PRESERVED, DETERIORATED, AND PREMORBIDLY IMPAIRED PATTERNS OF INTELLECTUAL ABILITY 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 OF PHILOSOPHY

GRADUATE PROGRAM IN PSYCHOLOGY
YORK UNIVERSITY
TORONTO, ONTARIO

SEPTEMBER 2016

ABSTRACT

Objective: Although impaired general intellectual ability is a prevalent feature in schizophrenia, patterns suggesting preserved, deteriorated, and premorbidly impaired intellect have also been identified. The main purpose of this investigation was to examine the clinical, cognitive, and neuroanatomical characteristics of these intellectual subtypes, and to establish the value and validity of this approach for reducing the heterogeneity of schizophrenia. **Methods:** A total of 71 patients with a diagnosis of schizophrenia or schizoaffective disorder and 66 healthy controls were assessed. A 'preserved' performance pattern (n=29) was defined by average-range estimated premorbid and current IQ with no evidence of decline (premorbid- current IQ difference <10 points). A 'deteriorated' pattern (n=14) was defined by a difference between estimated premorbid and current IQ estimates of 10 points or more. A 'premorbidly impaired' pattern (n=14) was defined by below average estimated premorbid and current IQ and no evidence of decline greater than 10 points. The groups were compared on demographic, neurocognitive, clinical, and neuroanatomical variables. **Results:** Patients with the preserved pattern outperformed those meeting criteria for deteriorated and premorbidly impaired intellectual ability on a composite measure of neurocognitive ability, as well as on indicators of processing speed, attention, working memory, verbal and visual memory, and social cognition. However, preserved patients scored lower than control participants on tests of processing speed, verbal memory, and reasoning/problem solving. Patients demonstrating the deteriorated and premorbidly impaired patterns were indistinguishable across all cognitive measures. The patient groups were clinically indistinguishable from each other and showed a similar pattern of widespread cortical thinning compared to controls. **Conclusions:** Cognitive impairment is a core feature of schizophrenia present to some degree in all patients, regardless of their intellectual

status. Therefore, IQ fails to capture the true breadth of cognitive impairment in schizophrenia. Although the preserved subtype has partial validation, comprehensive neurocognitive data provides little support for the distinctiveness of deteriorative relative to premorbid intellectual compromise. Cognitive ability and symptom severity represent independent disease processes in schizophrenia, and cortical thinning across the brain appears to reflect a shared disease process with no association to intellectual or cognitive status.

Acknowledgements

I would like to express my deepest gratitude to my advisor Dr. Walter Heinrichs for his full support, expert guidance, understanding, and encouragement throughout my study and research. In addition, I express my appreciation to Dr. Joel Goldberg and Dr. Keith Schneider for having served on my committee. Their thoughtful questions and comments were valued greatly.

Many thanks to my fellow labmates, volunteers, and research assistants who contributed to the success of this project. Their contributions are sincerely appreciated and gratefully acknowledged. A special thank you to Ashley Miles for her invaluable friendship and endless support over the past nine years.

I would like to extend my sincerest thanks and appreciation to my parents who supported me and helped me throughout my life and during this study. You can take all the credit for much of what I have achieved and what I will achieve in the future. In addition, many thanks to my sisters, parents-in-law, and brothers-in-law for their love and support.

Last but not least, I would like to thank my dearest husband and my best friend Maurice for his unconditional love, patience, and continual support throughout my academic career; I would not have been able to complete this dissertation without your continuous love and encouragement. I dedicate this dissertation to you and to our two lovely boys, Thiago and Maddox, who are the pride and joy of my life.

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Introduction

Schizophrenia is a complex and heterogeneous syndrome characterized by strange and questionable beliefs, a profound disruption in emotion and sensory experiences, and a broad range of unusual behaviours. Patients often experience delusions and hallucinations, disorganized behaviour, social withdrawal, loss of interest, and reduced motivation (Andreasen & Flaum, 1991). Many also experience general distress, depression, and anxiety (Buckley, Miller, Lehrer, & Castle, 2009). Schizophrenia is arguably the most disturbing, puzzling, and stigmatized of all psychological disorders, with a lifetime prevalence of approximately 1% (Government of Canada, 2006; Jablensky, 2000). It is also one of the most debilitating disorders, constituting the fifth leading cause of disability in developed countries worldwide, according to the World Health Organization (Murray & Lopez, 1997). In fact, when both clinical and social/functional dimensions are considered, research shows that only 1 in 7 individuals with schizophrenia 'recover' and that recovery rates have not increased in recent decades despite substantial enhancements in treatment options (Jaaskelainen et al., 2013). This serious condition carries a heavy financial burden estimated to be $6.85 billion in Canada in 2004, including health care expenditures and lost productivity due to early morbidity and mortality (Goeree et al., 2005). Indeed, the majority of patients are unemployed, and they are over-represented in prisons, homeless shelters, and socially disadvantaged populations (Bellack et al., 2007).

Heterogeneity in Schizophrenia

Despite decades of scientific research implicating schizophrenia as a neuropsychiatric disease, the etiology, neuropathology, and neuropathophysiology of the illness remain largely

unknown. Many have argued that this is in part due to the extensive heterogeneity observed in people with the illness. Indeed, it has been suggested that this illness is best understood not as a single disease entity with pleiotropic manifestations, but rather as a heterogeneous collection of pathogenetically distinct subtypes that have been amalgamated and investigated as a single diagnostic category (Basso, Nasrallah, Olson, & Bornstein, 1998; Bellak, 1994; Carpenter, Buchanan, Kirkpatrick, Tamminga, & Wood, 1993; Gottesman & Gould, 2003; Heinrichs, 2004; Jablensky, 2006). In fact, in his seminal work, Bleuler (1911) coined the term "schizophrenia" to replace "*dementia praecox*" and emphasized that it "is not a disease in the strict sense, but appears to be a group of diseases…Therefore we should speak of schizophrenias in the plural."

The heterogeneity in schizophrenia involves widespread variability in symptom expression, course, neurocognitive function, functional outcome, and biological findings. The symptoms of schizophrenia span a broad array of psychopathology and exhibit a remarkable amount of interindividual variability and temporal inconsistency. In addition, the onset of symptoms may be insidious in nature or rather abrupt. Cognitive deficits in schizophrenia are heterogeneous as well, ranging from persistent generalized impairment to slight focal deficits or virtually average or even superior performance. Further, although the idea of functional decline as a diagnostic hallmark of schizophrenia is reflected in current classifications and diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013), functional impairments are not universal. In fact, the functional status of patients can range from near normal to severe dependency and disability. Schizophrenia is also probably biologically heterogeneous and resists reduction to well-characterized causal mechanisms and pathologies. Genetic linkage and association studies have targeted multiple candidate loci and genes, but rejected the parsimonious hypothesis that all schizophrenia is

caused by the same pattern of genetic mutations, brain dysmorphology and neurochemical abnormalities (Jablensky, 2006). It appears that schizophrenia has a multifarious neurobiology with various genes, gene interactions, and epigenetic effects influencing risk. Accordingly, well-characterized causal mechanisms and pathologies are far from being established (Bray, 2008; Maric & Svrakic, 2012; Rees, O'Donovan, & Owen, 2015). It has been argued that such inherent phenotypic variation indicates etiologic heterogeneity, and raises questions about the ability of the broad clinical category of schizophrenia to establish biologically homogeneous populations for genetic etiological research. Therefore, one can argue that the phenotypic variability in schizophrenia has been the principal barrier in the search for the causes of this devastating illness.

Subtyping Schizophrenia

To address this heterogeneity, numerous attempts have been undertaken to develop schemas to organize the illness and identify more homogeneous groups of patients with similar illness presentations within the schizophrenia patient population. Attempts to organize the complexity of the broad clinical definition of schizophrenia into simpler component disorders or subtypes have been made since the delineation of the diagnostic category, using clinical, behavioural, or biological criteria, as well as a variety of statistical methods such as factor and cluster analysis. Subtypes based on putative genetic indicators such as a positive family history for schizophrenia spectrum disorders have also been proposed (Lewis, Reveley, Reveley, Chitkara, & Murray, 1987). It has been argued that, ultimately, these subtypes may map onto parallel pathophysiologies, etiologies, and treatment approaches (Vaz & Heinrichs, 2006). The ultimate hope is that the aggregate label of 'schizophrenia' will one day be substituted by a

number of more accurate diagnoses based on distinct underlying etiologies and pathophysiologies.

Symptomatic Subtyping

The traditional approach to subtyping schizophrenia has involved the use of individual symptoms or clusters of symptoms to establish typologies and subclassifications (e.g., American Psychiatric Association, 1994; Crow, 1980; Hill, Ragland, Gur, & Gur, 2001; Morrison, Bellack, Wixted, & Mueser, 1990; Nicholson & Neufeld, 1993). Crow (1980) put forth a basic subclassification of schizophrenia, based on the prevalence of either positive or negative symptoms. 'Type I' (positive) schizophrenia was distinguished by a clinical profile characterized by hallucinations, delusions, and formal thought disorder, while patients with 'Type II' (negative) schizophrenia presented with social withdrawal, loss of volition, restricted affect, and poverty of thought, action, and speech. It was hypothesized that each illness variant has a unique treatment response because each reflects a distinct underlying biology and disease process. Dopaminergic dysfunction was presumed to underlie 'Type I' schizophrenia, while structural brain abnormalities were thought to underlie 'Type II' schizophrenia. Patients have also been classified into deficit and nondeficit schizophrenia, paranoid and non-paranoid subtypes among others (American Psychiatric Association, 1994; Kirkpatrick, Buchanan, Breier, & Carpenter, 1993). 'Deficit schizophrenia' is distinguished by persistent 'primary' negative symptoms, and is associated with reduced rates of paranoid ideation and depression, severe anhedonia, poor social functioning, resistance to treatment, and a higher risk of schizophrenia in relatives (Kirkpatrick, Ross, Walsh, Karkowski, & Kendler, 2000). There is evidence for the neuropsychological and neurobiological validity of the deficit syndrome as a distinct subtype, but no evidence thus far of

a specific genetic profile (Buchanan et al., 1994; Cohen, Forbes, Mann, & Blanchard, 2006; Jablensky, 2006; Rowland et al., 2009; Wonodi et al., 2006).

Although partially successful, these symptom typologies have not met the complementary challenges of demonstrating clinical and biological validity and trait-like temporal stability. In fact, most attempts at symptomatic subtyping have produced vague boundaries between subtypes, weak construct validity, and little diagnostic subtype temporal stability (Carpenter, Heinrichs, & Wagman, 1985; Helmes, 1991; Marneros, Deister, & Rohde, 1992). For example, while relatively stable over time and psychophysiologically distinct, the paranoid subtype overlaps symptomatically with psychotic mood disorder and is neuropsychologically indistinguishable from non-paranoid schizophrenia (Jeon & Polich, 2003; Lake, 2008; McGlashan & Fenton, 1991). Heinrichs and Awad (1993) argued that subtyping resulting from symptom ratings was lacking because the ratings reflect subjective judgment, fluctuate over time, and may be difficult to link up directly to neural mechanisms, making symptoms unsuitable for use as subtype demarcations in the search for the cause of schizophrenia. Furthermore, symptomatic variance accounts for only moderate amounts of variance in functionality (Green, 1996). This suggests that alternative methods of dividing and organizing schizophrenia into distinct component syndromes should be utilized.

