton, 2018; Seitz et al., 2016; Whitford et al., 2014; Wisner et al., 2019). Lastly, aberrations in the sagittal stratum is associated with positive symptoms (e.g., auditory verbal hallucinations), facial recognition, and emotion perception (Jou et al., 2011; Oestreich, McCarthy-Jones, & Whitford, 2016; Seitz et al., 2016).

### **Hypotheses**

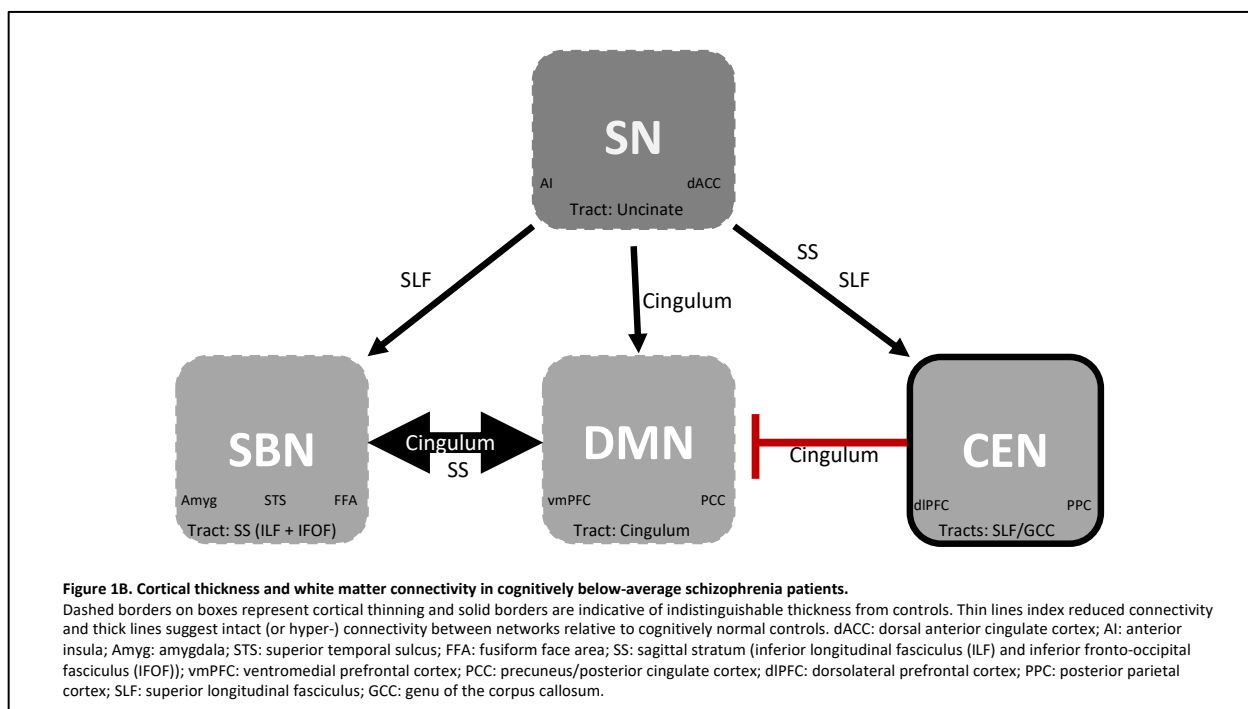
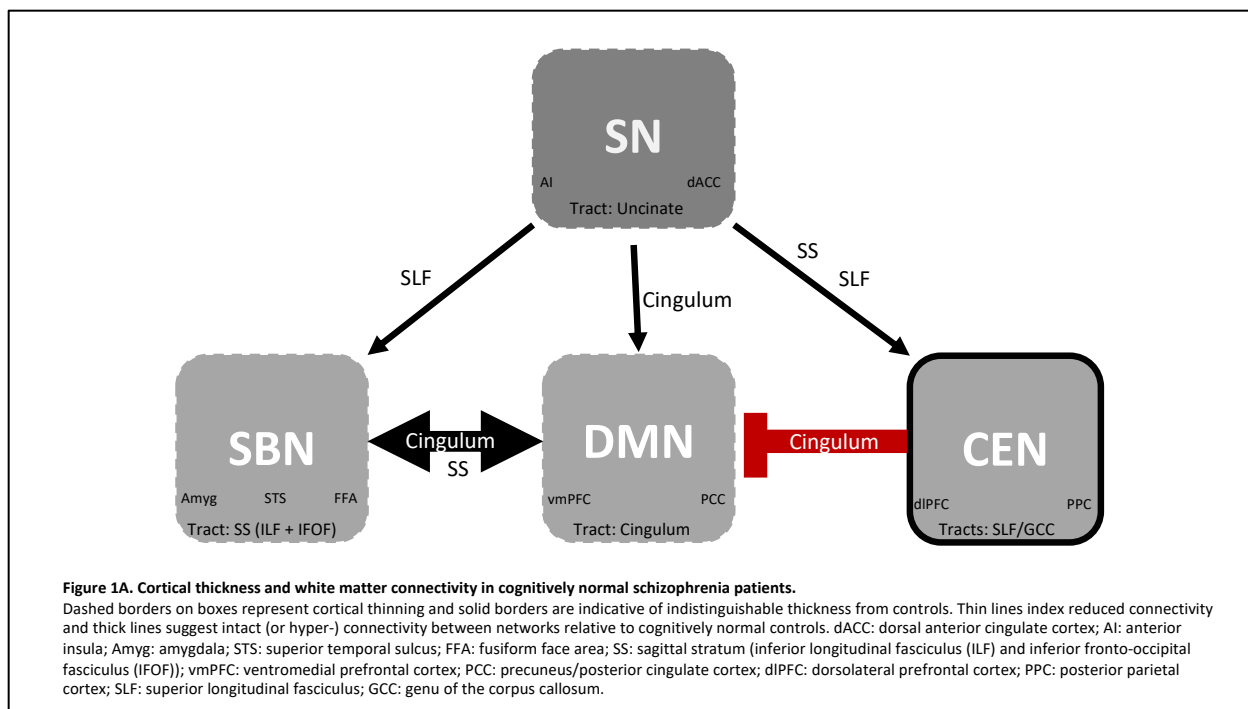
Building on a program of research from the Heinrichs' schizophrenia lab (Heinrichs et al., 2017; Muharib et al., 2014), it was hypothesized that 1) cognitively normal and below-

normal range patients will have comparable severity of psychopathological symptoms; 2) on intellectual functioning, standard consensus (with the exception of performance on processing speed), and adjunct specialized cognitive measures, cognitively normal range patients and controls will have inappreciable differences in performance, both cognitively normal range groups will outperform the below-normal range groups, and below range patients and controls will have identical neurocognitive performance profiles; 3) cortical thinning patterns will be largely comparable between patient groups reflecting a common underlying psychopathology, with notable thinning in SN, DMN, and SBN when compared to cognitively normal controls.

4) However, it was predicted that cognitively normal and below-normal range patients will have dissimilar white matter connectivity patterns between CEN and DMN (see Figure 1A and 1B) to account for the differing cognitive performance profiles in the patient groups. Specifically, we expected that cognitively below-average patients will have reduced connectivity between CEN and DMN as compared to cognitively normal patients. However, this could not be directly measured in our imaging analyses given that the same tracts allow communication between and within networks. We hypothesized that both patient groups will have compromised white matter integrity across four tracts measured in this study given their associations to cognitive functioning and psychotic symptoms (i.e., genu of the corpus callosum, uncinate fasciculus, cingulum, and sagittal stratum), when compared with cognitively normal range controls. We predicted that below-normal range patients will have greater reductions than cognitively normal range patients (relative to cognitively normal range controls) given the presence of both disease processes in this group (i.e., cognitive impairment and psychotic symptoms).

We hypothesized that the integrity of the superior longitudinal fasciculus will

differentiate the patient groups given this areas role in cognition. It was anticipated that there will be no difference between the cognitively normal range patients and controls. However, significant group differences were expected between the cognitively normal range groups and their below-normal range counterparts. Taken together, similarities found between cognitively normal range and below-normal range patients will highlight shared underlying neural mechanisms of the disease, while dissimilarities will pinpoint processes possibly linked specifically to cognitive impairment and/or comorbidity. It was predicted that whole-brain white matter integrity will be lower among patients than cognitively normal range controls, which has been consistently shown (Kelly et al., 2018).



## Methods

### Participants

Patients ( $n = 73$ ) were recruited from active outpatient rehabilitation programs in Hamilton, Ontario, Canada and include the Cleghorn Early Intervention Clinic (St. Joseph's Healthcare Hamilton), the Hamilton Program for Schizophrenia, the Schizophrenia Outpatient Clinic (St. Joseph's Healthcare Hamilton), Schizophrenia Services of Ontario, Hamilton Chapter, Path Employment Services and the Wellington Psychiatric Outreach Program. Criteria for participation in the study included: 1) a diagnosis of schizophrenia or schizoaffective disorder confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1996), with no concurrent diagnosis of substance use disorder; 2) a history free of developmental or learning disability; 3) a history free of neurological or endocrine disorder; and 4) being between age 18–65 years. Comparison control participants ( $n = 64$ ) were recruited through local newspaper and online classified advertisements for paid research participation. Furthermore, advertisements targeting community, employment and social service agencies that cater to unskilled and less educated populations were utilized to maximize the recruitment of control participants with below-normal range cognitive functioning. Interested individuals were screened to rule out a history of neurological, endocrine, psychiatric, or substance use disorders. All participants were required to be free of MRI contraindications, were given monetary compensation for their time, and provided their written informed consent. The research was approved by York University and St. Joseph's Healthcare Hamilton ethics review boards and in compliance with the Helsinki Declaration.

## **Clinical Measures**

Medical charts were reviewed for individuals with schizophrenia to verify class of antipsychotic medication(s) and their dosages, as well as document other psychotropic medications taken at the time of the study. Additionally, the Social and Psychiatric History Schedule was used to document patients' demographic information (i.e., age, education, marital status, and employment history) and psychiatric history. Clinical symptom severity was measured with the 30-item Positive and Negative Syndrome Scale (PANSS; Opler, Kay, Lindenmayer, & Fiszbein, 1999) via a semi-structured clinical interview to assess positive, negative, and general psychotic symptoms. Positive symptoms as assessed on the PANSS positive scale include delusions, conceptual disorganization, hallucinations, grandiosity, suspiciousness or persecution, hyperactivity, and hostility. The severity of negative symptoms is expressed on the PANSS negative scale as blunted affect, emotional and social withdrawal, poor rapport, difficulty in abstract thinking, and stereotypic thinking. Lastly, the general scale is a measure of global psychopathology and is comprised of poor insight and judgment, disorientation, unusual thought content, poor attention, depression, anxiety, feelings of guilt, motor retardation, and somatic concern. A composite score reflects the difference between the positive and negative scores. PANSS scales are rated on a 7-point Likert scale to capture a range of symptoms classified as absent to extreme psychopathology.