Cognitive Subtyping

To address the problems of objectivity and stability and afford an alternative to symptomatic subtyping, researchers have suggested that subtyping procedures should include cognitive variables, with patients grouped according to neuropsychological profiles (Goldstein, 1994; Goldstein, Allen, & Seaton, 1998; Heinrichs, 2001; Palmer et al., 1997; Paulsen et al., 1995). In fact, going back to the inception of the diagnostic category at the turn of the 20th

century, Kraepelin (1909) asserted that *dementia praecox* is a cognitive disorder accompanied by delusions and hallucinations, but fundamentally typified by "weakening of the mainsprings of volition," "lowered mental efficiency," "unsteadiness of attention," "inability to sift, arrange and correct ideas, and to accomplish mental grouping of ideas." In his seminal accounts of dementia praecox, Bleuler (1943, 1950) reasoned that deficits in "associative" thinking were "fundamental" aberrations in schizophrenia, while clinical symptoms such as delusions and hallucinations were only "accessory" (see Sharma & Harvey, 2000, for a review).

Indeed, it is now generally accepted that cognitive deficits, while heterogeneous in their own right, are core and enduring features of schizophrenia (Heinrichs, 2005; Schaefer, Giangrande, Weinberger, & Dickinson, 2013). Research in the last three decades has consistently established that a majority of patients with schizophrenia perform approximately 1.0 standard deviation below healthy people on multiple and diverse clinical neuropsychological measures (Dickinson, Ramsey, & Gold, 2007; Heinrichs, 2005; Keefe & Fenton, 2007). A recent large review and meta-analysis of cognitive studies from around the world, spanning several decades, found that patients with schizophrenia exhibit a generalized cognitive impairment, demonstrating that this finding has remained robust over time despite changes in assessment instruments and alterations in diagnostic criteria, and that it manifests similarly in different regions of the world despite linguistic and cultural difference (Schaefer, Giangrande, Weinberger, & Dickinson, 2013). Indeed, impairments in neuropsychological abilities are widespread and include working memory, attention, verbal learning and memory, visual learning and memory, language, reasoning and problem solving, speed of processing, executive function, social cognition, and in general intellectual ability (Aleman, Hijman, de Haan, & Khan, 1999; Berna et al., 2011; Dickinson et al., 2007; Elvevag & Goldberg, 2000; Green, Kern, & Heaton, 2004; Heinrichs,

2005; Heinrichs & Zakzanis, 1998; Lee & Park, 2005; Matza et al., 2006; Reichenberg & Harvey, 2007; Zakzanis, Troyer, Rich, & Heinrichs, 2000). In fact, in has been suggested that schizophrenia "manifests itself primarily in cognition" (Heinrichs, 2005). Furthermore, it appears that the degree of impairment across these cognitive domains is greatly interconnected. Dickinson and colleagues (2008) used structural equation modeling to show that approximately 64% of the variance in neuropsychological performance between schizophrenia patients and healthy control participants can be accounted for by a generalized deficit factor.

Advantages of Cognitive Subtyping

Neuropsychological test data offer several advantages over symptom ratings as criteria for subtyping procedures. Neurocognitive deficits are considered the most stable aspect of schizophrenia, with test-retest coefficients ranging from 0.70 to 0.85 (Albus et al., 2002; Bozikas & Andreou, 2011; Censits, Ragland, Gur, & Gur, 1997; Hoff et al., 1999). The stability of these deficits has been established in numerous studies. For example, cross-sectional studies reveal equivalence in the cognitive functioning of young patients with a short duration of illness, old patients with a short duration of illness, and old patients with a long duration of illness (Heaton et al., 1994; Jeste et al., 1995). In addition, there are no differences in cognitive performance between adolescent or first episode patients and chronic patients (Albus et al., 1996; Hoff, Riordan, O'Donnell, Morris, & DeLisi, 1992); and no significant differences between age groups (Hyde et al., 1994). The preponderance of evidence thus supports the notion of stability in most cognitive impairments.

In addition, neurocognitive performance is more objective and trait-like than symptom ratings, with potentially more direct ties to neurobiology and genetics. The latter reflects the field of neuropsychology's long history of research and extensive knowledge base on the

neurobiological basis of cognition (Gottesman & Gould, 2003; Heinrichs, 2004, 2005; Strauss & Sommerfeldt, 1994), which can be exploited in the pursuit of novel taxonomies for schizophrenia. In fact, there is evidence that performance on neurocognitive tests may be valuable in organizing the illness into more biologically homogeneous variants and subgroups (Heinrichs, 2005). For instance, schizophrenia patients with and without global cognitive impairment have distinct genetic profiles linked to susceptibility genes on chromosome 6, which in turn supports the idea that they represent true subtypes in schizophrenia (Hallmayer et al., 2005; Toulopoulou, Morris, Rabe-Hesketh, & Murray, 2003). In addition, differences in neurocognitive performance between patients with schizophrenia and healthy controls have emerged systematically as the most robust findings evidenced by significantly larger effect sizes when compared to the neuroimaging domain (Heinrichs, 2005). Altogether, these findings provide substantial support for taking a neurocognitive approach to the challenge of schizophrenia subtyping. Such subtypes promise to advance both understanding of the disease and the development of tailored treatment for persons with schizophrenia. This may be particularly so for the genetics of schizophrenia in which the development of cognitive subtypes looms as potential endophenotypes, which are features present in individuals with genetic variants of risk that could be assessable prior to the manifestation of the clinical symptoms (Gottesman & Gould, 2003). The endophenotypes would theoretically be more closely associated with the genetic variants of susceptibility of schizophrenia than the clinical phenotypes and their use could enhance the predictive power of the groups and afford better understanding of both disease pathophysiology and treatment outcome (Gottesman & Gould, 2003; Jablensky, 2006; Joyce & Roiser, 2007).

Finally, cognitive impairments consistently emerge as predictors or mediators and possibly even determinants of patients' ability to function independently in the community irrespective of clinical symptom severity (Bowie et al., 2008; Bowie & Harvey, 2005; Bowie, Reichenberg, Patterson, Heaton, & Harvey, 2006; Green et al., 2004; Keefe, Poe, Walker, & Harvey, 2006; Matza et al., 2006; Milev, Ho, Arndt, & Andreasen, 2005; Mohamed et al., 2008). Indeed, it has been argued that as much as 60% of the variance in real world outcome can be accounted for by cognitive ability (Green, Kern, Braff, & Mintz, 2000; Green et al., 2004), although more recent work has shown that the relationship between cognition and functional outcome is actually much more modest, with only 4% to 23% of functional outcome variance credited to cognitive performance (Fett et al., 2011). Nevertheless, the consistency of this association and the need to improve the functional outcome status of individuals with schizophrenia has prompted the introduction of different treatment initiatives and methodologies that focus on enhancing or mitigating impaired cognitive performance in schizophrenia (e.g., Green et al., 2004; Marder & Fenton, 2004; Carter & Barch, 2007). In response to failed attempts at augmenting functional outcome via symptomatic improvement, the logic behind this initiative is that enriching a patient's cognitive status should result in meaningful changes and enhancements in functional status and adjustment.

Impaired Cognition as a Core Feature

Importantly, the neurocognitive deficits observed in schizophrenia patients are intrinsic to the disorder and are not an epiphenomenon of the illness. There is substantial consensus in the literature that impairments in various cognitive domains are not reducible to secondary influences that reflect treatment with antipsychotic medications, recurrent hospitalization, social disadvantage, or years of chronic stress associated with receiving the diagnosis (Torrey, 2002;

Ma et al., 2007). They also persist following the amelioration of clinical symptoms and over the course of the illness (Elvevag & Goldberg, 2000; Heinrichs & Zakzanis, 1998; Hoff et al., 1999; Hughes et al., 2003; Martinez-Aran et al., 2002; Rund et al., 2004); exist in the pre-psychotic period and at the onset of illness (Brewer et al., 2005; Johnstone, Ebmeier, Miller, Owens, & Lawrie, 2005; Lencz et al., 2006; Lewandowski, Cohen, & Ongur, 2011; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009); occur in unaffected people with elevated risk (Cannon et al., 2000; Fusar-Poli et al., 2007; Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004; Whalley, Harris, & Lawrie, 2007); are unrelated to the chronicity of the illness or its duration (Heaton et al., 2001; Hoff et al., 1999; Kurtz, Seltzer, Ferrand, & Wexler, 2005), and are more severe in schizophrenia, as compared with other psychotic illnesses (Altshuler et al., 2004).

Intellectual/Cognitive Deterioration

While cognitive impairment occurs across many ability areas, the universality, nature, onset and consequences of cognitive impairment in schizophrenia remain largely uncertain. It has been argued that the degree of intellectual deterioration subsequent to the onset of schizophrenia is central in the quest to identify more homogeneous groups within the schizophrenia patient population. This concept of intellectual decline, which was introduced by Kraepelin nearly a century ago, continues to figure prominently in the field of cognitive impairment in schizophrenia since intellectual status is believed to be an important correlate of most other cognitive and neuropsychological functions. In fact, it has been argued by some that almost all patients with schizophrenia undergo an intellectual function decrement (Keefe, Eesley, & Poe, 2005; Vaskinn et al., 2014). A decline in general intellectual ability may occur in tandem with the first psychotic episode and then persist over the course of illness (Goldberg, Hyde, Kleinman, & Weinberger, 1993; Kurtz, 2005; Nelson et al., 1990).

Indirect evidence for the notion of intellectual decline comes from studies of monozygotic twin pairs discordant for schizophrenia in which each affected individual is compared to his or her co-twin, thus controlling for age, sex, and genome as well as environmental influences such as educational opportunity and socioeconomic status. In studies implementing this design, the twin with schizophrenia consistently performs worse on neuropsychological testing compared to his or her unaffected co-twin, regardless of how well the affected twin performed. For example, Goldberg and colleagues (1995) showed that the unaffected twin scored an average of 10 points higher on IQ tests when compared to the affected twin. Kremen and colleagues (2000) showed that chronic schizophrenia patients who were matched one-to-one on education with healthy control participants tended to have estimated premorbid abilities that are a full standard deviation above healthy control participants with similar cognitive performance. This concept of intellectual decline following illness onset has also been supported by longitudinal studies (Lubin, Gieseking, & Williams, 1962; Schwartzman & Douglas, 1962), as well as by studies of first-episode patients (Goldberg, Karson, Leleszi, & Weinberger, 1988). A recent meta-analysis found that although a substantial proportion of children and adolescents who go on to develop schizophrenia have normal range cognitive performance before the onset of illness, they then suffer a decline into below-average ranges that coincides with the onset of symptoms (Bouzikas & Androu, 2011). Population-based estimates of intellectual deterioration indicate rates as high as 98% for patients with schizophrenia, who show a measurable decrement in intellect from premorbid levels (Keefe et al., 2005). These data suggest that patients with schizophrenia, even those who perform within normal limits on neurocognitive tests, have in fact undergone a substantial decline in their level of intellectual or cognitive functioning.

Premorbid Intellectual/Cognitive Impairments

However, intellectual decline after the onset of schizophrenia is not universally characteristic and may precede substantially the development of frank psychotic illness (Russell, Munro, Jones, Hemsley, & Murray, 1997). Russell and colleagues (1997) suggested that cognitive impairments are inherent to the disease process and that any ensuing intellectual impairment is due to a pre-existing deficit that predates the manifestation of psychotic symptoms and is thus not reducible to the pathological process of disease onset. Indeed, research has consistently linked schizophrenia to a variety of early neurodevelopmental abnormalities (Murray & Lewis, 1987; Weinberger, 1987; Seidman, 1990) and there is substantial evidence in the literature that as a group, individuals who later will be hospitalized for schizophrenia have impairments in various neurocognitive domains that precede the manifestation of psychotic symptoms (Bilder et al., 2000; Davidson et al., 1999; Kremen et al., 1998). For example, research has shown that deficits in perception, memory, language, and attention surface in early childhood long before the emergence of any psychotic symptoms (Cannon et al., 2000; Cornblatt, Obuchowski, Roberts, Pollack, & Erlenmeyer-Kimling, 1999; Erlenmeyer-Kimling et al., 2000).

One measure that has received a great deal of attention as a potential indicator of early neurodevelopmental abnormality is general intellectual functioning or IQ. Several study designs allow for estimates of premorbid IQ, including retrospective studies of school-, recruit-, or clinic-based testing, longitudinal birth or recruit cohort studies, and studies of population samples at genetic risk for schizophrenia (Agnew-Blais & Seidman, 2013; Khandaker, Barnett, White, & Jones, 2011; Woodberry, Giuliano, & Seidman, 2008). There are numerous retrospective estimates of low premorbid function (e.g., Torrey, Bowler, Taylor, & Gottesman, 1994) and

there are recent reports documenting low IQ in a substantial proportion of children and adolescents who later develop schizophrenia (e.g., Cannon et al., 2000, 2002; Khandaker et al., 2011). In addition, large birth cohorts have found that individuals who later develop schizophrenia were often delayed in achieving neuromotor developmental milestones, have premorbid speech abnormalities, and have on average lower levels of educational achievement (Crow, Done, & Sacker, 1995; Poulton et al., 2000, Sorensen et al., 2010). Jones and colleagues (1994) using the 1946 birth cohort, obtained premorbid cognitive scores and found impairments in the educational test scores at ages 8, 11, and 15 of participants who later developed schizophrenia, and this was unrelated to the sex or social class of the subject. In a cohort of males conscripted into the Swedish army in 1969-1970, David and colleagues (1997) found a robust relationship between IQ and later risk of developing schizophrenia. In another Swedish conscript cohort, Gunnell and colleagues (2002) found that IQ score at the age of 18 years was correlated with risk of developing early-onset schizophrenia, and this relationship persisted after controlling for potential confounders such as prenatal adversity and obstetric complications. In the National Child Development Study, subjects were prospectively followed and it was found that those who developed schizophrenia had lower IQ scores at the age of 11 years compared with controls (Done, Crow, Johnstone, & Sacker, 1994). Similarly, in the Dunedin longitudinal birth cohort study, lower childhood IQ scores and receptive language impairments were found in children who subsequently developed schizophrenia (Cannon et al., 2002; Reichenberg et al., 2010). In a case-control study of high school recruits for the Israeli military service, individuals with schizophrenia showed significant premorbid deficits on all intellectual measures and on measures of reading and reading comprehension (Reichenberg et al., 2002). The last quantitative review of the literature, which was published in 2008, suggested that years before the onset of

psychotic symptoms, individuals with schizophrenia, as a group, exhibit mean IQ scores roughly one-half of a standard deviation below that of healthy controls (Woodberry et al., 2008). These precursors of schizophrenia corroborate the hypothesis that psychosis arises from a cognitively compromised brain.

Intellectual/Cognitive Preservation

However, not all patients with schizophrenia show intellectual or cognitive impairments according to standard clinical norms. In fact, some studies have described high functioning schizophrenia patients with normal intellectual functioning and no or minimal cognitive deficits (e.g., Palmer et al., 1997; Kremen, Seidman, Faraone, Toomey, Tsuang, 2000; Rangel et al., 2015). Meta-analytic findings aggregated from hundreds of studies and thousands of schizophrenia patients and healthy participants imply that 70-75% of the schizophrenia patient population performs below general population values on many standard neuropsychological tests (Heinrichs, 2005). Hence, a substantial minority, 20-25%, must overlap with healthy people on many standard cognitive tasks. Indeed, a number of studies have corroborated the implications of meta-analytic findings and identified groups of patients with schizophrenia displaying statistically average levels of neuropsychological functioning (Ammari, Heinrichs, & Miles, 2010; Heinrichs et al., 2008; Leung, Bowie, & Harvey, 2008; Kremen et al., 2000; Palmer, Dawes, & Heaton, 2009; Palmer et al., 1997; Rund et al., 2006; Weickert et al., 2000; Wexler et al., 2009). In a seminal study, using a combination of expert ratings and normative criteria, Palmer and colleagues (1997) identified 27.5% of their sample of schizophrenia patients as neuropsychologically normal on a variety of cognitive measures, including general intellectual ability or IQ. This subgroup was statistically indistinguishable from the control group on a comprehensive test battery. Numerous later studies corroborated a 20-30% overall prevalence of

performance normality in schizophrenia across settings and samples (Allen, Goldstein, & Warnick, 2003; Kremen et al., 2000; Weikert et al., 2000). Furthermore, there are reports of even higher-functioning patient subgroups. Recent studies show that a much smaller, but potentially important, subgroup of patients demonstrates verbal ability at or above the 90th percentile, based on Vocabulary scores from the Wechsler Adult Intelligence Scale (Heinrichs et al., 2008), an indicator of general intellectual ability. Others have also identified patients who have IQs above the average range (Kremen, Seidman, Faraone, & Tsuang, 2001; McCabe, Maloney, Stain, Loughland, & Carr, 2012; Weikert et al., 2000; Wilk et al., 2005). These cognitively exceptional schizophrenia patients are indistinguishable from demographically matched control participants on a wide range of neuropsychological measures.

It has been argued that the occurrence of intellectual and cognitive normality in schizophrenia may still reflect a decline from superior ability preceding the onset of the illness (e.g., Wilk et al., 2005). Therefore patients who currently perform in the average range on cognitive tasks, including IQ measures, would have theoretically scored in the above-average range had they been assessed prior to illness onset. Nonetheless, they share the cognitively impairing disease process with the rest of the patient population and thus undergo cognitive deterioration into the average range following the onset of their illness. Consequently, an additional criterion for normality used by some researchers requires equivalence between current and estimated premorbid levels-of-performance. Oral reading tasks are often used to provide estimates of premorbid cognitive capabilities insofar as they are believed to reflect preserved abilities routinely acquired before the onset of schizophrenia (Allen et al., 2003; Harvey et al., 2000; Lezak, Howieson, Loring, Hannay, & Fischer, 2004; Warnock, Allen, & Goldstein, 2000). Many studies of premorbid abilities in patients with normal cognitive performance did not find

any evidence of a discrepancy between current and premorbid estimates of cognitive functioning based on reading tasks (McCabe et al., 2012; Heinrichs et al., 2008; Weikert et al., 2000). Therefore, schizophrenia can occur in the relative absence of cognitive impairment in a minority of patients, and there is no evidence that these patients have undergone a decline in their intellectual ability. Furthermore, it seems doubtful that the 20%-30% of cognitively normal schizophrenia patients in typical outpatient samples would all have had superior cognitive abilities had they not become ill, as that is an inexplicably large proportion of people to have cognitive capabilities one to two standard deviations above the population mean.

Patterns of Intellectual Ability in Schizophrenia

In light of the heterogeneity in intellectual performance patterns observed in schizophrenia and given the inconsistencies in the literature regarding issues of intellectual decline, premorbid impairments, and preserved abilities, a typology comprising preserved, deteriorated, and premorbidly impaired intellectual ability patterns has been proposed and received partial support (Badcock, Dragović, Waters, & Jablensky, 2005; Leeson et al., 2011). Research has suggested that patients with relatively preserved intellect function at higher levels in the community and maintain that level of functioning for longer periods of time when compared to more typical patients (Ammari et al., 2010; McKibbin, Brekke, Sires, Jeste, & Patterson, 2004; Wells et al., 2015). They also tend to have fewer symptoms and receive less anticholinergic medication than their neuropsychologically impaired counterparts (Palmer et al., 1997; Seidman, Cassens, Kremen, & Pepple, 1992; Wells et al., 2015).

Murray and associates (Murray & Lewis, 1987; Murray, Jones, O'Callaghan, Takei, & Sham, 1992) proposed an etiological theory which could explain the existence of intellectually preserved and impaired subgroups. They suggested that schizophrenia has a different

neurodevelopmental cause in impaired patients, which has its roots in genetic deficiencies and early risk factors such as birth complications. These patients are distinguished by premorbid motor and behavioural problems, cognitive deficits, inferior social adjustment, early illness onset, and more severe negative symptoms. The intellectually preserved patients also have a susceptibility to decompensate into psychosis, but there is less evidence of a neurodevelopmental disease and they are less likely to exhibit premorbid problems or cognitive impairments. The existence of such patients could have significant implications for understanding the neuropathology of schizophrenia in that they suggest that psychotic symptoms and neurocognitive function are relatively independent dimensions of the disorder.

Structural abnormalities in Schizophrenia

Innovations in imaging technology have stimulated the enormous upsurge of schizophrenia research over the last three decades. This research is driven by inferences that the disease develops, at least partly, as a result of deficiencies in aspects of brain structure and function. Indeed, complex and widespread patterns of brain abnormalities appear to be a hallmark of schizophrenia and are believed to be shaped by a combination of neurodevelopmental and neurodegenerative abnormalities (Keshavan, Tandon, Boutros, & Nasrallah, 2008). In this view, schizophrenia is a neurobiologic disorder affecting the development and formation of brain structures, which consequently disrupts neuropsychological functioning (Keshavan et al., 2008). While impaired cognitive performance is believed to signal the neuropathological disease process rather than the unstable and sometimes volatile nature of the clinical symptoms, the neuropathological substrates of cognitive impairment in schizophrenia are not well established and relatively few consistent findings have emerged to map neurobiology directly onto neurocognitive performance. Nevertheless, intricate and

heterogeneous patterns of structural aberrations may underlie the heterogeneity observed in neurocognitive functioning. Analysis of brain morphology in schizophrenia patients with differing intellectual profiles can help explicate the relationships between cognitive functioning and disease-related alterations in brain anatomy.

Indeed, recent work has suggested that differences in the level of neurocognitive impairment are related to differential patterns of structural change in the cerebral cortex. Specifically, it has been argued that cortical thickness is particularly relevant in terms of illness etiology. In fact, one of the principal pathological findings in the brains of those affected with schizophrenia involves abnormal cortical thinning (Cannon et al., 2015). Reduced cortical thickness has also been demonstrated in the unaffected siblings of patients with the disorder (Goldman et al., 2009; Goghari, Rehm, Carter, & MacDonald, 2007; Gogtay et al., 2007), suggesting a possible relationship of these cortical changes to the genetic liability for developing the illness. Indeed, schizophrenia's strongest genetic association involves variation in the major histocompatibility complex (MHC) locus, which mediates synapse elimination during postnatal development in mice (Sekar et al., 2016). Sekar and colleagues (2016) argued that excessive or inappropriate synaptic pruning during adolescence and early adulthood contribute to the development of the illness and may help explain the observed cortical thinning. Overall, widespread reductions in cortical thickness across various brain regions have been reported in schizophrenia patients with cognitive impairments, particularly in frontal and temporal regions (Goldman et al., 2009; Kuperberg et al., 2003; Nesvag et al., 2008; Schultz et al., 2010). Reasonably consistent relationships are also reported between verbal memory impairment and cortical thinning in the medial temporal lobe (Antonova, Sharma, Morris, & Kumari, 2004; Gur, Keshavan, & Lawrie, 2007; Lawrie, Johnstone, & Weinberger, 2004). A number of meta-

analyses have synthesized evidence on several aspects of fronto-temporal anatomy in schizophrenia. Bora and colleagues (2011) corroborated findings of reduced cortical thickness in prefrontal, temporal, and parietal cortices (Bora et al., 2011).

Only a handful of studies have investigated differences in the brain structure of cognitive subgroups in schizophrenia. An investigation by Wexler and colleagues (2009) used structural MRI to compare cognitively "near normal" and cognitively impaired patients on detailed measures of regional brain volumes of gray and white matter across the cerebrum. Patients were assigned to the neuropsychologically near normal subgroup if they scored within 0.5 standard deviation of comparison participants on four tests of attention and verbal and nonverbal working memory and to the neuropsychologically impaired group if they scored at least 1.0 standard deviation below that of comparison participants. sMRI scanning revealed markedly smaller white matter volumes in sensorimotor and parietal regions and larger volumes of the lateral ventricles in the impaired patients when compared to the cognitively intact patients, who were indistinguishable from healthy controls. However, both patient groups had markedly less gray matter volume throughout the cerebrum and markedly larger third ventricles than healthy comparison participants. Cobia and colleagues (2011) found that 'neuropsychologically near-normal' schizophrenia patients, defined using a series of clustering algorithms, exhibited reduced cortical thinning when compared to healthy controls. They concluded that a compelling association exists between cognitive impairment and cortical thinning in schizophrenia, where patients with normal or near-normal cognitive abilities also exhibit normal or near-normal cortical thickness patterns.