## **Neurocognitive Measures**

The MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB; Nuechterlein et al., 2008) was administered to assess cognitive abilities typically found disrupted in schizophrenia and schizophrenia-related disorders. The MCCB was developed by experts as a consensus among the

academic community and the National Institutes of Health (NIH) to include in the battery individual measures of *processing speed* (Category fluency, Symbol coding, Trail making A), *attention/vigilance* (Continuous Performance Test, Identical Pairs [CPT-IP]), *working memory* (Letter-Number Sequencing [WAIS-III], Spatial Span [Wechsler Memory Scale III]), *verbal learning* (Hopkins Verbal Learning Test-Revised), *visual learning* (Brief Visuospatial Memory Test-Revised), *reasoning and problem solving* (Mazes (Neuropsychological Assessment Battery [NAB]), and *social cognition* (Mayer-Salovey-Caruso Emotional Intelligence Test [MSCEIT] – Managing Emotions), which yields a composite index of overall performance. The MCCB was developed to provide a consensus battery of neurocognitive measures in schizophrenia that were amenable to change and would thus be suitable targets for cognitive remediation and treatment. The MCCB assesses key modifiable cognitive domains and captures more cognitive variance than IQ alone (August, Kiwanuka, McMahon, & Gold, 2012; Nuechterlein et al., 2008).

Standard measures of general intellectual ability were also included to assess participants' verbal and visual skills. The Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) were used to provide a robust estimate of general intelligence (or intelligence quotient (IQ); Alwin & McCammon, 2001). Indeed, verbal ability tends to measure crystallized intelligence, which typically withstands psychiatric illness (Sheppard & Vernon, 2008). For the WASI Vocabulary subtest, participants were asked to generate definitions to words whereas the Matrix Reasoning subtest was used to assess participants' visual reasoning skills required to accurately complete sequencing patterns. The Reading subtest of the Wide Range Achievement Test (WRAT-4; Wilkinson & Robertson, 2006), another test of verbal ability, was used to estimate premorbid intellectual ability. For this task, participants were asked to read words that became increasingly

challenging to pronounce due to their phonological complexity and infrequency. It is considered an indicator of premorbid functioning because the skill of decoding words is typically learned prior to disease onset and is less susceptible to psychiatric and neurological illness (Nelson & O'Connell, 1978; Bright & van der Linde, 2018). Of note, other cognitive measures (e.g., processing speed, working memory, declarative memory) are vulnerable to the underlying psychiatric disease process (Nuechterlein, Barch, Gold, Goldberg, Green, & Heaton, 2004).

Adjunct measures of social cognition included Theory-of-Mind or reasoning about the mental states of a person, as measured by the Faux Pas Recognition Test (Stone, Baron-Cohen, & Knight, 1998) and the Reading the Mind in the Eyes test (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). The Faux Pas Recognition Test requires that participants listen to short stories and infer whether a character unintentionally committed a faux pas against another causing embarrassment. The Reading the Mind in the Eyes test is a visual task that involves inferring thoughts and emotions from photographs of a person's eyes. Theory of mind has been linked to positive symptoms (e.g., paranoid delusions) and symptoms of disorganization such that individuals with these symptoms tend to be significantly impaired in their ability to infer others' mental states (i.e., thoughts, beliefs, and intentions) "to explain, manipulate and predict behaviour" (Brüne, 2005; Dudley, Taylor, Wickham, & Hutton, 2016; Kinderman & Bentall, 1996; Sprong, Schothorst, Vos, Hox, van Engeland, 2007).

The "beads" task was used to measure faulty decision-making in probabilistic reasoning ("jumping to conclusions"; Garety & Freeman, 2013). In this task, participants are required to decide from which of 2 "jars" individually-presented colored "beads" were drawn. The jars contained either a 60:40 ratio of red to blue beads or blue to red beads, and the number of trials taken to decide was the dependent variable. Meta-analytic studies provide some support for the



sensitivity of the beads task to psychotic psychopathology, particularly in individuals with delusions; though there is some suggestion that other variables may mediate or account for these findings (e.g., general intellectual ability; So, Siu, Wong, Chan, & Garety, 2016; Ross, McKay, Coltheart, & Langdon, 2015).

### **Group Assignment**

Patients and controls were assigned to the cognitively normal or below-normal range based on their MCCB *T* composite score, an index of their overall performance on the 7 domains (i.e., working memory, attention, verbal memory, processing speed, reasoning and problem-solving, visual learning, and social cognition). Group assignment was carried out using the criterion of a *T* score of  $50 \pm 10$ , which represents a normative mean performance in a standardized distribution. Thus, participants who performed in the range of 40 to 60 were assigned to the cognitively normal range group, and those with performances lower than 40 were assigned to the below-normal range groups, consistent with group assignment criteria completed in other studies (Heinrichs et al., 2015; Muharib et al., 2014). The resulting group compilation was such that there were 16 cognitively normal and 48 cognitively below-normal schizophrenia patients as well as 36 cognitively normal and 21 below-normal controls. Thus, this study sample included 121 participants (N=121).

### **Scan Acquisition**

Structural magnetic resonance imaging and diffusion tensor (MRI and DTI) were collected for all participants. Magnetic resonance images were acquired using a 3.0 Tesla whole body short bore General Electric System scanner equipped with an 8-channel parallel receiver head coil at St. Joseph's Healthcare Hamilton, in Hamilton, Ontario, Canada. High-resolution T1-weighted axial anatomical images were collected with a 3D fast-spoiled gradient-echo

sequence resulting in 152 slices using the following parameters: slice thickness = 2mm, with 1 mm overlap, time to repetition (TR) = 7.5ms, time to echo (TE) = 2.1ms, flip angle = 12°, number of excitations (NEX) = 1, field of view (FOV) = 24 cm, acquisition matrix = 512 x 512, and receiver bandwidth (rBW) = +/-62.5 kHz. DTI was conducted using a spin echo planar imaging sequence with 5  $b=0$  volumes and 29 noncolinear diffusion directions at  $b = 1000\text{s/mm}^2$ . Fifty-three axial slices were acquired (2.4mm thick, no gap) for full brain coverage, using the following imaging parameters: TR/TE = 15000/85.9ms, FOV = 24cm, matrix = 128 x 128, rBW = +/-250kHz. The DTI image acquisition was repeated to achieve the effect of 2 NEX.

### **Preprocessing**

For cortical thickness, cortical surface reconstruction and thickness were calculated using Freesurfer's automated processing pipeline (version 5.1.0, <http://surfer.nmr.harvard.edu>). A full description of this technique has been described (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000). Preprocessing procedures commenced with skull stripping, motion correction, and spatial and intensity normalization. Subsequently, a surface-based tessellation of gray matter/pial and gray matter/white matter boundaries were generated across 160,000 vertices in each hemisphere. Surface reconstruction was then visually inspected (slice-by-slice) for accuracy, and manual edits were repeatedly performed to correct inaccuracies until the inspection of the scan was acceptable. Images were then registered to a high-dimensional spherical average to align cortical folds across subjects. Cortical thickness was calculated as the shortest distance between the pial surface to the gray/white matter border at each vertex, and maps were smoothed using a 10mm full-width-half-maximum Gaussian kernel. Data processing was completed by an imaging expert collaborator who was blind to the subject group.

Tract-based spatial statistics (TBSS) allows for nonlinear alignments and projections of tracts onto average tract representations, which allows for voxel-by-voxel group comparisons on diffusion parameters. Specifically, DTI data were preprocessed with FSL 5.0.6 (FMRIB Diffusion Toolbar and TBSS software tools; Smith et al., 2006). Data were first corrected for head movement and eddy currents using FMRIB's Diffusion Toolbox (FDT), followed by application of brain-extraction to each image with the Brain Extraction Tool (also found in FSL; Smith, 2002) to differentiate the brain from skull structures and extract FA values throughout the brain. Subsequently, each voxel within the brain mask was fitted to a tensor model. FMRIB's FLIRT and FNIRT (the linear and nonlinear registration tools, respectively) were utilized to align the FA data into the Montreal Neurological Institute's (MNI-152 1mm<sup>3</sup>) standard space. Consequently, a mean FA skeleton image (thresholded at  $FA \geq 0.2$ ) was created from voxels found at the centres of major white matter tracts. TBSS thus ensures that common tracts are not formed from voxels within the distal extremes of white matter tracts that have greater intersubject variability, that is, where FA values would be compromised by poor registration or volume effects (such as areas close to the CSF or grey matter). Each participant's aligned FA images were mapped onto the mean FA skeleton image in the common MNI space. Lastly, voxel-wise group statistics were extracted from FSL and fed into SPSS for further analyses. MD and RD values were similarly processed and aligned to the FA skeleton.

### **Statistical Analyses**

Data analyses were completed using the Statistical Package for the Social Sciences (SPSS), Version 24. Group differences on continuous demographic variables (i.e., age and education) were examined using an analysis of variance (ANOVA), while Pearson's chi-square statistic was used on categorical data (i.e., gender and handedness). Independent samples t-test

and chi-square analyses were conducted to determine whether the patient groups differed in illness severity (PANSS symptom ratings, number of hospitalizations across the lifetime, employment and independent living status), class of antipsychotic medication, diagnosis (schizophrenia vs. schizoaffective/whether patients were on a mood stabilizer), and duration of illness (time since first psychiatric treatment for present disorder in years).

Prior to parametric statistical testing of cognitive measures (i.e., premorbid and current estimates of intelligence, MCCB domains and composite, and adjunct social cognitive measures), Levene's test for equality of variances was performed. If Levene's test was violated, Hartley's Fmax test (David, Hartley, & Pearson, 1954) was examined to ensure the variance ratio was below the critical value. An analysis of variance (ANOVA) or multivariate analysis of covariance (MANOVA) was carried out on the mean (raw, standard, or T-) scores for the cognitive measures to examine possible between group differences. However, covariance analyses (i.e., ANCOVA or MANCOVA) will be carried out instead if there were any significant demographic effects. Significant comparisons were further examined using Bonferroni post hoc analyses.