Study Aim 1

In light of these considerations, the first aim of the present investigation was to identify and estimate the prevalence of intellectual performance patterns corresponding to preserved, deteriorated, and premorbidly impaired ability in a large sample of schizophrenia patients through application of algorithms derived from standard cognitive test data. Subtypes based on intellectual ability may organize and reduce the heterogeneity of schizophrenia, aid in the prediction of functional outcome, and lend themselves to biological validation. A detailed characterization of these intellectual subtypes may be important in targeting appropriate treatment approaches, management of symptoms and deficits, and establishing or determining services for patients with schizophrenia. Given that the course and progression of schizophrenia is highly variable, the ability to predict long-term functional outcome would be extremely helpful for treatment and rehabilitation planning.

For the purpose of this study, premorbid intellectual ability was estimated using a word reading measure. Oral single-word reading tests are widely viewed as an index of premorbid ability insofar as they are believed to reflect preserved abilities routinely acquired before the onset of schizophrenia (Allen et al., 2003; Harvey et al., 2000; Kremen, Seidman, Faraone, Pepple, Lyons, & Tsuang, 1996; Lezak et al., 2004; Warnock et al., 2000) and seem to resist the influence of various types of acquired diffuse and multi-focal neurological disease (see Franzen, Burgess, & Smith-Seemiller, 1997 for a review). It is also believed to be a skill resistant to a variety of psychiatric disorders including schizophrenia (Bright, Jaldow & Kopelman, 2002; Green et al., 2008; Harvey et al., 2006; Heinrichs & Zakzanis, 1998; Miller, Marks & Halperin, 2005; Rolstad et al., 2008). Therefore, a reading score is a feasible predictor of whether a patient's current intellectual or cognitive ability is congruent with earlier expectations. For the

purposes of this study, global cognitive ability will be considered in terms of verbal and nonverbal ability. Verbal ability, indexed by vocabulary test scores, and nonverbal ability, indexed by reasoning with visual shapes and patterns, are robust indicators of general intelligence. IQ-based estimates of global cognitive ability may deviate from levels of performance observed on reading tests. For example, Badcock and colleagues (2005) reported subgroups of schizophrenia patients with normal range IQ and reading scores, below normal reading and IQ scores, but also a subgroup with below average IQ scores and normal range reading. These differences provided the basis for the proposed intellectual subtypes.

Study Aim 2

The second aim of this study was to evaluate the cognitive validity of these intellectual subtypes by comparing performance on independent adjunct measures of cognitive ability and relative to the performance of healthy research participants. Although some studies found that schizophrenia patients with average range intellectual ability are truly free of other cognitive deficits (Ammari et al., 2010), others found that patients may perform in the average range on a composite score like IQ, but still demonstrate abnormalities in executive, attention-related, memory, and processing speed abilities (Allen et al., 2003; Gray, McMahon, & Gold, 2013; Holthausen et al., 2002; Joyce et al., 2002; Kremen et al., 2000; Weickert et al., 2000) when compared directly with a healthy control group. These cognitive domains are highly vulnerable to many neurological events and disease processes. For example, Weickert and colleagues (2000) compared standard assessments of premorbid and current IQ and reported that patients with schizophrenia displaying preserved intellectual ability exhibited a cognitive profile that was similar to that of healthy controls except on specific tasks of attention and executive functioning (Wisconsin Card Sorting Test and Continuous Performance Test). They concluded that executive

impairment comprises a “necessary type of cognitive impairment in schizophrenia” (Weickert et al., 2000). Similarly, Kremen and colleagues (2001) reported that patients with preserved IQ exhibit a broad spectrum of compromised neuropsychological performance when compared with IQ-matched controls. Gray and colleagues (2013) argued that general intellectual ability or IQ does not explain the generalized deficit observed across multiple cognitive domains in schizophrenia. They found that patients performed on average one full standard deviation worse on a neuropsychological battery than what would be expected based solely on their current and estimated premorbid IQ scores.

In exploring the question of preserved cognitive ability in schizophrenia, evidence from specialized “cognitive neuropsychiatry” tasks will also be considered. These more specialized and less frequently utilized tasks evolved from research on cognitive biases and social reasoning in patients with psychotic disorders, and they include probabilistic reasoning, source attribution, and theory-of-mind paradigms. Research has suggested that more severe levels of psychopathology, particularly symptoms such as delusions and thought disorder, are associated with deficient performance on tests tapping these abilities (Brune, 2005; Bora, Yucel, & Pantelis, 2009; Corcoran, Mercer, & Frith, 1995; Dudley, Taylor, Wickham, & Hutton, 2015; Frith & Corcoran, 1996; Garety, Hemsley, & Wessely, 1991; Garety et al., 2005; Kinderman & Bentall, 1996). These specially constructed measures have not, thus far, been applied to the study of intellectual subtypes in schizophrenia. The notion of bias or style in cognitive processing refers to both formal and social reasoning partiality and includes a propensity to make decisions based on inadequate data, a resistance to disconfirmatory information, and ‘self-serving’ attributions in social situations. For example, the most often cited effect originates from the observation that schizophrenia patients with persecutory delusions are inclined to ‘jump to conclusions’ and make

impulsive and premature decisions exclusive of sufficient information on probabilistic reasoning tasks (Dudley et al., 2015; Lincoln, Ziegler, Mehl, & Rief, 2010; Garety et al., 1991; Garety et al., 2005; So, Garety, Peters, & Kapur, 2010). Delusional patients also tend to rigidly hold their beliefs and refuse to consider any disconfirmatory evidence (Woodward, Moritz, Cuttler, & Whitman, 2006). In addition, these patients have trouble envisioning others' intentions or drawing plausible conclusions about the motives of others (Corcoran et al., 1995; Frith & Corcoran, 1996; Brune, 2005; Harrington, Langdon, Siegert, & McClure, 2005; Harrington, Siegert, & McClure, 2005), an ability widely known as Theory of Mind which has been defined as the "capacity to represent one's own and other persons' mental states" (Brune, 2005, p 21). Schizophrenia patients also demonstrate a persistent "externalizing" attribution style in that they often assign the causes of undesirable or negative personal occurrences to other people or to the external world (Kinderman & Bentall, 1996; Kaney & Bentall, 1989).

Although there is some evidence that the 'jumping to conclusions' tendency is independent of general intellectual ability (Langdon, Ward, & Coltheart, 2010; van Hooren et al., 2008), very little is known about whether there are consistent patterns of association between other cognitive biases and general intellectual ability. Thus, the question of whether the proposed intellectual subtypes demonstrate the same degree of cognitive biases despite their distinct intellectual profiles will be explored. Roncone and colleagues (2002) asserted that intellectual ability is an insufficient explanation for the observed theory-of-mind deficits in schizophrenia. On the other hand, other studies found that performance on tests requiring schizophrenia patients to discern the intentions of others was associated with IQ (Brune, 2003), as well as with tests of memory (Greig, Bryson, & Bell, 2004) and executive function (Greig et al., 2004; Langdon, Coltheart, Ward, & Catts, 2002). Nevertheless, the majority of evidence implicates level of

psychopathology as a better predictor than intellect or cognitive ability of performance on tests tapping cognitive bias or style.

Study Aim 3

The third aim was to assess the severity of clinical symptoms across the intellectual subtypes. Numerous findings have shown that relations between symptom dimensions or severity and neurocognitive performance are feeble or often nonexistent across many clinical samples (Berenbaum, Kerns, Vernon, & Gomez, 2008; Dibben, Rice, Laws, & McKenna, 2009; Dominguez, Viechtbauer, Simons, Van Os & Krabbendam, 2009; Heinrichs et al., 2008; Waters, Badcock, Dragovic, & Jablensky, 2009; Wexler et al., 2009). For example, comparisons of cognitively impaired and normal or near-normal schizophrenia patients have repeatedly shown that cognitive performance, including IQ, and positive symptoms such as delusions and hallucinations are independent (Ammari et al., 2010; Cobia et al., 2011; Heinrichs et al., 2008; Holthausen et al., 2002; Palmer et al., 1997; Wexler et al., 2009). On the other hand, there have been reports of moderate correlations between negative symptoms and standard neurocognitive tasks, although the common variance is seldom more than 15% (Ammari et al., 2010; Cobia et al., 2011; de Gracia Dominguez, Viechtbauer, Simons, van Os, & Krabbendam, 2009; Greenwood, Sigmundsson, Morris, & Wykes, 2000; Vaz & Heinrichs, 2006; Palmer et al., 1997), but others failed to find a relationship (Holthausen et al., 2002; Heinrichs et al., 2008; Palmer et al., 1997; Wexler et al., 2009). A similar discrepancy occurs with regards to disorganization symptoms in schizophrenia (Holthausen et al., 2002; Cobia et al., 2011). Dominguez and colleagues (2009) systematically reviewed 58 studies published between 1986 and 2007 and synthesized the reported correlations between symptoms and cognitive performance in schizophrenia. They found that negative and disorganized symptom dimensions

were significantly but modestly associated with cognitive deficits, whereas positive and depressive dimensions of psychopathology were not associated with neurocognitive measures. Another independently conducted meta-analysis largely corroborated these results (Ventura, Thames, Wood, Guzik, & Hellemann, 2010).

Study Aim 4

Finally, this study aims to examine the neuroanatomical characteristics of these potentially important subgroups using cortical thickness mapping. Although the brain imaging literature on schizophrenia patient-control differences in regional anatomy and physiology is vast, relatively few consistent findings have emerged to map neurobiology directly onto cognitive performance (Ragland, Yoon, Minzenberg, & Carter, 2007). Further, there has been no detailed examination of cortical thinning patterns to compare patients with preserved, deteriorated, and premorbidly impaired intellect. The only published study of brain structure anomalies in intellectually-defined subgroups of schizophrenia patients found that those with below-average estimated premorbid ability exhibit evidence of early cerebral hypoplasia, whereas intellectually preserved and deteriorated patients show evidence of brain tissue loss consistent with progression or later cerebral dysmaturation (Woodward & Heckers, 2015). However, this study specifically examined intracranial and total brain volume and did not include an analysis of cortical thinning patterns. All other studies examining the brain structure of schizophrenia patients grouped according to cognitive variables have been limited to comparing cognitively normal and impaired patients, without consideration of intellectual status or pattern.

Biological validation of the proposed intellectual subtypes requires the demonstration that differences in intellect between the patient groups correspond to neurobiological differences

indicating that these behavioural distinctions map onto neural substrates. Overall, studying the characteristics of the proposed intellectual subtypes may inform our understanding of specific heterogeneous pathophysiological processes underlying the illness. Further, results should provide an indication of whether these subtypes hold potential as organizing principles for research on the heterogeneity of schizophrenia. It is possible that these patient subgroups differ in their intellectual abilities because they have fundamentally distinct illnesses in terms of their underlying pathophysiology and thus also in their effects on the structure and function of the brain. Alternatively, the underlying brain abnormalities may differ on a quantitative versus qualitative scale, which would support a dimensional view of the illness. For example, the intellectually preserved subtype may constitute an aggregate of patients with less severe cognitive impairments and potentially less marked neurobiological abnormalities than those observed in patients with deteriorated and premorbidly impaired intellect.

Model and Hypotheses

The working model is that each of the proposed intellectual patterns represents a distinct illness variant within the schizophrenia patient population, each with a corresponding expression of psychopathology, cognitive profile, and neurobiological substrate. The most compelling validation of the proposed intellectual subtypes necessitates evidence of shared as well as non-shared characteristics. While there may be substantial individual differences in the expression of particular symptoms, the three intellectual patient groups have a common diagnosis and consequently a shared clinical syndrome of psychopathology. A great deal of evidence suggests that psychopathology, especially psychotic symptoms, and impaired intellectual or cognitive performance are separable processes in schizophrenia. If the psychopathological and neurocognitive manifestations of schizophrenia originate from autonomous disease processes,

then all patient groups should exhibit comparable symptom severity levels regardless of their discrepant intellectual profiles. Such weak or absent associations between intellectual or cognitive functioning and psychopathology make it difficult to argue that a single disease process underlies both psychosis and impaired cognition in schizophrenia. Instead, the lack of consistent relationship implies a dual-process disease model wherein cognitive deficits may occur in the absence of psychotic symptoms and vice versa. In light of the evidence, it is hypothesized that the intellectual subgroups will be indistinguishable from each other on symptom severity measures.

Accordingly, key neural systems mediating this psychopathology are also shared across the three subtypes. These shared illness characteristics presumably reflect the psychosis-producing process. To that extent, patterns of intellectual profiles may be of little relevance to the neuropathological and pathophysiological mechanisms underlying the psychiatric symptoms in schizophrenia. However, the three patient groups do not share the same level of intellectual and possibly cognitive performance. It follows then that these groups will also be neurobiologically distinct, signifying the relative preservation and pathology of underlying neuromechanisms. For example, if intellectually preserved patients have the psychosis-producing process that defines the illness, but little of the defective cognition observed in more typical patients, this behavioural difference should demonstrate biological validity by mapping onto cerebral differences. In other words, patients with preserved intellectual profiles may also demonstrate ‘preserved’ brain structure commensurate with their intellectual and cognitive status. Two patterns of cortical thinning are hypothesized; one pattern that is shared by all patient groups and that distinguishes them from healthy comparison subjects and one that distinguishes

the patient groups from each other and thereby associates with intellectual or cognitive performance.

Based on previous studies, it is hypothesized that patients with both premorbid and morbid intellectual deficits would exhibit more generalized or widespread deficits in cognitive performance, including memory, visuospatial perception, attention, executive function, language, and psychomotor deficits. Correspondingly, it is hypothesized that these findings would associate with widespread cortex dysfunction in the premorbidly impaired group. On the other hand, it is hypothesized that patients with evidence of intellectual decline following the onset of schizophrenia will display impairments in executive functioning, attentional abilities, and memory. This would implicate frontotemporal dysfunction. Finally, it is hypothesized that patients meeting the criteria of intellectual preservation will present with a milder and more limited range of cognitive impairments and demonstrate a less marked neuropathological pattern, with smaller regions of thinning consequent to a cognitively milder form of the disease.

2. Method

2.1 Participants

Patients were recruited from both inpatient and outpatient settings in Hamilton, Ontario, Canada that required active program attendance and comprised vocational and/or social rehabilitation and training activities. Settings included the Hamilton Program for Schizophrenia (HPS), the Community Schizophrenia Service (CSS, St. Joseph's Healthcare Hamilton), the Cleghorn Early Intervention in Psychosis Clinic (St. Joseph's Healthcare Hamilton), the Schizophrenia and Community Integration Service (St. Joseph's Healthcare Hamilton), Schizophrenia Services of Ontario, Hamilton Chapter, Path Employment Services, and the Wellington Psychiatric Outreach Program.

Male and female participants who met the following criteria were included: (1) diagnosis of schizophrenia or schizoaffective disorder by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 2000) criteria confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders-Patient version (SCID; First, Spitzer, Miriam, & Williams, 2002); (2) age 18-65 years; (3) no history of serious neurological or endocrine disorder, including head trauma, epilepsy, Cushing's disease or thyroid disorder; (4) no concurrent diagnosis of substance use disorder; (5) no history of developmental or learning disability; (6) ability to understand spoken English sufficiently to comprehend testing procedures; (7) willingness and ability to sign informed consent; (8) eligibility for MRI scanning procedure and; (9) normal or corrected vision. A total of 71 patients, including 44 males and 27 females, met inclusion criteria. Patients ranged from 20 to 63 years of age, with a mean of 41.27 (SD = 10.63).

Healthy control participants (n = 66) were recruited through local postings and advertisements for paid research participation in community newspapers and online classified advertisements in Hamilton, Ontario and Toronto, Ontario. Potential control participants were screened for medical and psychiatric illness and history of substance use disorders. This recruitment effort yielded 38 males and 28 females, ranging from 19 to 65 years of age, with a mean age of 39.61 (SD = 12.12). All participants provided written informed consent and were paid for their time. The project was approved by the institutional review board at each research site and by the research ethics board at St. Joseph's Healthcare Hamilton and York University.

2.2 Psychopathology Measures

Patients' medical charts were reviewed to determine presence, type (e.g., haloperidol, clozapine, olanzapine) and dose of anti-psychotic medications. The presence and type of other

psychotropic medications were also recorded. Current symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS; Opler, Kay, Lindenmayer, & Fiszbein, 1999). The PANSS provides severity ratings of positive, negative, and general psychiatric symptoms common to patients with schizophrenia based on a semi-structured interview format. More specifically, the positive scale assesses symptoms such as delusions, hallucinations, conceptual disorganization, grandiosity, and persecutory ideation; the negative scale addresses blunted affect, emotional and social withdrawal, poor rapport, and rigidity of attitudes and beliefs. The general scale assesses symptoms such as somatic preoccupation, anxiety and tension, feelings of guilt, depression, odd mannerisms, bizarre thought content, disorientation and insight, and disturbance of volition. Each of the 30 items which constitute these three broad scales is scored on a 7-point scale, with detailed rating anchors ranging from the absence of symptoms to extreme psychopathology. The PANSS has shown high internal reliability and homogeneity among its items, with coefficients ranging from .73 to .83 (Kay, Opler, & Fiszbein, 2000). Furthermore, test-retest reliability indices for unremitted patients ranged from .77 to .89 on the core scales. The positive and negative scales are inversely correlated with each other once their common association with general psychopathology is extracted, supporting their mutually exclusive dimensions. Inter-rater reliability has been shown to vary between .83 and .87.

2.3 Cognitive Performance Measures

Neuropsychological tests measuring several aspects of cognitive brain function were administered to all patients and healthy participants. English language versions of all measures were used. These measures included the Vocabulary and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). The Vocabulary measure is an index of verbal ability, and requires participants to provide word definitions. Matrix

Reasoning provides an index of non-verbal ability, and involves logical reasoning with visual patterns. These two sets of abilities provided an estimate of current IQ. IQ provides a single, global metric that reflects the overall intellectual ability of an individual and is believed to reflect enduring cognitive traits. Notably, the two-subtest WASI does not include measures of working memory or processing speed. Consequently, WASI-estimated IQ scores are likely to be higher than actual Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997) and WAIS-IV (Wechsler, 2008) scores.

The Reading subtest of the Wide Range Achievement Test – Fourth Edition (WRAT-4; Wilkinson & Robertson, 2006), which requires individuals to read aloud a list of words with increasingly more difficult pronunciations, was used to estimate premorbid intellectual ability. As previously stated, the Reading subtest of the WRAT4 is thought to reflect preserved abilities, since it is a test of decoding skills normally acquired before the onset of disease and appear to be less vulnerable than other abilities to several neurological and psychiatric disease processes including schizophrenia (Allen et al., 2003; Goldberg et al., 1995; Harvey et al., 2000; Kremen et al., 1996; Warnock et al., 2000).

The MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB) was also administered (Nuechterlein et al., 2008). The standardized battery includes 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 and memory (Hopkins Verbal Learning Test-Revised), visual learning and memory (Brief Visuospatial Memory Test-Revised), reasoning and problem solving (Mazes [Neuropsychological Assessment Battery]), and social

cognition (Mayer-Salovey-Caruso Emotional Intelligence Test [MSCEIT]). It also yields a composite index of overall performance. The battery is regarded by experts as pertinent to schizophrenia and schizophrenia-related disorders and was formulated following a broad-based consensus process including the academic community and the National Institutes of Health (NIH; Nuechterlein et al., 2004). It is the only measure of cognitive performance that was developed under NIMH contract with contribution from the U.S. Food and Drug Administration. Consequently, it is recommended for all clinical trials of cognition-enhancing medications for schizophrenia. The selection of tests was based on considerations of efficiency, validity and reliability, and the nature and number of separable ability factors underpinning cognitive performance in schizophrenia patients (Nuechterlein et al., 2004).

In addition, four specialized cognitive neuropsychiatry tests of biased reasoning, cognitive processing style, and social cognition were administered. Biased probabilistic reasoning was measured with a recent modification (Speechley, Whitman, & Woodward, 2010) of the standard 'jumping to conclusions' task initially developed by Garety and colleagues (Garety et al., 1991). In this probabilistic reasoning task (also known as the "Beads Task"), subjects judged which of two jars a sequence of coloured beads had been taken from. Difficulty was manipulated by varying the ratios of coloured beads in the jars. After each bead was drawn, participants were asked if they would like to see more beads (i.e., if they would like more information) or if they could say, with certainty, from which of the jars the beads were being drawn. The key variable was the number of beads requested by the participant before making a decision.

Two aspects of social cognition with established sensitivity to positive symptoms were also assessed: an externalizing attribution tendency and theory-of-mind. As previously stated,

patients with delusions have difficulty imagining the intentions of others (Corcoran et al., 1995; Frith & Corcoran, 1996; Brüne, 2005) and tend to blame others for negative events (Kinderman & Bentall, 1996). Externalizing attributions for negative events were measured with the Internal, Personal and Situational Attributions Questionnaire (IPSAQ), which was developed and validated by Kinderman and Bentall (1997) as well as by independent investigators (Donohoe et al., 2008; Mizrahi, Addington, Remington, & Kapur, 2008). The IPSAQ is composed of 32 hypothetical social situations, half depicting situations with positive outcomes and half depicting situations with negative outcomes. The respondent is asked to provide the one most likely causal explanation for each situation. The respondent is then asked to classify this cause as being something due to themselves (internal attribution), something due to another person or persons (external-personal), or something due to the circumstances or chance (external-situational).

Theory-of-mind or reasoning about the mental states of other people was measured with the Faux Pas Recognition Test (Stone, Baron-Cohen, & Knight, 1998; Gregory et al., 2002) and the Reading the Mind in the Eyes test (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). The Faux Pas is a verbal task that requires that the participant recognize whether a character in a short story may have inadvertently hurt the feelings of someone else, whereas the Reading the Mind in the Eyes test is a visual task that requires making deductions about the emotions from images of different people's eyes. All measures were administered and scored by trained clinical research assistants using standard administration instructions and guidelines provided in the manuals.

2.4 Classification of Participants

As previously mentioned, current intellectual functioning was estimated based on the Vocabulary and Matrix Reasoning subtests of the WASI, from which reliable estimates of Full

Scale IQ (FSIQ) can be derived (Wechsler, 1999). An estimate of prior intellectual function was obtained from the Reading subtest of the the Wide Range Achievement Test – 4th Edition (WRAT-4, Wilkinson & Robertson, 2006), which measures recognition and pronunciation of printed words. Based on the categorization method previously described by Weickert and colleagues (2000), patients were classified into three distinct intellectual level subgroups as follows: (1) those displaying a decline in IQ (≥ 10 points) as evidenced by the difference between current IQ (based on a 2-subtest version of the WASI) and premorbid IQ (based on WRAT-4 Reading standard score), who will be referred to as intellectually deteriorated (n = 14); (2) those displaying both premorbid and current IQ estimates below 90 and no evidence of IQ decline greater than 10 points, who will be referred to as premorbidly impaired (n=14), which is consistent with the work of David and colleagues (1997) and with conventional usage (less than the 16th percentile, Wechsler, 1997); and (3) those whose premorbid and current IQ estimates were above 90 and who demonstrated less than a 10-point difference between their premorbid IQ based on WRAT-4 Reading and their current IQ based on the WASI, who will be referred to as intellectually preserved (n=29). Existence of a 10-point IQ decline took precedence to either of the cut-off strategies described. The control group met criteria for the preserved pattern (n=36). This classification method has been consistently used by investigators examining preserved, deteriorated, and premorbidly impaired intellect in patients with schizophrenia (e.g., Ammari et al., 2014; Badcock et al., 2005; Wells et al., 2015).