Cortical parcellations were obtained for regions of interest (ROIs) using the Destrieux cortical atlas in Freesurfer (as outlined by Destrieux, Fischl, Dale, & Halgren, 2010; Fischl et al., 2010), which provides bilateral hemispheric parcellation of gyral and sulcal structures. A priori ROIs were chosen for analysis in SPSS for each network (DMN, SN, CEN, and SBN; see Heinrichs et al., 2017; Kennedy & Adolphs, 2012; McMenamin, Langeslag, Sirbu, Padmala, & Pessoa, 2014; Menon & Uddin, 2010). Four network values were calculated for the cortical thickness data by averaging each networks' ROIs. This approach was favourable because thickness changes among individuals with schizophrenia tend to be widespread rather than

localized and prevented the multiple comparisons problem (i.e., elevated false positives or type I error; Bennet, Wolford, & Miller, 2009; Lindquist & Mejia, 2015). Of note, ROIs common to multiple networks were included given that a brain region can belong to different networks (Najafi et al., 2016).

Between-group comparisons and network analyses of cortical thickness and white matter tracts affiliated with key nodes from the DMN, CEN, SN, and SBN were performed. The data were first exported from Freesurfer and FSL software packages and fed into SPSS. Mean network thickness values were compared between groups. For DTI data, tract-based spatial statistical (TBSS) analyses were employed to determine fiber coherence and possible pathology. Specifically, FA, MD, and RD measures were used to examine tract integrity between key hubs within and between each network: anterior insula to anterior cingulate cortex (salience network), posterior parietal cortex and dorsolateral prefrontal cortex (central executive network), posterior cingulate cortex and ventromedial prefrontal cortex (default mode network), and between the amygdala and superior temporal sulcus (social brain network).

Levene's test for inequality of variances was again conducted. Subsequently, a MANCOVA was performed to examine the effect of cognitive/diagnostic group status (i.e., cognitively normal range (CNR) patients and comparison controls, as well as below-normal range (BNR) patients and comparison controls) on cortical thickness and white matter integrity. Both age and education were included as covariates.

## **Results**

### **Demographic Characteristics**

Group demographic and clinical characteristics are displayed in Table 1. Among the patient groups, below-normal range (BNR) patients were between 20 to 63 years of age and

completed 8 to 18 years of education while cognitively normal range (CNR) patients ranged from 25 to 50 years old with 12 to 16 years of education. For the control groups, BNR controls were between 30 and 60 years of age and had achieved between 7 to 12 years of education; CNR controls ranged between 19 to 66 years old and obtained 11 to 18 years of schooling. Bonferroni corrected post hoc comparisons revealed that below-normal range (BNR) patients were older and less educated than cognitively normal range (CNR) patients. Additionally, BNR controls were less educated than all other participant groups. Gender and right-handedness were relatively equal across groups.

**Table 1**

*Demographic Characteristics for Cognitively Normal Range (CNR) and Below-Normal Range (BNR) Patients and Controls*

Variable	1.CNR Patients (n=16)	2.CNR Controls (n=36)	3.BNR Patients (n = 48)	4.BNR Controls (n =21)	Statistic
Age, years ( <i>M, SD</i> )	34.13 (7.82)	37.86 (12.32)	43.83 (9.82)	40.81 (9.23)	$F_{3, 117} = 4.47^{**}$
Education, years ( <i>M, SD</i> )	14.44 (1.41)	13.33 (1.60)	12.45 (2.23)	10.43 (1.66)	$F_{3, 117} = 16.55^{***}$
Gender, males ( <i>n, %</i> )	10 (63%)	23 (64%)	31 (65%)	13 (62%)	$\chi^2_3 = 0.06$
Handedness, Right ( <i>n, %</i> )	14 (88%)	31 (86%)	37 (77%)	18 (86%)	$\chi^2_6 = 2.73$
WRAT-4 Reading <i>SS (M, SD)</i>	100.38 (7.54)	101.36 (8.57)	89.43 (10.50)	83.90 (9.07)	$F_{3, 115} = 10.50^{***}$

WASI-IQ Estimate, <i>SS (M, SD)</i>	119.44 (5.05)	112.03 (15.49)	90.33 (18.86)	81.95 (12.24)	$F_{3,115} =$ 19.30***
MCCB composite <i>T</i> <i>(M, SD)</i>	47.06 (5.14)	50.47 (6.70)	24.88 (9.48)	27.00 (10.01)	$F_{3,115} =$ 58.17***

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*Note.* WRAT-4: Wide Range Achievement Test; WASI-IQ: Wechsler Abbreviated Scale of Intelligence-Intelligence Quotient (WASI-IQ), as measured by a combined score from the WASI Matrix Reasoning and Vocabulary subtests; MCCB: MATRICS Consensus Cognitive Battery; PANSS = Positive and Negative Syndrome Scale; \*  $p < .05$ , \*\*  $p < .01$ , \*\*\*  $p < .001$

### **Clinical Characteristics**

Clinical profiles for the two schizophrenia groups are presented in Table 2. Patient groups did not differ in psychiatric (i.e., positive, negative, general, or composite) symptomatology, ratio of patients with a schizoaffective vs. schizophrenia diagnosis or taking a mood stabilizer, age of illness onset, number of hospitalizations across the lifetime, employment and community living status, or class of antipsychotic medication. However, an Independent Samples t-test revealed that the two patient groups differed in their duration of illness (time since first psychiatric treatment) such that BNR patients had a longer illness duration than CNR patients.

**Table 2***Clinical Profiles for Cognitively Normal Range (CNR) and Below-Normal Range (BNR) Patients*

Variable	CNR Patients (n=16)	3.BNR Patients (n = 48)	Statistic
PANSS Positive <i>T (M, SD)</i>	39.00 (6.35)	42.98 (8.13)	$t_{62}= 1.78$
PANSS Negative <i>T (M, SD)</i>	37.38 (7.97)	39.04 (6.65)	$t_{62}= .83$
PANSS General <i>T (M, SD)</i>	38.00 (6.73)	42.02 (7.93)	$t_{62}= 1.82$
PANSS Composite <i>T (M, SD)</i>	52.69 (6.67)	53.29 (9.06)	$t_{62}= .25$
Schizoaffective (%)	44%	44%	$\chi^2_1 = .000$
Mood Stabilizer (%)	20%	12%	$\chi^2_1 = .55$
# of Hospitalizations ( <i>M, SD</i> ) <sup>1</sup>	3 (3.33)	5.79 (8.48)	$t_{56}= 1.27$
Age of Illness Onset, ( <i>M, SD</i> ) <sup>2</sup>	22.86 (5.78)	24.82 (7.73)	$t_{58}= .92$
Illness Duration, years ( <i>M, SD</i> ) <sup>2</sup>	11.26 (8.90)	18.79 (9.95)	$t_{58}= 2.66^{***}$
Unemployed (%) <sup>3</sup>	42%	38%	$\chi^2_3 = 4.54$
Independent Living (%) <sup>4</sup>	59%	57%	$\chi^2_1 = .023$
Medication (2 <sup>nd</sup> generation; %) <sup>6</sup>	87%	66%	$\chi^2_3 = 4.46$

Note: MCCB = MATRICS Consensus Cognitive Battery; PANSS = Positive and Negative Syndrome Scale; \*  $p \leq .05$ , \*\*  $p < .01$ , \*\*\*  $p < .001$ ; <sup>1</sup>based on n=58 due to missing data for 6 BNR patients; <sup>2</sup>based on n=60 due to missing data for 4 BNR patients; <sup>3</sup>based on n=59 due to missing data for 5 BNR patients; <sup>4</sup>based on n=51 due to missing data for 11 BNR and 2 CNR patients; <sup>5</sup>based on n=56 due to missing data for 7 BNR and 1 CNR patient.

### Neurocognitive Performance

Each group's performance on several cognitive measures is presented in Table 1 (above). Education and age were used as covariates given significant group differences. A two-way multivariate analysis of covariance (MANCOVA) revealed significant covariate effects for



education, while there was a trend towards significance for age ( $F(2, 114) = 6.50, p = .002$  and  $F(2, 114) = 2.66, p = .074$ , respectively). There was a significant main effect of cognitive status (i.e., cognitively normal versus below-normal range) on intellectual functioning ( $F(2, 114) = 26.25, p < .001$ ) such that on both WASI IQ estimate and WRAT reading test participants within the cognitively normal range groups had higher scores than their below-normal range counterparts. However, psychiatric status (i.e., patient versus control) was non-significant ( $F(2, 114) = 1.99, p = .141$ ). Furthermore, the interaction between psychiatric and cognitive status was non-significant ( $F(2, 114) = 2.15, p = .121$ ). Nonetheless, despite the non-significant interaction, a comparison between the four groups was considered important and meaningful (Wei, Carroll, Harden, & Wu, 2012), particularly in light of a priori predictions and the small and unequal sample sizes that suggest the study was underpowered to detect effects.

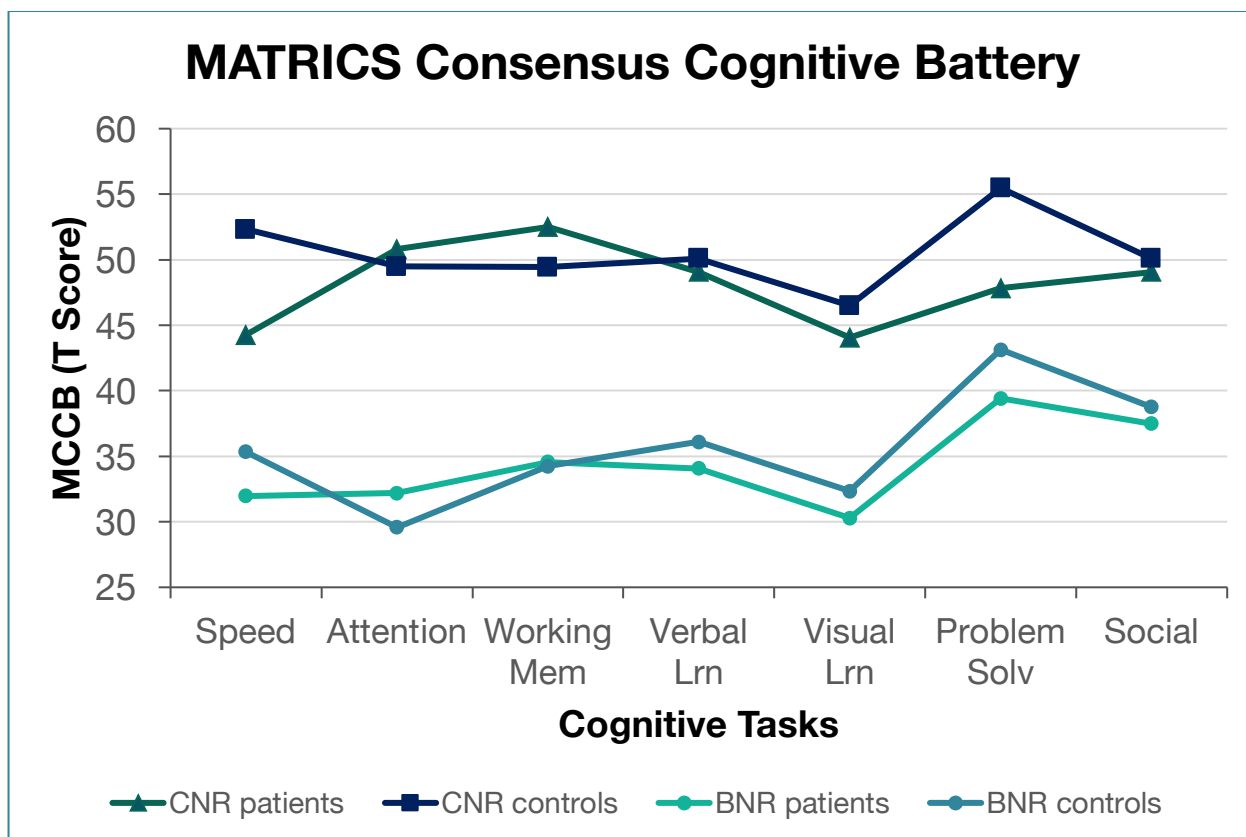
Accordingly, a one-way MANCOVA was conducted to examine which specific group comparisons significantly differed. Performance patterns between groups were equivalent across WASI IQ estimate and MCCB composite score. Specifically, both CNR patients and controls had higher scores than BNR patients and controls. However, there were no differences found between cognitively normal patients and controls, or between below-normal patients and controls. Across reading skill (used to estimate premorbid ability), group differences were similar, although scores between the two patient groups approached significance ( $p = .056$ ).

Group differences on specialized cognitive measures commonly used in schizophrenia research (i.e., performance on MCCB domains) are depicted in Figure 2. The covariate age was significant, while education was non-significant. There were significant main effects for both psychiatric (patient versus control) and cognitive status (cognitively normal versus below-normal

range; ( $F(7, 109) = 4.71, p < .001$  and  $F(7, 109) = 15.94, p < .001$ , respectively). However, there was no significant interaction ( $F(7, 109) = 1.16, p = .33$ ).

The effect of cognitive status on each domain specific MCCB scores was as follows: Speed of Processing ( $F(1, 115) = 25.93, p < .001$ ), Attention/Vigilance ( $F(1, 115) = 59.16, p < .001$ ), Working Memory ( $F(1, 115) = 44.66, p < .001$ ), Verbal Learning ( $F(1, 115) = 56.51, p < .001$ ), Visual Learning ( $F(1, 115) = 36.51, p < .001$ ), Reasoning and Problem Solving ( $F(1, 115) = 23.41, p < .001$ ), and Social Cognition ( $F(1, 117) = 12.94, p < .001$ ). The effect of psychiatric status was significant for the Processing Speed and Reasoning and Problem Solving domains only ( $F(1, 115) = 12.80, p = .001$  and  $F(1, 115) = 13.50, p < .001$ , respectively). All other domains were non-significant: Attention/Vigilance ( $F(1, 115) = .28, p = .596$ ), Working Memory ( $F(1, 115) = .21, p = .649$ ), Verbal Learning ( $F(1, 115) = 1.76, p = .187$ ), Visual Learning ( $F(1, 115) = 1.32, p = .252$ ), and Social Cognition ( $F(1, 117) = .96, p = .330$ ).

Additionally, despite a non-significant interaction, a one-way MANCOVA was again conducted to examine specific group differences. Bonferroni adjusted post hoc analyses indicated that for the Processing Speed domain, cognitively normal range controls had faster reaction times than all other groups (i.e., cognitively normal patients, as well as below-normal range patients and controls). Cognitively normal range patients also had faster speed of processing than the below-normal range patients. With respect to the Attention/Vigilance domain, both cognitively normal range patients and controls obtained higher scores than their below-normal range counterparts. This pattern was also observed on the Working Memory, Verbal Learning, and Visual Learning domains of the MCCB. On the Reasoning and Problem Solving domain, cognitively normal range controls obtained higher scores than all other groups. Lastly, cognitively normal range controls and patients had higher scores than the below-normal range patients on the Social Cognition domain.



**Figure 2.** Performance profiles for patients and comparison controls across the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) domains.

### Adjunct Specialized Cognitive Measures

Levene's test for equality of variances was violated for the Faux Pas stories. Examination of the variance ratio using Hartley's Fmax test revealed ratios below the critical value of 3. On adjunct social cognitive measures, a two-way MANCOVA revealed a main effect of cognitive status ( $F(4, 110) = 9.58, p < .001$ ) on all 3 cognitive measures (Faux Pas questions on the Faux Pas test:  $F(1, 113) = 21.00, p < .001$ , Control questions on the Faux Pas test:  $F(1, 113) = 4.00, p = .048$ ; Reading the Mind in the Eyes:  $F(1, 113) = 18.79, p < .001$ , and the probabilistic reasoning (beads) task:  $F(1, 113) = 7.71, p = .006$ . Specifically, cognitively normal range participants outperformed cognitively below-normal range participants. Psychiatric status had a trend towards significance ( $F(4, 110) = 2.42, p = .053$ ), but its effect on specific tasks were non-significant upon

further investigations. There was no interaction effect; age and education were non-significant covariates.

A subsequent one-way MANCOVA conducted to examine specific group differences was significant ( $F(18, 306) = 4.77, p < .001$ ); again, neither age nor education were significant covariates. Table 3 displays results from adjunct cognitive measures. Further investigations revealed significant effects for the Faux Pas questions on the Faux Pas test, Reading the Mind in the Eyes, and the probabilistic reasoning (beads) task. Bonferroni adjusted post hoc analyses indicated that cognitively normal range controls had higher scores than the below-normal range groups on Faux Pas stories suggestive of greater accuracy at detecting when a faux pas was committed. Cognitively normal range patients outperformed their below-normal range patient counterparts. An equivalent pattern was observed on the Reading the Mind in the Eyes test reflecting that the two cognitively normal range groups outperformed the below-normal range patients in identifying the emotions depicted in the eyes of subjects in a photograph. Cognitively normal range controls also outperformed below-normal range controls. On a probabilistic reasoning task, the below-normal range control group drew fewer beads prior to decision-making (suggestive of “jumping to conclusions”) when compared to the cognitively normal range groups.

**Table 3**

*Adjunct Cognitive Performance across Cognitively Normal Range (CNR) and Below-Normal Range (BNR) Patients and Controls*

Variable	1.CNR Patients (n=16)	2.CNR Controls (n=36)	3.BNR Patients (n=47)	4.BNR Controls (n=20)	<i>F</i> (3, 113)	Bonferroni adjusted Comparisons
Faux Pas test						
FP questions	49.31 (5.43)	50.69 (4.68)	35.56 (13.18)	41.00 (11.64)	14.64***	1>3; 2>3,4
CN questions	19.81 (.40)	19.83 (.56)	18.77 (2.07)	18.65 (1.66)	2.37	
Reading the Mind	25.81 (3.23)	27.56 (3.35)	21.21 (4.86)	21.65 (5.31)	12.09***	1>3; 2>3,4
Probabilistic Reasoning						
Red/Blue Beads	10.44 (2.42)	9.11 (4.21)	7.51 (4.99)	4.60 (3.24)	2.93*	1,2>4

\*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\* $p < .001$ ; FP: Faux Pas; CN: Control.

### Cortical Thickness

With respect to whole-brain cortical thickness, the two-way MANCOVA revealed a significant effect of psychiatric status such that controls had greater cortical thickness than patients ( $F(4, 112) = 3.15, p = .017$ ). However, there was no effect of cognitive status. Nonetheless, there was a significant interaction between psychiatric and cognitive status, ( $F(4, 112) = 2.61, p = .039$ ), though further investigations were non-significant. While age was a significant covariate ( $F(4, 112) = 16.06, p < .001$ ), education was non-significant. Similarly, network analyses revealed significant group differences between patients and controls ( $F(4, 112) = 4.81, p = .001$ ) for the DMN, SN, and SBN, but not the CEN. For these three networks,

controls had greater cortical thickness than patients. There was no effect of cognitive status on network cortical thickness, and the interaction was similarly non-significant.

A one-way MANCOVA (see Table 4) was conducted as a follow-up to examine specific group differences and revealed that CNR controls had greater whole-brain thickness than BNR patients only. As for network analyses, univariate  $F$  ratios were significant for the DMN, SN, and SBN, but not the CEN (see Table 5). Pairwise comparisons revealed that CNR controls had greater cortical thickness than both patient subgroups in the DMN and SN, but SBN pairwise comparisons did not survive Bonferroni corrections. For the SBN, there was a trend for the comparison between CNR controls and BNR patients, with the former having greater cortical thickness ( $p = 0.071$ ). The covariate age was significant ( $F(4, 112) = 13.88, p < .001$ , partial  $\eta^2 = .33$ ), while education was not ( $F(4, 112) = .86, p = .490$ , partial  $\eta^2 = .03$ ).

### **Tract Based Spatial Statistics: Group by Tract Analysis**

With respect to average whole-brain fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD), there was no effect of cognitive status, but there was a significant main effect of psychiatric status on average RD and FA only ( $F(4, 112) = 3.15, p = .017$ , partial  $\eta^2 = .10$ ) such that controls had greater FA and lower RD than patients. There was a significant interaction ( $F(4, 112) = 2.61, p = .039$ ), though further analyses showed significance for average FA only ( $F(1, 115) = 5.08, p = .026$ ), with controls having greater FA than patients. The covariate age was significant while education was not ( $F(4, 112) = 16.06, p < .001$  and  $F(4, 112) = .40, p = .809$ , respectively).

Additional analyses were performed by conducting a one-way MANCOVA to examine group differences in light of a priori predictions, current significant interaction, and consideration of the study's small and unequal sample sizes. Using Bonferroni adjusted pairwise comparisons,

cognitively normal range (CNR) controls had higher average FA than both schizophrenia patient groups, and lower RD values than the same, after controlling for age and education (see Table 4).