2.5 MRI Acquisition Parameters

All participants underwent MRI scanning at the Brain Imaging Research Centre, Brain-Body Institute, St. Joseph's Healthcare Hamilton. Scans were acquired using a 3.0 Tesla whole body short bore General Electric MRI scanner with an 8-channel parallel receiver head coil. High-

resolution images were obtained with a T1-weighted three-dimensional (3D) fast spoiled gradient (SPGR) echo sequence with inversion recovery preparation. The anatomical image had 152 slices (2 mm thick with 1 mm overlap) with the following imaging parameters: time to repetition (TR)/ echo time (TE) = 7.5/2.1 ms, TI = 450 ms, field of view (FOV) = 24 cm, acquisition matrix size = 512 x 512, flip angle = 12^{o}, receiver bandwidth (rBW) = +/-62.5 kHz, and number of excitations (NEX) = 1.

2.6 MRI Processing

The structural T1-weighted images collected for each participant were pre-processed in order to segment the brain and to align cortical structures across the subjects using the FreeSurfer toolkit version 5.1.0 (http://surfer.nmr.mgh.harvard.edu; Dale, Fischl, & Sereno, 1999; Fischl, Sereno, & Dale, 1999). Cortical thickness was defined as the distance between pial surface to the gray/white matter border at each vertex. Each MR image was intensity corrected, skull stripped and then automatically segmented into gray and white matter volumes. These segmentations were then manually inspected and edited for accuracy according to established guidelines (Segonne, Pacheco, & Fischl, 2007). This method uses both intensity and continuity information from the entire three dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl & Dale, 2000). A 2-dimensional smoothing kernel was applied along the cortical surface with a 20mm full-width/half-maximum window. Spherical maps for each subject were morphed into a common spherical atlas using a nonlinear surface-registration procedure that allows for high-registration, surface-based averaging, and comparison of cortical measurements across subjects.

2.7 Statistical Analyses

The Statistical Package for the Social Sciences (SPSS), Version 23.0, was used for data analysis. Independent sample *t*-tests and Chi-square statistics were used to examine differences in demographic variables. Other statistical tests for the analysis of categorical data were considered, but the Chi-square statistic was deemed to be the most suitable. Group comparisons on symptom and neuropsychological measures were conducted using analysis of variance (ANOVA) models and planned comparisons, followed by Bonferroni post hoc comparisons. Predictions that specify directionality used 1-tailed tests and all others used 2-tailed tests. The same statistical analysis applied to test the prediction regarding the cognitive neuropsychiatry measures.

Scans were analyzed and processed using FreeSurfer release 5.1.0. Surfaced-based analysis of cortical thickness involved generation of statistical surface maps utilizing a general linear model to display differences in thickness between groups at every vertex. Key demographic variables were not controlled, as these variables did not statistically differ between groups. False Discovery Rate (FDR), which controls for the expected proportion of false positives in a statistical test, was applied to adjust for multiple comparisons at a value of 0.05 (Genovese, Lazar, & Nichols, 2002). Based on anatomical boundary schemes from FreeSurfer, regions of interest (ROIs) were mapped across all subjects and mean per hemisphere thickness values were derived. The region of interest means were then entered as dependent variables in analysis of variance (ANOVA) models, followed by Bonferroni post hoc comparisons.

3. Results

3.1 Clinically-based Subgrouping Analyses

Of the 96 patients recruited, intellectual decline of at least 10 points from premorbid

levels as measured by WRAT-4 Reading occurred in approximately 20% (n=14) of the patients (the intellectually deteriorated group). Similarly, approximately 20% (n=14) showed low premorbid intellect based on WRAT-4 Reading scores, combined with low average current IQ (the premorbidly impaired group). Approximately 40% (n=29) of the patients were classified as intellectually preserved with both current and premorbid IQ based on WRAT-4 Reading scores within normal limits. Roughly 80% of the patient sample was captured by these psychometrically-defined groups. Table 3 provides the mean IQ and WRAT-4 Reading standard scores for patients and controls.

3.2 Demographic Characteristics

Demographic characteristics of the patient groups and comparison controls are presented in Table 1. The patient groups ranged from 20 to 63 years of age, whereas the healthy control group varied from 19 to 64. All groups were predominately male and Canadian-born, with English as their first spoken language. There were no significant group differences in age, sex composition, or in years of education.

3.3 Clinical Characteristics of Patient Groups

Clinical characteristics of the patient groups are presented in Table 2; these include the PANSS subscales, ratio of inpatients in each patient group, ratio of patients with schizoaffective disorder in each patient group, duration of illness, and current medications. Duration of illness was measured from the time of each patient's first treatment or hospitalization. On the basis of a χ^2 analysis, diagnosis (schizophrenia vs. schizoaffective disorder) and psychiatric treatment (inpatient vs. outpatient) were not found to be significantly associated with the intellectual subgroups. As seen in Table 2, all patient groups were comprised predominantly of outpatients, with the average being approximately 86% (range 79-90%). The rates of schizoaffective disorder

were comparable across the three patient groups, with the average being approximately 44% (range 29-52%). Patient groups also did not differ in duration of illness, with the average being approximately 18 years (range 14.9-21.1 years). Finally, patient groups did not differ in frequency of treatment with second-generation antipsychotic medication, anti-Parkinson medication, antidepressant medication, anxiolytics, or lithium. At the time of testing, most patients (86%) were receiving atypical neuroleptic medications, usually Clozaril (clozapine), Risperdal (risperidone), Seroquel (quetiapine), or Zyprexa (olanzapine). Approximately 35% of patients were taking antidepressant medication, 28% were receiving anxiolytics, 14% were taking anti-Parkinson medication, and 12% were receiving lithium.

As indicated in Table 2, a univariate *F* test indicated a significant main effect of Group ($F(2, 54) = 3.67$, $p = .032$) for the positive subscale of the PANSS. Although post hoc *t* tests (with Bonferroni adjustment) showed that patients with premorbid impairments experienced higher rates of positive symptoms compared to the patients with preserved abilities, this only approached statistical significance ($p = .053$). The schizophrenia patient groups did not differ significantly in terms of the severity of negative or general symptoms. All patient subgroups were also indistinguishable in activation symptoms; thought disturbance; paranoia; anergia; and depression (see Table 2).

3.4 Neurocognitive Performance

Cognitive data for the four groups are presented in Table 3. As expected, given the basis for the classification scheme used to categorize patients into subgroups, there were significant differences in premorbid and current IQ scores as measured by the WRAT-4 and WASI, respectively. Bonferroni comparisons identified that patients with preserved intellect had significantly higher scores than patients with either deteriorated or premorbidly impaired intellect

for both WRAT-4 ($p_{DP, IP} < .001$) and WASI IQ scores, ($p_{DP, IP} < .001$). In addition, patients with deteriorated intellect had higher WRAT-4 scores than patients with premorbidly impaired intellect ($p = .005$).

MCCB performance profiles of the patient and control groups are presented in Figure 1. As indicated in Table 3, Univariate *F* tests indicated a significant main effect of Group for the composite score of the MCCB (F (3, 89) = 70.31, $p < .001$) and for each domain as follows: Speed of Processing (F (3, 89) = 27.88, $p < .001$), Attention/Vigilance (F (3, 89) = 25.96, $p < .001$), Working Memory (F (3, 89) = 35.90, $p < .001$), Verbal Learning (F (3, 89) = 30.82, $p < .001$), Visual Learning (F (3, 89) = 27.07, $p < .001$), Reasoning and Problem Solving (F (3, 89) = 22.05, $p < .001$), and Social Cognition (F (3, 89) = 10.78, $p < .001$). Compared to deteriorated and premorbidly impaired patients, post hoc *t* tests with Bonferroni adjusted *p* values showed that intellectually preserved patients achieved significantly higher scores on the composite score of the MCCB ($p_{DP, IP} < .001$) and on six out of the seven individual domains: Speed of Processing ($p_{DP} = .001$, $p_{IP} = .005$), Attention/Vigilance ($p_{DP, IP} < .001$), Working Memory ($p_{DP, IP} < .001$), Verbal Learning ($p_{DP, IP} < .001$), Visual Learning ($p_{DP, IP} < .001$), and Social Cognition ($p_{DP} = .003$, $p_{IP} = .047$). Furthermore, preserved patients and healthy control participants did not differ on the attention/vigilance, working memory, visual learning and memory, and social cognition domains of the MCCB. However, preserved patients scored lower than the healthy control participants on the composite score of the MCCB ($p < .001$) and on the processing speed ($p < .001$), verbal learning and memory ($p = .014$), and reasoning/problem solving ($p < .001$) subscales. Patients with deteriorated and premorbidly impaired profiles were statistically equivalent on all MCCB indicators.

On a test measuring biased probabilistic reasoning (Beads task), a univariate *F* test

indicated a significant main effect of Group (F (3, 89) = 4.15, p = .008). Post hoc t tests with Bonferroni adjusted p values showed that deteriorated patients scored lower than preserved patients (p = .026) and control participants (p = .039). There were no differences between patients with deteriorated and premorbidly impaired profiles on this task. On a test measuring an externalizing attribution tendency (IPSAQ), there were no significant differences between any of the groups. On the verbal theory-of-mind measure (Faux Pas), a univariate F test indicated a significant main effect of Group (F (3, 89) = 20.90, p < .001). Post hoc t tests with Bonferroni adjusted p values showed that deteriorated and premorbidly impaired patients scored lower when compared to preserved patients ($p_{DP, IP}$ < .001) and healthy participants ($p_{DP, IP}$ < .001). There were again no differences between patients with deteriorated and premorbidly impaired profiles on this task. On the visual theory-of-mind measure (Reading the Mind in the Eyes), a univariate F test indicated a significant main effect of Group (F (3, 89) = 39.26, p < .001). Post hoc t tests with Bonferroni adjusted p values showed that all patient groups scored lower than the control group (p_{PP} = .03, $p_{DP, IP}$ < .001). However, preserved patients achieved significantly higher scores on this measure when compared to deteriorated and premorbidly impaired patients ($p_{DP, IP}$ < .001). There were no differences between patients with deteriorated and premorbidly impaired profiles on this task.

3.5 Group Differences in Vertex-Based Cortical Thickness

When all schizophrenia patients, regardless of their intellectual subtype classification, were compared to healthy control participants, statistical surface thickness maps revealed prominent thinning of the cortex (Figure 2). Regions included right hemisphere supramarginal and lateral occipital areas, as well as selective bilateral thinning in the superior, middle, and inferior temporal gyri. On the medial aspects, right hemisphere precuneus and bilateral lingual

and fusiform thinning was also present, with some mild involvement of the left posterior cingulate. Examination of cortical thickness mapping in preserved patients, contrasted with control subjects (Figure 3), revealed a pattern similar to that above. Namely, thinning in left hemisphere inferior parietal and fusiform regions, as well as right hemisphere supramarginal areas. In addition, there was bilateral thinning in the posterior cingulate and in the superior, middle, and inferior temporal gyri. All of these results met FDR (false-discovery rate) correction for multiple comparisons at a rate of $p < 0.05$.

Examination of cortical thickness mapping in premorbidly impaired patients, contrasted with control subjects (Figure 4), revealed trend thinning in frontal and temporal regions; however, these differences did not survive FDR correction for multiple comparisons. Initial examination of cortical thickness mapping contrasting the three patient groups revealed mild thinning in different brain regions, but none survived FDR correction for multiple comparisons, indicating a lack of significant vertex-wise cortical thinning between these three patient groups. Uncorrected statistical maps revealed trend cortical thinning between the deteriorated and premorbidly impaired patient groups (Figure 5) in frontal and temporal regions, but none of these findings survived FDR correction for multiple comparisons.