**Table 4**

*Average Whole-Brain Fractional Anisotropy, Mean Diffusivity, Radial Diffusivity, and Cortical Thickness in Cognitively Normal Range (CNR) and Below-Normal Range (BNR) Patients and Controls*

Variable	1.CNR Patients (n=16)	2.CNR Controls (n=36)	3.BNR Patients (n=48)	4.BNR Controls (n=21)	<i>F</i> (3, 115)	Bonferroni Adjusted Comparisons
FA ( <i>M, SD</i> )	.48 (.02)	.50 (.03)	.47 (.03)	.47 (.03)	4.85**	2>1,3
MD ( <i>M, SD</i> )	.80x10 <sup>-3</sup> (.03x10 <sup>-3</sup> )	.80x10 <sup>-3</sup> (.02x10 <sup>-3</sup> )	.80x10 <sup>-3</sup> (.02x10 <sup>-3</sup> )	.78x10 <sup>-3</sup> (.04x10 <sup>-3</sup> )	.92	NA
RD ( <i>M, SD</i> )	1.49x10 <sup>-3</sup> (.12x10 <sup>-3</sup> )	1.39x10 <sup>-3</sup> (.14x10 <sup>-3</sup> )	1.52x10 <sup>-3</sup> (.14x10 <sup>-3</sup> )	1.46x10 <sup>-3</sup> (.16x10 <sup>-3</sup> )	5.16**	2<1,3
CT ( <i>M, SD</i> )	2.49 (.09)	2.55 (.11)	2.44 (.11)	2.50 (.13)	4.53**	2>3

\*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\* $p < .001$ . The means and standard deviations are displayed for diffusion tensor imaging measures (including fractional anisotropy (FA), mean diffusivity (MD), and radial diffusivity (RD)), and cortical thickness (CT).

Examining individual tracts, there was a main effect of psychiatric status ( $F(15, 101) = 1.97, p = .025$ ). Further analyses revealed significant group differences for the FA of the genu of the corpus callosum (GCC;  $F(1, 115) = 4.12, p = .045$  and uncinate (UNC;  $F(1, 115) = 5.40, p = .022$ ); UNC medial diffusivity ( $F(1, 115) = 4.63, p = .034$ ), and for RD of the GCC and sagittal stratum (SS;  $F(1, 115) = 5.02, p = .027$  and  $F(1, 115) = 10.50, p = .002$ , respectively). Of note, the  $p$  value for the superior longitudinal fasciculus (SLF) was marginally significant ( $F(1, 115) = 3.77, p = .055$ ). The results suggest that controls have greater white matter integrity than patients.

The main effect of cognitive status was non-significant. Additionally, the interaction between the two factors approached significance ( $F_{15, 101} = 1.64, p = .075$ ), although further examination revealed significance for the GCC radial diffusivity alone ( $F(1, 115) = 4.95, p = .028$ ). The covariate age was significant ( $F(15, 101) = 3.81, p < .001$ ), while education was not.

A one-way MANCOVA was again conducted to examine specific group differences. The analyses revealed significant group differences for RD, while FA and MD were non-significant (see Table 5). The genu of the corpus callosum (GCC), superior longitudinal fasciculus (SLF), and the sagittal stratum (SS; which includes the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus) were the only tracts with significant  $F$  ratios. For the GCC, CNR controls had lower values than both patient groups. With respect to the SLF, CNR controls had lower RD values than below-normal range (BNR) patients only, while for the SS CNR controls had lower RD values than CNR patients. The covariate age was significant ( $F(5, 111) = 5.07, p < .001$ , partial  $\eta^2 = .19$ ), and education was non-significant ( $F(5, 111) = 1.84, p = .111$ , partial  $\eta^2 = .08$ ).



**Table 5**

*Fractional Anisotropy (mm), Mean Diffusivity, and Radial Diffusivity of Key Tracts in Cognitively Normal Range (CNR) and Below-Normal Range (BNR) Patients and Controls*

Variable	1.CNR Patients (n=16)	2.CNR Controls (n=36)	3.BNR Patients (n=48)	4.BNR Controls (n=21)	<i>F</i> (3, 115)	Bonferroni Adjusted Comparisons
Fractional anisotropy					1.42	
CGC ( <i>M</i> , <i>SD</i> )	.62 (.04)	.64 (.05)	.62 (.04)	.63 (.05)		
GCC ( <i>M</i> , <i>SD</i> )	.69 (.03)	.70 (.03)	.69 (.03)	.70 (.04)		
SLF ( <i>M</i> , <i>SD</i> )	.53 (.03)	.53 (.03)	.52 (.02)	.53 (.03)		
SS ( <i>M</i> , <i>SD</i> )	.58 (.04)	.58 (.03)	.57 (.03)	.58 (.04)		
UNC ( <i>M</i> , <i>SD</i> )	.60 (.04)	.62 (.04)	.62 (.05)	.63 (.06)		
Mean diffusivity					1.33	
CGC ( <i>M</i> , <i>SD</i> )	.77x10 <sup>-3</sup> (.03x10 <sup>-3</sup> )	.79x10 <sup>-3</sup> (.03x10 <sup>-3</sup> )	.78x10 <sup>-3</sup> (.03x10 <sup>-3</sup> )	.77x10 <sup>-3</sup> (.05x10 <sup>-3</sup> )		

GCC ( <i>M</i> , SD)	.84x10 <sup>-3</sup> (.06x10 <sup>-3</sup> )	.84x10 <sup>-3</sup> (.04x10 <sup>-3</sup> )	.84x10 <sup>-3</sup> (.05x10 <sup>-3</sup> )	.80x10 <sup>-3</sup> (.07x10 <sup>-3</sup> )		
SLF ( <i>M</i> , SD)	.75x10 <sup>-3</sup> (.04x10 <sup>-3</sup> )	.76x10 <sup>-3</sup> (.03x10 <sup>-3</sup> )	.76x10 <sup>-3</sup> (.03x10 <sup>-3</sup> )	.74x10 <sup>-3</sup> (.04x10 <sup>-3</sup> )		
SS ( <i>M</i> , SD)	.83x10 <sup>-3</sup> (.05x10 <sup>-3</sup> )	.83x10 <sup>-3</sup> (.03x10 <sup>-3</sup> )	.83x10 <sup>-3</sup> (.03x10 <sup>-3</sup> )	.81x10 <sup>-3</sup> (.05x10 <sup>-3</sup> )		
UNC ( <i>M</i> , SD)	.87x10 <sup>-3</sup> (.05x10 <sup>-3</sup> )	.85x10 <sup>-3</sup> (.06x10 <sup>-3</sup> )	.87x10 <sup>-3</sup> (.06x10 <sup>-3</sup> )	.84x10 <sup>-3</sup> (.07x10 <sup>-3</sup> )		
Radial diffusivity					2.00*	
CGC ( <i>M</i> , SD)	.96x10 <sup>-3</sup> (.09x10 <sup>-3</sup> )	.90x10 <sup>-3</sup> (.08x10 <sup>-3</sup> )	.96x10 <sup>-3</sup> (.10x10 <sup>-3</sup> )	.95x10 <sup>-3</sup> (.11x10 <sup>-3</sup> )	2.27	
GCC ( <i>M</i> , SD)	2.15x10 <sup>-3</sup> (.31x10 <sup>-3</sup> )	1.85x10 <sup>-3</sup> (.40x10 <sup>-3</sup> )	2.12x10 <sup>-3</sup> (.32x10 <sup>-3</sup> )	2.02x10 <sup>-3</sup> (.25x10 <sup>-3</sup> )	5.61**	2<1,3
SLF ( <i>M</i> , SD)	1.03x10 <sup>-3</sup>	.95x10 <sup>-3</sup>	1.05x10 <sup>-3</sup>	1.03x10 <sup>-3</sup>	3.48*	2<3

	(.13x10 <sup>-3</sup> )	(.12x10 <sup>-3</sup> )	(.13x10 <sup>-3</sup> )	(.14x10 <sup>-3</sup> )		
SS ( <i>M</i> , <i>SD</i> )	1.47x10 <sup>-3</sup> (.30x10 <sup>-3</sup> )	1.29x10 <sup>-3</sup> (.26x10 <sup>-3</sup> )	1.49x10 <sup>-3</sup> (.29x10 <sup>-3</sup> )	1.36x10 <sup>-3</sup> (.18x10 <sup>-3</sup> )	4.09**	2<1
UNC ( <i>M</i> , <i>SD</i> )	2.87x10 <sup>-3</sup> (.13x10 <sup>-3</sup> )	2.85x10 <sup>-3</sup> (.24x10 <sup>-3</sup> )	2.90x10 <sup>-3</sup> (.17x10 <sup>-3</sup> )	2.84x10 <sup>-3</sup> (.27x10 <sup>-3</sup> )	.73	
Cortical Thickness Networks					3.00**	
Central Executive ( <i>M</i> , <i>SD</i> )	2.56 (.10)	2.58 (.15)	2.51 (.13)	2.56 (.16)	.99	
Default Mode ( <i>M</i> , <i>SD</i> )	2.75 (.13)	2.85 (.13)	2.70 (.14)	2.79 (.15)	7.80***	2>1,3
Saliency ( <i>M</i> , <i>SD</i> )	2.74 (.12)	2.82 (.14)	2.69 (.14)	2.76 (.15)	4.84**	2>1,3
Social Brain ( <i>M</i> , <i>SD</i> )	2.67 (.12)	2.74 (.12)	2.65 (.12)	2.70 (.15)	3.09*	non-sig.

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\*  $p < .05$ ; \*\*  $p < .01$ ; \*\*\*  $p < .001$ ; CGC: cingulum (cingulate gyrus); GCC: genu of the corpus callosum; SLF: superior longitudinal fasciculus; SS: sagittal stratum (includes the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus); UF: uncinate fasciculus; Mean and radial diffusivity relatively small values and rounded to three decimal places.

## Summary of Findings

**Table 6**

*A Summary of the Study's Predictions, Neuroimaging Results and whether the Hypotheses were Supported, as well as Supportive Evidence from the Cognitive Data*

<b>Variables</b>	<b>Hypothesis</b>	<b>Neuroimaging Results</b>	<b>Hypothesis supported</b>	<b>Support from the Cognitive Data</b>
<b>Cortical Thickness</b>	Both patient groups will have comparable cortical thinning patterns in the <i>salience network</i> relative to cognitively normal controls	Cognitively normal range (CNR) controls had greater thickness than both patient groups; no difference between control groups	✓	
	Both patient groups will have comparable cortical thinning patterns in the <i>default mode network</i> relative to cognitively normal controls	CNR controls had greater thickness than both patient groups; no difference between control groups.	✓	
	Both patient groups will have comparable cortical thinning patterns in the <i>social brain network</i> relative to cognitively normal controls	CNR controls had greater cortical thickness than below-normal range (BNR) patients: trend towards significance	✗	On social cognitive measures, CNR controls outperformed BNR patients on 3 of 4 tasks; CNR patients and controls did not differ
<b>White Matter Integrity</b>	Both patient groups will show dysconnectivity in the <i>genu of the corpus callosum</i>	Both patient groups had reduced white matter integrity than cognitively normal range controls	✓	
	Both patient groups will show dysconnectivity in the <i>uncinate fasciculus</i>	Not significant	✗	

	Both patient groups will show dysconnectivity in the <i>cingulum</i>	Not significant	✗	
	Both patient groups will show dysconnectivity in the <i>sagittal stratum</i>	Cognitively normal range controls had greater white matter integrity than cognitively normal range patients	✗	On most social cognitive measures, CNR controls outperformed BNR groups; CNR patients outperformed BNR patients
	Cognitively normal range patients and controls will have comparable white matter integrity in the <i>superior longitudinal fasciculus (SLF)</i> ; group differences were expected between cognitively normal and below-normal range participants	Cognitively normal range patients and controls did not differ; Cognitively normal range controls and below-normal range patients differed; No other group differences were observed	✓ ✓ ✗	CNR groups outscored BNR groups on processing speed, attention, and working memory
	Cognitively normal range controls will have greater <i>whole-brain connectivity</i> than both patient groups	Cognitively normal range controls had greater whole-brain connectivity (increased fractional anisotropy and decreased radial diffusivity) than both patient groups	✓	

## Discussion

The goal of the current study was to investigate whether psychotic illness and cognitive impairment represent independent disease processes by comparing cortical structure and network connectivity across cognitively normal and impaired patients and controls. Specifically, we investigated whether aberrations in brain networks' cortical thickness and/or structural connectivity are associated with cognitive impairment and/or the severity of psychotic psychopathology. Overall, we found neuroimaging evidence that cognitive impairment and psychotic illness are separable disease processes. The findings suggest that the inclusion of both cognitively normal range patients and below-normal range controls in schizophrenia research is beneficial to help identify the separable effects of cognition and psychosis on behavioural and neuroimaging data.