3.6 Group Differences in ROI-based Cortical Thickness

The widespread thinning pattern in schizophrenia patients (Figure 2) was used as the basis for a focused ROI approach. Comparison of thickness values within the thinning pattern ROIs revealed several significant differences between groups (Table 4). For preserved patients and controls, significant differences were evident in the right superior temporal sulcus ($p = .017$), left fusiform gyrus ($p = .004$), and right frontal pole ($p = .013$), as well as in bilateral inferior parietal cortex ($p_{\text{Right}} = .026$; $p_{\text{Left}} = .030$), middle temporal gyri ($p_{\text{Right}} = .002$; $p_{\text{Left}} = .002$), and

supramarginal areas ($p_{Right} = .002$; $p_{Left} = .035$). For premorbidly impaired patients and controls, significant differences were noted in the right superior temporal sulcus ($p = .032$), inferior parietal lobule ($p = .041$), middle temporal gyrus ($p = .025$), and precuneus ($p = .047$), as well as bilateral fusiform regions ($p_{Right} = .031$; $p_{Left} = .003$). For deteriorated and preserved patients, significant differences were evident in the left lateral orbitofrontal cortex ($p = .012$) and the pars triangularis of the inferior frontal gyrus ($p = .017$). The deteriorated and premorbidly impaired patients differed in only one area, the left *pars triangularis* of the inferior frontal gyrus ($p = .029$).

Discussion

There is increasing consensus that schizophrenia is not a single disease, but rather a collection of several overlapping illnesses. Although most patients demonstrate a generalized deficit across multiple cognitive domains assessed by widely used clinical neuropsychological measures, there is extensive variability in the extent of impairment. Thus, several attempts have been made to organize the illness into more homogeneous groups of patients, with hopes of providing insight to a more accurate definition of schizophrenia. The aim of the present investigation was to identify and estimate the prevalence of intellectual performance patterns corresponding to preserved, deteriorated, and premorbidly impaired ability, and to examine the value and validity of this approach for reducing the heterogeneity of schizophrenia. The intellectual subtypes were compared on independent adjunct measures of cognitive ability and symptom profile and severity. Neuroanatomical characteristics of these subtypes were also investigated in order to better understand the relationship between intellectual or cognitive impairment and neuropathology in schizophrenia.

The findings of the present investigation confirm previous research demonstrating three

distinct neuropsychological profiles in schizophrenia and may provide further insight into the developmental processes involved. On the basis of widely used indicators of current and premorbid IQ, this study successfully identified the proposed intellectual subtypes; one representing preserved intellectual ability (i.e., preserved patients; PP), another representing a deteriorated pattern (i.e., deteriorated patients; DP), and a third representing a premorbidly impaired patient group (i.e., impaired patients; IP). Roughly 80% of the patient sample was distributed across these psychometrically-defined groups. Approximately 40% of the patient sample was identified as being intellectually preserved, which is consistent with the percentages found in some other studies. Using similar means of estimating current and premorbid IQ to identify schizophrenia patients as being intellectually preserved, several investigations reported a 25-40% overall prevalence of intellectual preservation in schizophrenia (Ammari et al., 2014; Badcock et al., 2005; Weickert et al., 2000; Wells et al., 2015). The intellectually deteriorated subtype constituted approximately 20% of the original patient sample, which is somewhat lower than the 25-50% overall prevalence found in some other studies (Ammari et al., 2014; Badcock et al., 2005; Weickert et al., 2000; Wells et al., 2015). The reason for the discrepancy is unclear given that similar classification criteria and means of estimating current and premorbid IQ were utilized in this study. There is also no reason to suspect that the sample is not representative of the schizophrenia patient population since similar prevalence rates of intellectual preservation reported by other investigators were observed in this study. Further, total patient mean IQ of approximately 89 in this study is consistent with others, and the sex ratios are also similar to those reported by others (Ammari et al., 2014; Lieberman et al., 1992; Mortensen et al., 1999). Finally, the premorbidly impaired subtype also constituted approximately 20% of the original patient sample, which is consistent with the percentages found by other investigators (Ammari et

al., 2014; Badcock et al., 2005; Weickert et al., 2000; Wells et al., 2015). Inevitably, the findings of this study will pertain to only a subset of patients, reflecting the inherent heterogeneity of the schizophrenia diagnosis. Nevertheless, a considerable proportion of the original patient sample, approximately 80%, was captured by this intellectual typology.

Preserved Group

The data of the present investigation provide partial validation of the three proposed intellectual subtypes as distinct illness variants. In keeping with prior studies, the results confirm the existence of a subgroup of schizophrenia patients with preserved intellectual abilities. Intellectually preserved patients reported similar levels of symptom severity relative to intellectually deteriorated and premorbidly impaired patients. This was the case across all symptom indicators including positive, negative, and general symptoms. Intellectually preserved patients were also indistinguishable from the other patient subtypes in activation symptoms; thought disturbance; paranoia; anergia; and depression. This suggests no attenuation of the psychotic process in these patients.

The abilities of intellectually preserved patients in several aspects of cognition (e.g., attention, working memory, visual learning and memory, and verbal measures of social cognition) approximated those of healthy adults. However, this preserved intellectual ability level did not associate with complete normality of cognitive skills. The preserved patients scored lower than the healthy control participants on indictors of processing speed, verbal learning and memory, reasoning/problem solving, and on a visual theory-of-mind measure. Nevertheless, intellectually preserved patients did show an advantage relative to more typical patients (i.e., patients with deteriorated or premorbidly impaired intellect) on indicators of processing speed, attention, working memory, verbal learning and memory, visual learning and memory, and social

cognition including theory-of-mind. This suggests that intellectual preservation in schizophrenia associates with significantly better cognitive ability across multiple domains. The only exception was on a test measuring reasoning and problem solving (‘Mazes’ task), in which there were no significant differences between the patient groups. The lack of between-group differences among patients on the reasoning/problem solving domain of the MCCB may be explained by reduced sensitivity of the ‘Mazes’ task to executive dysfunction. Consistent with this, other investigators found that this domain does not appear to be sensitive to impairment in schizophrenia patients as it has the smallest between-group differences when compared to controls (Gray et al., 2013). Other measures of problem solving, such as the Wisconsin Card Sorting task, often engender evidence of a greater gap between schizophrenia patients and controls. Intellectually preserved patients also outperformed those with a deteriorating pattern on a measure of probabilistic reasoning, suggesting that they are less likely to ‘jump to conclusions’ prematurely. Therefore, chronic schizophrenia can exist in the context of preserved general intellectual ability and at least some additional aspects of cognition.

In terms of biological validity, cortical thickness mapping in intellectually preserved patients revealed a pattern of widespread thinning in the cortex when compared to healthy control participants. More specifically, there was significant thinning in left hemisphere inferior parietal and fusiform regions, as well as right hemisphere supramarginal areas. Furthermore, there was bilateral thinning in the posterior cingulate and in the superior, middle, and inferior temporal gyri. When a focused ROI approach was employed, significant differences were evident between preserved patients and controls in the right superior temporal sulcus, left fusiform gyrus, and right frontal pole, as well as in bilateral inferior parietal cortex, middle temporal gyri, and supramarginal areas. Notably, this pattern of thinning was similar to that

observed in the other patient groups.

When intellectually preserved patients were compared to the other patient groups, differences emerged between the preserved and deteriorated patients in the left lateral orbitofrontal cortex and the pars triangularis of the inferior frontal gyrus. There were no significant differences between the preserved and premorbidly impaired patient groups. That the premorbidly impaired group demonstrates no neurobiological differences from the preserved group, yet significantly differs from them on most cognitive measures is surprising. Indeed, one would expect the biggest differences between these two groups given their markedly distinct cognitive profiles. Nevertheless, uncorrected contrast maps for these comparisons suggest trend differences, indicating subtle characteristics unique to these groups may exist.

Deteriorated Group

The findings of this study also support the existence of a subgroup of schizophrenia patients displaying a general intellectual decline from estimated premorbid levels based on WRAT-4 Reading scores. This diminution was obtained in only 20% of patients in this sample. In terms of symptom profile, patients with deteriorated intellect reported similar levels of symptom severity compared to the other patient subtypes. Cognitively, patients with this deteriorated intellectual pattern performed lower than healthy control participants on all measures of neurocognitive functioning assessed. They were also significantly impaired relative to intellectually preserved patients on all cognitive measures with the exception of reasoning and problem solving (‘Mazes’ task). They were also disadvantaged relative to preserved patients on specialized cognitive neuropsychiatry tests tapping biased reasoning and theory-of-mind. Unlike previous findings, intellectual decline appears to affect all cognitive domains equally in this study. Weickert and colleagues (2000) found that intellectual decline observed in the deteriorated

patient group was implicated with frontotemporal dysfunction in that patients had impairments in memory, executive function, and attention. In this study, intellectual decline was also associated with deficits in processing speed and social cognition. Compared to patients with premorbid impairments, they were indistinguishable on all domains of neurocognitive functioning assessed, including specialized cognitive neuropsychiatry tests tapping biased reasoning and theory-of-mind.

Regarding biological validity, cortical thickness mapping in intellectually deteriorated patients revealed a pattern of widespread thinning in the cortex similar to that seen in the other patient groups when they were compared to healthy control participants. When compared to premorbidly impaired patients, uncorrected statistical maps revealed trend cortical thinning in frontal and temporal regions, but none of these findings survived FDR correction for multiple comparisons. When a focused ROI approach was employed, the deteriorated and premorbidly impaired patients differed in only one area, the left *pars triangularis* of the inferior frontal gyrus. As stated above, significant differences were evident between deteriorated and preserved patients in the left lateral orbitofrontal cortex and the pars triangularis of the inferior frontal gyrus.

Premorbidly-Impaired Group

Finally, the findings support the existence of a subgroup of schizophrenia patients having a premorbid intellectual impairment with no evidence of disease-related decline following the onset of illness. This suggests that their intellectual deficit is not attributable to symptom onset or diagnosis. In terms of symptom expression, this patient subtype did not associate with a unique clinical profile as similar levels of symptom severity were reported by these patients compared to the other patient subtypes. From a cognitive standpoint, patients with this premorbidly impaired intellectual pattern performed lower than healthy control participants on all measures of

neurocognitive functioning assessed. They were also significantly compromised relative to intellectually preserved patients on most measures of cognitive functioning assessed; the only exception being reasoning and problem solving. Further, they were disadvantaged relative to preserved patients on specialized theory-of-mind tests. Compared to patients displaying a pattern of deteriorated intellect, they were indistinguishable on all domains of neurocognitive functioning, including specialized cognitive neuropsychiatry tests tapping biased reasoning and theory-of-mind.

In terms of biological validity, cortical thickness mapping in premorbidly impaired patients revealed trend thinning in frontal and temporal regions when compared to healthy controls, but none of these findings survived FDR correction for multiple comparisons. When a focused ROI approach was employed, significant differences were noted in the right superior temporal sulcus, inferior parietal lobule, middle temporal gyrus, and precuneus, as well as bilateral fusiform regions. When premorbidly impaired patients were compared to the other patient groups, uncorrected statistical maps revealed trend cortical thinning between the premorbidly impaired and deteriorated patient groups in frontal and temporal regions, but again none of these findings survived FDR correction for multiple comparisons. When a focused ROI approach was employed, the premorbidly impaired and deteriorated patients differed in only one area, the left *pars triangularis* of the inferior frontal gyrus.