### *Hypothesis 1*

*Cognitively normal and below-normal range patients will have comparable severity of psychopathological symptoms.*

The data revealed that cognitively normal and below-normal range patients were indistinguishable in the severity of psychiatric symptoms and illness impact (i.e., positive, negative, and general symptoms; diagnosis of schizoaffective vs. schizophrenia, antipsychotic and mood stabilizer medications, number of hospitalizations, as well as employment and community living status). However, on average, below-normal range (BNR) patients had a longer duration of illness than cognitively normal range patients. This finding is perhaps consistent with the BNR patients' older age. The comparable symptom severity levels and illness impact across patient groups suggest that differences found on neurocognitive measures or neurobiological findings are largely influenced by underlying processes contributing to their different cognitive profiles or at least that the differences found are not driven by the severity of psychotic symptoms.

*Hypothesis 2*

*On intellectual functioning, standard consensus (except for processing speed), and adjunct specialized cognitive measures, cognitively normal range groups will have inappreciable differences in performance (and likewise the below average range groups) and outperform their below-average range counterparts.*

As noted earlier, BNR patients were less educated and older than the cognitively normal range patients, and BNR controls were less educated than all other comparison groups. Thus, age and education were used as covariates. In general, the cognitive data suggest that cognitive impairment and psychosis are largely independent, consistent with the extant literature (de Gracia Dominguez et al., 2009; Heinrichs et al., 2015). Specifically, performance profiles on standard consensus cognitive measures were such that the cognitively normal range participant groups achieved higher neurocognitive performance than individuals belonging to the below-average range cognitive groups. Additionally, these findings on standard cognitive measures were complemented by the lack of within group differences. This performance pattern was also observed on 4 of 7 domains of the MATRICS Consensus Cognitive Battery (MCCB), including the Attention/Vigilance, Working Memory, Verbal Learning, and Visual Learning indices. The three exceptions include the domains of Processing Speed, Reasoning and Problem Solving, and Social Cognition. On the Processing Speed domain, cognitively normal range controls outperformed all other groups, including cognitively normal range patients. Additionally, among the two patient groups, those within the cognitively normal range obtained higher performance than the below-normal range group. There were no differences found between the below-normal range groups. For Reasoning and Problem Solving, cognitively normal range controls again achieved higher scores than all other participant groups. Lastly, performance within ability level was indistinguishable on the Social Cognition index; however, there was a significant difference between ability level such that cognitively normal range patients and controls obtained higher scores than below-normal range patients.

Importantly, given that MCCB domain scores are highly correlated with the MCCB composite that was used to create the groups, these findings are not surprising. Thus, the inclusion of independent cognitive measures was warranted to corroborate findings and/or provide additional information. First, performance patterns on other measures of intellectual functioning (i.e., estimate of premorbid intelligence and IQ estimate) revealed no significant difference between patients and controls within the same cognitive ability level, though there was a significant difference between ability levels. Thus, that cognitively normal patients and controls had higher estimates of premorbid intelligence and IQ than below-normal range patients and controls provide support for the use of the MCCB composite normality criterion. Thus, within a given ability level, these groups were indistinguishable on premorbid ability and IQ estimate, consistent with our typology.

Taken together, the data consistently revealed that processing speed and reasoning/problem-solving are sensitive to both psychosis and cognitive impairment. That is, even when the effects of age and education were controlled, both patient groups and below-normal range controls significantly underperformed cognitive normal range comparison controls. Processing speed is considered to be sensitive to schizophrenia illness with the relatively largest effect size of all cognitive domains found impaired (Schaefer, Giangrande, Weinberger, & Dickinson, 2013). Reduced speed of processing has previously been found among cognitively normal range individuals with schizophrenia (Heinrichs et al., 2015; Holthausen et al., 2002; Vaskinn, Ueland, Melle, Agartz, Andreassen, & Sundet, 2014). Processing speed is also highly correlated with overall cognitive functioning, particularly higher-order functioning, and it is a good indicator of cognitive decline (Kail & Salthouse, 1994; Chopra, Shaw, Shaw, Sachdev, Anstey, & Cherbuin, 2018). Our study's findings of diminished processing speed and reasoning



skills among below average range controls are consistent with the evidence that these abilities are linked to overall cognition.

Meta-analytic studies and systematic reviews suggest that both processing speed and reasoning abilities, which are also linked to general cognition, are among the cognitive domains that correlate with functional outcome (Fett et al., 2011; Green, 1996; Green et al., 2004). Patients within this study had high rates of unemployment, at approximately 40%. Although employment rates were not assessed for the below-normal range control group, many were recruited from employment services and individuals with low education within the community typically have higher rates of unemployment than community dwellers with higher levels of education (Statistics Canada). Indeed, in 2011 (around the time of this research), employment rates ranged from 4.4% among individuals with “above Bachelor’s degree” to 13.4% in those with up to 8 years of education. The unemployment rate among community dwellers with some high school education, like our below-normal range control group, was 10.5%. According to the Ontario Labour Force Survey (December 2012), the unemployment rate within the general population was approximately 7.9% in 2011, with the overall Canadian rates at around 7% annually (with the exception of more recent rates at a low of 5.5% (Statistics Canada, 2012, 2019). Comparatively, both cognitive ability and schizophrenia illness impact overall functioning within the community, but schizophrenia illness understandably has a more profound impact on functioning.

It is known that social cognition, which is typically impaired in schizophrenia, is an additional strong predictor of functional outcome (as measured by occupational achievement, interpersonal relationships, and ability to manage instrumental activities of daily living) as well as illness recovery (Dodell-Feder, Tully, & Hooker, 2015; Green, Lee, & Ochsner, 2013).

Individuals with good social cognitive skills, as measured on the Social Cognition index of the MCCB, readily identify, differentiate, understand, and manage emotions or emotional reactions (Savla, Vella, Armstrong, Penn, & Twamley, 2012). From the current findings, it appears that social cognitive deficit is present only in cognitively compromised individuals with schizophrenia (and not in either cognitively normal range patients or below-normal range controls). This finding would suggest a comorbid effect of both cognitive and psychotic illness influencing social cognitive processing. However, adjunct measures of social cognition were also included to corroborate findings from the MCCB.

The chosen adjunct measures of social cognition and probabilistic reasoning were included in light of evidence supporting their sensitivity to psychotic thinking (e.g., delusions). Overall, the outcome of these measures was congruent with findings that reduced overall cognitive abilities underly poor social cognitive and reasoning skills and not psychosis alone. On these specialized psychopathology-sensitive cognitive measures, patients and controls within the cognitively normal range group were again indistinguishable, and they typically outperformed the below-normal range patients and/or controls. Specifically, on tests of Theory-of-Mind or social reasoning about the mental states of a person, the below-normal range patients and controls had more significant difficulty than control participants in the normal range group when trying to make inferences about others' mental states from facial expressions or identifying whether a faux pas committed in a social interaction was intentional. Below-normal range participant groups were indistinguishable on these measures. Thus, these findings suggest that low general cognitive ability is sufficient for impairment in social cognition, particularly theory of mind.

Additionally, it was the below-normal range controls, but not patients, that were more

likely to “jump to conclusions” on a probabilistic reasoning task. This finding was surprising as it invalidates the Jumping to Conclusions (JTC) test as being sensitive to psychotic (particularly, delusional) thinking (So et al., 2016; Ross et al., 2015). Some research evidence suggests, however, that the link between delusional thinking and “jumping to conclusions” disappears once general cognitive functioning is controlled (Bentall et al., 2009; Ross et al., 2015). Another study found a small effect of a reduction in hasty decision-making once cognitive remediation training was provided (which includes training on attention, working memory, and executive functions; Andreou, Schneider, Balzan, Luedecke, Roesch-Ely, Mortiz, 2015). This finding provides support for a link between hasty decision-making with minimal information and reduced working memory and executive functions (Andreou et al., 2015; Garety et al., 2013, 2014).

Alternatively, it may be that the beads task fails to measure true faulty decision-making due to methodological limitations, reduced motivation/effort, or possible poor comprehension of instructions (Ross et al., 2015). It may also be that the task is only effective in detecting the jumping to conclusions bias when delusional thinking is extreme in clinical samples versus nonclinical comparison samples or on account of a possible nonlinear relationship between the JTC bias and severity of delusional thinking (So & Kwok, 2015). Nonetheless, our findings fit within the context of this literature linking the JTC bias to cognitive impairment rather than delusions. The data also underscore the utility in investigating both cognitive normality and impairment among patients and comparison controls in schizophrenia research. Taken together, the data revealed that cognition and psychosis are independent disease processes as well as comorbidities.

### *Hypothesis 3*

*Cortical thinning patterns will be largely comparable between patient groups reflecting a*

*common underlying psychopathology, with notable thinning in SN, DMN, and SBN when compared to cognitively normal controls.*

Consistent with our predictions, cortical thickness network analyses revealed significant group differences in the salience, default mode, and social brain networks but not the central executive network. However, only the salience and default mode networks remained significant following Bonferroni post hoc corrections. Consistent with findings from Heinrichs' and colleagues (2017) using some of the same overlapping participants, cognitively normal controls had greater cortical thickness in the SN and DMN networks than both patient groups with no differences between the patient groups. These findings suggest that cortical thickness is indicative of shared underlying psychotic psychopathology unrelated to cognitive status. Of note, cortical thickness among the control groups were also indistinguishable, which provides further support that cognitive performance and cortical thickness are independent.

With respect to the SBN, the comparison between cognitively normal range controls and below-normal range patients approached significance, with the patient group exhibiting significant cortical thinning in these brain regions. If this finding can be replicated with a larger sample size, it would underscore a point of divergence between the patient groups. That is, it may be that at least in these brain regions patients with comorbid cognitive impairment and psychosis fair worse than the typical comparison controls, while patients with normal thinning in this area have preserved cognitive functioning. Thus, this finding would suggest that cortical thinning in the SBN may contribute to comorbid psychotic psychopathology and cognitive impairment.

Of note, this finding is consistent with the results from performance on the social cognitive measures. As a reminder, cognitively normal range controls outperformed below-normal range patients; however, there were no significant differences between cognitively

normal patients and controls. Additionally, the behavioural data was more sensitive in picking up significant group differences between cognitively normal and below-normal range controls as well as between the two patient groups. The sensitivity of neurocognitive data to group differences has been previously illustrated (Heinrichs 2005). Here, the data suggest that perhaps group differences on social cognitive measures index cognitive ability and not psychopathology. Taken together, the data point to psychotic psychopathology and cognitive impairment as dissociable disease processes; the results are further suggestive of an influence of cortical thinning in the SBN on social cognitive impairment in below-normal range patients. Nonetheless, cortical thickness in the SN and DMN, in particular, indexes a shared disease process.

#### *Hypothesis 4*

*We hypothesized that both patient groups will have compromised white matter integrity across all four tracts given their associations to cognitive functioning and psychotic symptoms (i.e., genu of the corpus callosum, uncinate fasciculus, cingulum, and sagittal stratum), when compared with cognitively normal range controls. We predicted that below-normal range patients will have greater reductions than cognitively normal range patients (relative to cognitively normal range controls) given the presence of both disease processes among this group (i.e., cognitive impairment and psychotic symptoms). We hypothesized that the integrity of the superior longitudinal fasciculus may differentiate the patient groups given this areas role in cognition. It was anticipated that there will be no difference between the cognitively normal range patients and controls. However, significant group differences were expected between the cognitively normal range groups and their below-normal range counterparts. Whole-brain white matter integrity will be lower among patients than cognitively normal range controls, which has been consistently shown (Kelly et al., 2018).*

First, cognitively normal range controls had greater average whole-brain fractional anisotropy (FA) and lower radial diffusivity (RD) than both patient groups following corrections for age and years of education. These results are consistent with the extant literature, with a recent meta-analysis study by Kelly and colleagues (2018) showing the largest effect size mean difference between schizophrenia participants and controls in average FA. Of note, decreased FA usually results from either increased RD (indicative of myelin damage) or reduced axial

diffusivity (suggestive of axonal injury, but not measured in the current study) (Alexander et al., 2007). Our findings of the microstructural white matter abnormalities observed were reflective of myelin disintegration in light of the difference in radial diffusivity, which fit well with previous findings (Kelly et al., 2018).

With respect to specific tracts, only average RD (and not FA or mean diffusivity) was significant for 3 of the five tracts (i.e., the genu of the corpus callosum, superior longitudinal fasciculus, and sagittal stratum), after controlling for age and years of education. Of course, a failure to detect group differences in average FA may be due to low sample size combined with a possible increased sensitivity of RD in detecting group differences in myelination of these particular tracts. It is possible to detect modest changes in myelination as measured by RD with intact anisotropy (Alba-Ferrara & de Erausquin, 2013). Cognitively normal range controls were observed to have reduced RD suggestive of greater myelin integrity in the genu of the corpus callosum when compared to both patient groups. Cognitively normal range controls also had reduced RD in the superior longitudinal fasciculus compared to the below-normal range patients only as well as reduced average RD in the sagittal stratum in comparison to cognitively normal range patients.

As predicted, both cognitively normal and below-normal range patients had reduced white matter integrity of the genu of the corpus callosum (GCC) when compared to cognitively normal range controls. These results are in keeping with previous findings that suggest that the GCC is involved in psychotic symptomatology as well as prefrontal cortex interhemispheric communication important for cognition (Di Biase et al., 2017; Kelly et al., 2018). Thus, the GCC indexes both cognitive status and the psychotic disease process, and evidence of its possible demyelination in patients supports the dysconnectivity hypothesis (Brandl et al., 2019;

Pettersson-Yeo et al., 2011). The indistinguishable GCC structural pattern between the patient groups highlight shared underlying neural mechanisms of the disease that give rise to psychosis and/or cognitive impairment. Of course, we cannot rule out the possibility that differences between patient groups were undetected because of the small sample size and/or controlling the effect of education.

Despite the sagittal stratum's role in both social cognitive processes (e.g., facial recognition and emotional perception) and positive symptoms (Jou et al., 2011; Oestreich, McCarthy-Jones, & Whitford, 2016; Seitz et al., 2016), only comparisons between the cognitively normal range groups differed. The behavioural data from this study do not corroborate these findings. Indeed, both cognitively normal range patients and controls were indistinguishable on social cognitive measures. The present data suggest that perhaps increased RD in cognitively normal range patients may index more efficient connectivity. Previous research evidence has shown that greater cortical thickness does not always mean better functioning, while cortical thinning can index cortical efficiency (Meyer, Liem, Hirsiger, Jäncke, & Hänggi, 2014). Similarly, higher FA has been linked to cognitive deficits in some populations (Alba-Ferrara & de Erausquin, 2013; Hoefl et al., 2007). Perhaps the opposite is also true in that reduced FA (due to increased RD) may indicate greater efficiency in thinking among cognitively normal range patients.

Lastly, it was hypothesized that the superior longitudinal fasciculus (SLF) would differentiate the patient groups in light of its association with cognitive control (e.g., working memory) and processing speed (Schaeffer et al., 2015; Turken et al., 2008). The cognitively normal range control group differed from the below-normal range patient group only, while no significant differences were found between the cognitively normal range groups, below-normal

range groups, or the two patient groups. Nonetheless, the significant group difference here is an important finding as it replicates well-established evidence between the usual comparison groups in schizophrenia research for this tract (Kelly et al., 2018; Schaeffer et al., 2015). The data suggest that the more typical cognitively compromised patients have greater myelin damage in this tract relative to cognitively normal controls. Indeed, cognitive control deficits have been linked to dorsolateral prefrontal cortex aberrations given its connections (e.g., via the SLF) to a wide range of brain areas, which include the parietal cortex, thalamus and striatum (Barch & Ceaser, 2012).

Of note, our neurocognitive data similarly showed cognitively normal range controls outperformed below average patients on measures of processing speed and executive functions (i.e., reasoning and problem-solving). However, the behavioural data were more sensitive in picking up differences between cognitively normal patients and the cognitively below-normal range patients and/or controls on measures. It has been previously argued that structural imaging studies tend to be less sensitive in detecting disease effects relative to neurocognitive performance data in schizophrenia research (Heinrichs, 2005). Additionally, structural imaging data can be variable from study to study with relatively modest effect sizes even with large sample sizes (Kelly et al., 2018). Our results support the findings that neurocognitive performance is sensitive in distinguishing the impact of psychotic illness from cognitive impairment.

In sum, the current findings suggest that cortical dysconnectivity in schizophrenia spans across networks and accounts for the neurocognitive dysfunction, psychotic features, or presence of both in keeping with the extant literature (Pettersson-Yeo et al., 2011). In the current study, the results suggest that aberrant GCC white matter integrity may underlie the psychopathology of



schizophrenia illness given the shared disruptions in both cognitively normal and below-normal range patient groups. On the other hand, demyelination of the SLF appears to be associated with comorbid psychosis and cognitive impairment, while increased RD of the SS may index more efficient connectivity in cognitively normal range patients. Similarities found between cognitively normal range and below-normal range patients highlight shared underlying neural mechanisms of the disease, while dissimilarities pinpoint processes possibly linked specifically to cognitive status and/or comorbidity of psychosis and cognitive impairment. Thus, our findings show that white matter disintegration partially dissociates cognitive impairment and psychosis in schizophrenia illness.

### **Limitations**

A major limitation of the present study was the relatively small sample size, particularly in the cognitively normal range group. Indeed, we may have been underpowered to detect significant group differences between the patients on both cognitive performance (e.g., MCCB composite score) and imaging measures (i.e., cortical thickness, fractional anisotropy, medial diffusivity, and radial diffusivity) because of sample size, particularly after employing multiple comparison procedures. Studies have failed to find significant differences in fractional anisotropy when sample sizes are small (Wheeler & Voineskos, 2014). Nonetheless, cognitively normal range individuals with schizophrenia represent 15-25% of the patient population (Ammari, Heinrichs, & Miles, 2010; Heinrichs et al. 2008; Muharib, Heinrichs, Miles, Pinnock, McDermid Vaz, & Ammari, 2014; Palmer et al., 1997), and our study's sample had a rate of 25%, which is at the upper end. Nevertheless, the promising current findings combined with the potential scientific value inherent in cognitively normal schizophrenia samples support the

importance for continued attempts to recruit this minority clinical population despite its challenges.

Although this study uses a convenience sample where only structural (and not functional) data were collected, structural integrity is closely related to functional connectivity (Hermundstad et al., 2013). Recent imaging data suggests that at least in some brain regions, functional dysconnectivity and diminished gray matter volume overlap and have a bi-directional relationship (Brandl et al., 2019). Of course, possible inconsistencies in our findings relative to the literature could be due to poor manual tracing for regions of interest or poor fractional anisotropy registration (Palaniyappan & Liddle, 2012). However, the imaging data preprocessing was carried out by imaging experts who underwent several inspections of the scans for quality control. The white matter results replicated previous data. Previous investigations have questioned the value in examining tract-based differences given the variability between studies as well as the fact that stable group differences are likely based in network approaches across the brain (Wheeler & Voineskos, 2014).

For the cortical thickness data, there were no group differences found for either the central executive or the social brain network, though there was a trend for the latter between the cognitively normal range controls relative to typically cognitively compromised patients. Despite both networks importance in at least distinguishing more broadly between schizophrenia patients and controls (Anticevic et al., 2012; Hu et al., 2017; Menon, 2011; Nekovarova, Fajnerova, Horacek, & Spaniel, 2014), the failure to detect differences in this study may be due to the inclusion of the same regions of interest in two or more network thickness values. Thus, these values were neither independent, nor differentially weighted and thus their true contributions within a network was not accounted for. The anterior insular cortex, for example, is known for

its role in cognitive control and emotional awareness (Uddin, Nomi, Hebert-Seropian, Ghaziri, & Boucher, 2017); it is included in the salience, central executive, and social brain networks. Taken together, the present study provides some support for the importance of different network cortical thinning patterns, but these findings need to be corroborated.

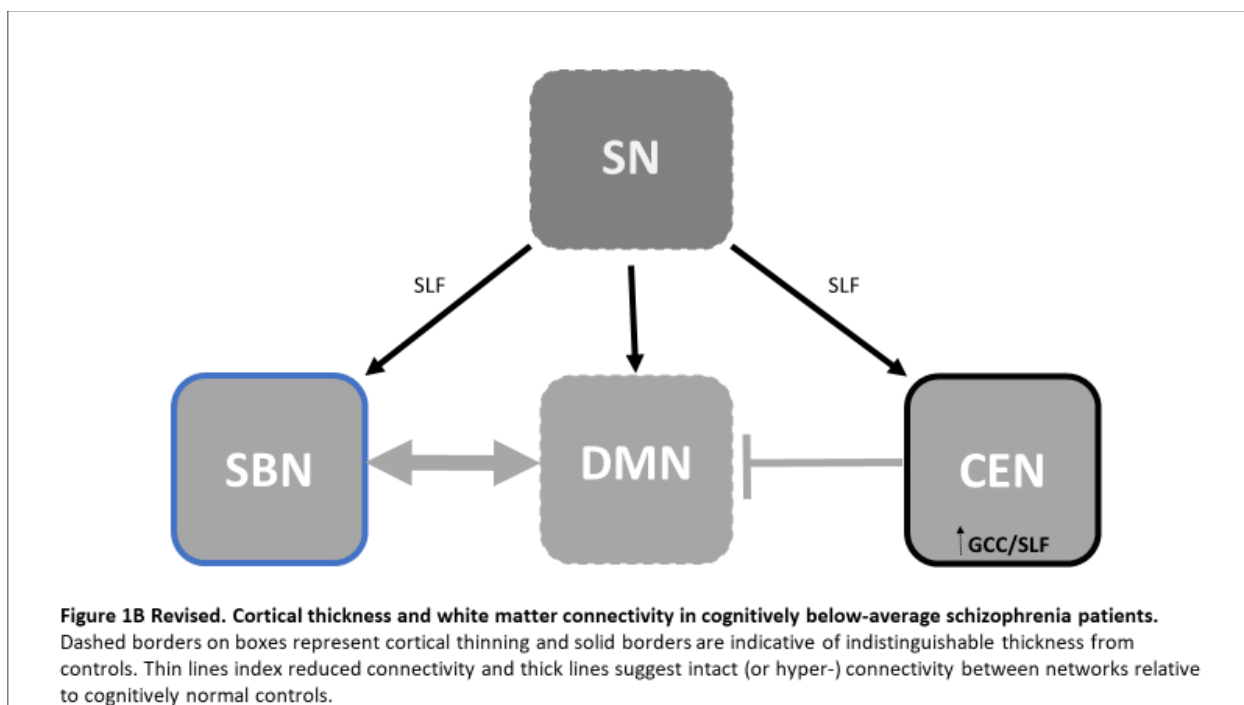
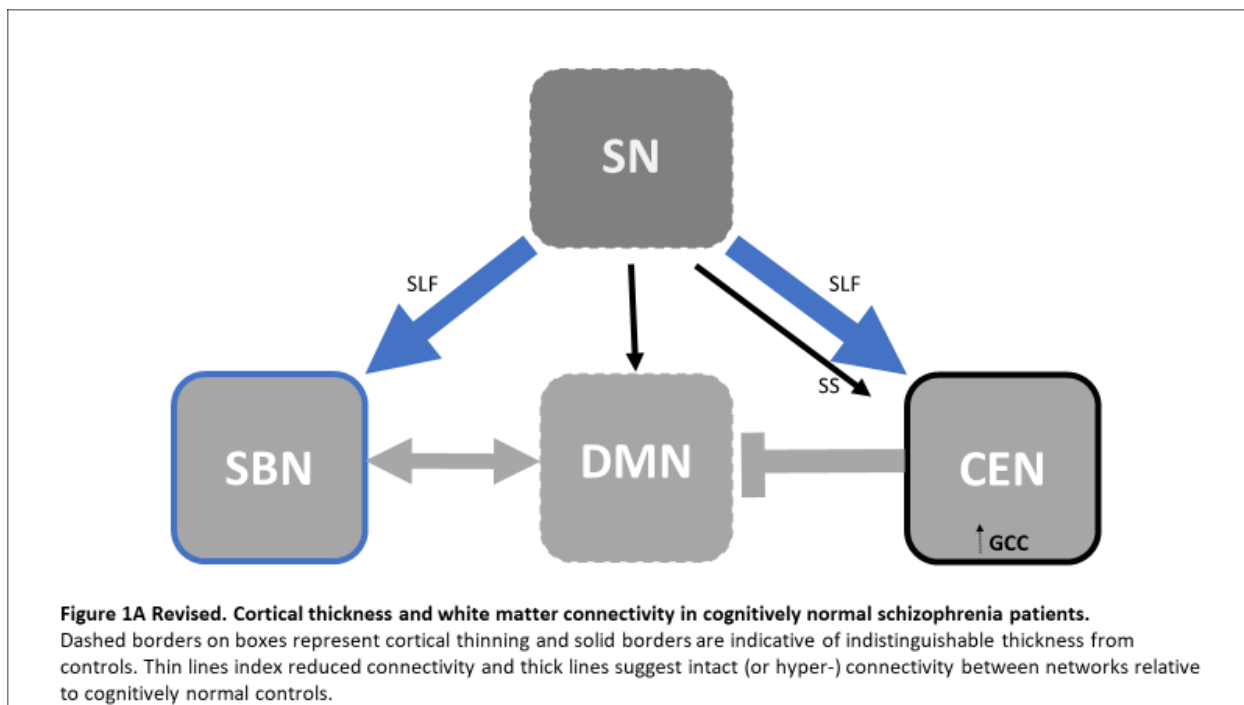
Another possibility is that if schizophrenia illness is indeed a syndrome, it is possible that the way patients were grouped in our study precluded finding significant structural differences as within group heterogeneity dilutes effects and reduces statistical power (Brandl et al., 2019). There were also some group differences on demographic and clinical characteristics; for example, below-normal range patients were older and less educated than cognitive normal range patients with longer duration of illness. However, given that schizophrenia is characterized by cognitive impairment and a possible neurodegenerative process (such that the disease may cause accelerated aging in some patients) controlling for education and age can be inappropriate and possibly dampen effects (Czepielewski et al., 2017; di Biase et al., 2017; Nguyen, Eyler, & Jeste, 2017). Thus, that significant findings remained after using age and education as covariates suggest relatively robust differences. Additionally, in light of findings of social cognitive deficits among comparison controls that fall in the below average range, there may have been undiagnosed psychiatric problems. However, controls were screened to rule out any neurological, endocrine, psychiatric, or substance use disorders, though a non-patient edition of the structured clinical interview for DSM-IV (First et al., 1996) was not used.

### **Conclusions**

This study aimed to examine whether psychotic illness and cognitive impairment were dissociable illness processes as indexed by cortical network abnormalities and/or structural dysconnectivity. The presence of a minority of patients with intact cognition with largely

comparable symptom severity to more cognitively impaired individuals with schizophrenia suggests that these illness processes are indeed independent. According to predictions, cognitively normal range and below-normal range individuals with schizophrenia had discrepant cognitive profiles. Similarities found between the two patient groups may index sensitivity to brain aberrations due to psychotic illness. Discrepancies between cognitively normal and below-normal range patients suggest a possible influence of cognitive impairment. In particular, among controls with below-normal range cognitive abilities, there was evidence of poor performance on supposed specialized psychopathology-sensitive cognitive measures. In general, the behavioural data supported the separable and comorbid contribution of cognition and psychosis to the neurocognitive profile.

With respect to the neurobiological findings, cognitively normal range controls had greater cortical thickness than cognitively normal and below-normal range patients; while the patient groups were indistinguishable. Thus, cortical thickness seems to reflect schizophrenia illness irrespective of cognitive status, particularly in the salience and default mode networks consistent with findings from Heinrichs and colleagues (2017). This finding is also in keeping with the neurodevelopmental hypothesis of schizophrenia and evidence of both genetic abnormalities and early disruptions in brain development (e.g., arrested cell distribution, excessive pruning, diminished myelination) up until early adulthood that predispose individuals to the illness (Birmbaum & Weinberger, 2017). However, we did not find evidence to support that the social brain network is similarly disrupted across both patient groups. In fact, this brain network may underlie comorbid psychopathology and cognitive impairment and thus represent dissimilarities between the two patient populations (see below for updated versions of the diagrams presented earlier – changes highlighted in blue).



Furthermore, the data revealed that the integrity of particular tracts can independently reflect psychotic psychopathology or cognitive status; tract integrity may also be affected by comorbid cognitive impairment and psychosis. The genu of the corpus callosum was

demyelinated (as indexed by increased radial diffusivity) across patient populations, indicative of a common illness effect which further supports the dysconnectivity hypothesis of schizophrenia. Of course, similar patterns of white matter integrity may also index similarities in cognitive performance as a result of the illness (e.g., reasoning and problem solving), while dissimilarities in tract integrity may suggest distinct pathways that give rise to cognitive abnormalities.

The more typical patients with cognitive compromise had greater myelin degeneration in the superior longitudinal fasciculus when compared to cognitively normal range controls (see Figure 1B Revised). The cognitively normal range patients and controls, however, were indistinguishable. Here, the imaging results support cognitive impairment and psychosis as distinct illness processes. These findings were also consistent with the neurocognitive data in that this control group outperformed below-normal range participants on measures of executive functions and processing speed, abilities supported by the superior longitudinal fasciculus. Nonetheless, while cognitively normal range patients outperformed their cognitively below-normal range patient counterparts on information processing speed, they were outperformed by cognitively normal range controls on both cognitive domains. Our results provide support for the increased sensitivity of cognitive performance (relative to neuroimaging) in helping to dissociate schizophrenia illness from cognitive impairment. Additional support for the sensitivity of cognitive assessment comes from our findings that the cognitively normal range groups had different connectivity patterns in the sagittal stratum. This pattern, however, may be indicative of cortical efficiency that gives rise to intact cognition in cognitively normal range patients.

Taken together, the data add further support that cognitive impairment and psychotic illness represent dissociable, yet highly comorbid disease processes as indexed by cortical thinning and dysconnectivity within and between key networks. Additionally, our results

highlight the importance of including both cognitively normal range patients and cognitively compromised comparison controls in schizophrenia research. The inclusion of these minority participant populations aid in teasing apart the specific contributions of cognitive status and psychotic illness. Evidently, studies that utilize longitudinal data, larger sample size, and multimodal neuroimaging approaches are needed to corroborate the current findings. These studies may further our understanding of schizophrenia as an illness or syndrome to aid in its classification and treatment.

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