Cognitive and Symptom Validity of the Intellectual Subtypes

Demonstrating the value and construct validity of particular psychometric performance patterns is particularly challenging for investigators attempting to reduce the heterogeneity of the schizophrenia diagnosis by identifying more homogeneous groups of patients. It appears that the criteria utilized in this study for defining intellectual preservation in schizophrenia produced a

partially valid subgroup. Intellectually preserved patients were indistinguishable from healthy control participants on a number of neurocognitive measures assessed, including attention, working memory, visual learning and memory, and social cognition. However, they scored lower than controls on indictors of processing speed, verbal learning and memory, and reasoning/problem solving. This is consistent with previous reports in which direct comparison with healthy control participants has often found disparities in certain abilities including abstraction and executive functioning (Allen et al., 2003; Kremen et al., 2000; Weickert et al., 2000) and attention (Kremen et al., 2001). Indeed, some have concluded that executive dysfunction often coexists with preserved IQ and may constitute a "necessary type of cognitive impairment in schizophrenia" (Weickert et al., 2000). There is also a longstanding notion in the literature that reduced processing speed is a characteristic feature of schizophrenia that does not preclude relatively preserved performance on IQ measures (Badcock, Williams, Anderson, & Jablensky, 2004; Dickinson et al., 2008; Pantelis et al., 1997; Hartman, Steketee, Silva, Lanning, & McCann, 2002; Vaskinn et al., 2014; Vinogradov et al., 2003; Wilk et al., 2005). Therefore, the findings from this study lend support to the idea that cognitive impairment is a core feature of schizophrenia present to some degree in all patients, regardless of whether or not intellectual abilities are preserved. Thus, using neurocognition as a biomarker in genetic studies is warranted. In terms of psychopathological validity, intellectually preserved patients reported similar levels of symptom severity relative to intellectually deteriorated and premorbidly impaired patients, suggesting that improved intellect and cognition do not associate with a symptomatically milder form of the disease. This is inconsistent with other studies showing that patients in the preserved group show less negative symptoms than their impaired counterparts (Donohoe et al., 2006; MacCabe et al., 2012; Wells et al., 2015).

The case for the deteriorated and premorbidly impaired groups as distinct illness variants is more equivocal and cannot be determined definitively using the available data. There was no evidence that these two intellectual patterns map onto current clinical or neuropsychological status. The deteriorated and premorbidly impaired groups were statistically equivalent on all clinical and neurocognitive measures assessed. Indeed, the evidence strongly suggests that patients in the deteriorated and premorbidly impaired groups are better represented by one intellectually/cognitively impaired illness variant. Therefore, it may be more useful to collapse rather than separate these patient groups. One explanation for their resemblance may be that the reading-IQ ratios utilized in this study are simply non-pathological psychometric artifacts that also occur in healthy populations. Indeed, previous research found that the deteriorated pattern does in fact exist in the general population. For example, Ammari and colleagues (2014) found that approximately 11% of their healthy control sample showed the average reading-below average IQ "deterioration" profile. Therefore, premorbid-current IQ discrepancies may signify differential patterns of intellectual development and present capacity that are not unvaryingly or intrinsically pathological and without direct consequences for more comprehensive neurocognitive functioning. Therefore, although it is well established that the extent of cognitive dysfunction or relative absence of any cognitive impairment is a characterizing aspect of the schizophrenia illness, patient subgroups distinguished on the basis of reading and IQ scores may not reduce or help advance the heterogeneity issue in schizophrenia.

An alternative explanation for the equivalence between the deteriorated and premorbidly impaired groups is that a neurodevelopmental mechanism still underlies the cognitive impairments observed in the deteriorated subtype, since discreet neurodevelopmental alterations may pave the way for delayed psychiatric disturbance and cognitive deficits (Weinberger, 1987).

Indeed, one may propose several theoretical neurodevelopmental courses that ultimately give rise to the cognitive impairments observed in schizophrenia, including those in intelligence. One trajectory may be exemplified by profound and pervasive cognitive impairment discernible from early development long before the onset of any psychotic symptoms. Both the deteriorated and premorbidly impaired groups may follow that trajectory, albeit the former may be characterized by more subtle neurodevelopmental changes and may donate the appearance of deterioration coinciding with psychotic symptom onset. The preserved patient group may constitute a discrete subgroup of patients within the schizophrenia patient population who have suffered less neurodevelopmental damage than other more typically impaired patients (MacCabe, Aldouri, Fahy, Sham, & Murray, 2002; Murray, O'Callaghan, Castle, & Lewis, 1992). As a result, they have milder cognitive impairments, seemingly limited to the domains of processing speed, verbal learning and memory, and reasoning/problem solving. It is indeterminate at this time whether these impairments occur prior to or concur with the onset of psychotic symptoms.

Neurobiological Validation of the Intellectual Subtypes

As previously mentioned, only a small number of studies have investigated differences in the brain structure of subgroups in schizophrenia grouped according to neuropsychological profiles, and almost no available data bears on the neurobiological validity of the proposed intellectual subtypes. Biological validation of the proposed intellectual subtypes requires the demonstration that differences in intellectual patterns between the patient groups correspond to neurobiological differences. Woodward and Heckers (2015), the only study of brain structure abnormalities in intellectually-defined subgroups of schizophrenia patients, found that those with below-average estimated premorbid ability exhibit evidence of early cerebral hypoplasia, whereas intellectually preserved and deteriorated patients show evidence of brain tissue loss

consistent with progression or later cerebral dysmaturation. However, this study did not include an analysis of cortical thinning patterns in the proposed intellectual subgroups.

In the present study, the findings are consistent with previous reports that structural aspects of the cerebral cortex distinguish schizophrenia patients from healthy control participants. On the other hand, the neurobiological evidence bearing on the validity of the proposed intellectual subtypes is feeble. Although some trend differences emerged, the overall cortical thinning pattern was largely similar across the intellectual subtypes. Therefore, cortical thinning across the brain appears to reflect a shared disease process in schizophrenia with no association to intellectual or cognitive profile. Consequently, it is likely that a mutual neural mechanism begets the clinical symptoms in schizophrenia and that a separate mechanism underlies cognitive task performance (Dominguez et al., 2009). Specifically, the data does not support the notion that intellectually preserved patients may be a distinct subgroup within the schizophrenia patient population since they share a similar widespread cortical thinning pattern with more typical patients (i.e., those with deteriorated or premorbidly impaired intellect) when compared to healthy control participants. Therefore, the intellectually preserved subtype appears to be an aggregate of patients with less severe cognitive impairments; however, this cognitive advantage does not extend to a milder neurobiological form of the disorder evidenced by less marked neurobiological abnormalities than those observed in patients with deteriorated and premorbidly impaired intellect. This in inconsistent with other studies showing that cortical thinning is minimal in patients with normal or near-normal cognitive performance (Cobia et al., 2011).

The case for the deteriorated and premorbidly impaired groups as biologically distinct illness variants is even weaker. Although uncorrected statistical maps revealed trend cortical

thinning between the deteriorated and premorbidly impaired patient groups in frontal and temporal regions, none of these findings survived FDR correction for multiple comparisons. When a focused ROI approach was employed, the deteriorated and premorbidly impaired patients differed in only one area, the left *pars triangularis* of the inferior frontal gyrus, a region associated with the cognitive control of memory and in the semantic processing of language (Badre & Wagner, 2007; Mainy et al., 2007). Wisco and colleagues (2007) presented data showing that the *pars triangularis* specifically was highly distorted in schizophrenia patients compared with demographically matched control participants. They asserted that Broca's area is an especially plastic region of the brain in that its morphology can change dramatically from childhood to adulthood. This would be consistent with the notion that a neurodevelopmental mechanism underlies the cognitive impairments observed in the premorbidly impaired patient group. Nevertheless, despite this one difference, comprehensive neuroanatomical data provide little support for the distinctiveness of deteriorative relative to premorbid intellectual compromise.

IQ as a normality criterion

A complicating factor in the study of cognitive subtypes in schizophrenia is the nature of the criteria utilized to denote cognitive normality or preservation. It is well established that schizophrenia can occur in the relative absence of cognitive impairment in a minority of patients; however, definitions of cognitive normality in the literature are inconsistent and controversial. IQ is a universally used measure and one of the most often utilized methods for defining normality (e.g., Kremen et al., 2001). However, summary indices like IQ may be overly restrictive since they are obtained by collapsing across a number of subtests, likely concealing cognitive strengths and weaknesses in patients relative to healthy control participants (Wilk et al., 2005). The fact

that preserved patients still demonstrate deficiencies in processing speed, verbal learning and memory, and reasoning/problem solving when compared directly with healthy control participants suggests that general intellectual ability fails to capture the true breadth of cognitive impairment expressed in schizophrenia. Others have also found that patients show evidence of greater neuropsychological impairment than what would be expected based solely on their IQ (e.g., Gray et al., 2013; Vaskinn et al., 2014). It has been argued that more broadly-based measures should be used to determine cognitive normality instead. For example, when the MCCB composite score is used as a normality criterion, no subtest profile differences are found between cognitively normal schizophrenia patients and healthy controls (Muharib et al., 2014).

Cognition and Psychopathology

Impaired cognition is highly prevalent in schizophrenia and seen as a core feature of the illness, and the relationship between cognition and psychopathology has been extensively studied. Consistent with many reports in the literature (e.g., Dibben et al., 2009; Nieuwenstein, Aleman, & de Haan, 2001), data from the present investigation support the notion that cognitive ability and symptom severity represent distinct and dissociable comorbidities or independent disease processes in schizophrenia patients. There were no significant differences in the severity of symptoms between patients with generalized cognitive deficits (deteriorated or premorbidly impaired groups) and those with more limited cognitive impairments (preserved group). Therefore, it is possible for patients with preserved intellectual functioning and limited cognitive dysfunction to experience elevated as well as mild positive and negative symptoms. Contrariwise, patients with more typical generalized intellectual and cognitive deficits may also experience mild or severe symptoms. Indeed, in this study, there is no compelling evidence that any aspect of the clinical illness varies with intellectual or cognitive profile, including illness

duration, medication differences, or rates of schizoaffective disorder. The neurobiological data also support the notion that psychopathology and impaired cognitive functions are facilitated by dual and independent pathologies. Indeed, cortical thinning across the brain appears to reflect the shared psychotic disease process in schizophrenia, whether or not it is accompanied by impairment in the intellectual or cognitive functions assessed by standard performance tasks. Consequently, alternative indicators of neural structure and function should be considered in order to map theoretically useful cognitive-behavioral differences onto parallel pathophysiologies and etiologies.

In keeping with these findings, a large body of evidence suggests weak or absent relationships between the symptomatic and cognitive dimensions of the disorder. More specifically, several investigators have reported no significant differences in positive and negative symptom severities between patients with intellectual or cognitive impairments and patients with relatively normal intellect or cognition (Ammari et al., 2014; Holthausen et al., 2002; Kremen et al., 2000; Palmer et al., 1997; Vaskinn et al., 2014). More recent reviews have substantiated previous reports that associations between psychopathology, especially psychotic symptoms, and many standard cognitive tasks used in clinical neuropsychology, are unimpressive and often absent in schizophrenia (Berenbaum et al., 2008; Dibben et al., 2009; Dominguez et al., 2009). However, these findings contradict numerous studies linking low IQ or cognitive impairment with negative symptoms (e.g., Aleman et al., 1999; Ammari et al., 2010; Basso et al., 1998; Cameron et al., 2002; Cobia et al., 2011; Leeson et al., 2010; Moritz et al., 2001; Nieuwenstein et al., 2001; Stirling, Hellewell, & Hewitt, 1997; Wells et al., 2015). The discrepancy in findings may reflect in part the multiplicity of measures used by researchers to examine IQ or cognitive performance and illness symptoms. Numerous tests and protocols are

utilized with patients with schizophrenia, and it is possible that different measures may be assessing somewhat different facets of the same domain (Vaz & Heinrichs, 2002).

Furthermore, the association between the severity of general psychiatric symptoms and cognitive deficits in schizophrenia has attracted considerable interest in recent years. Several investigators reported that depressive symptoms relate significantly to cognitive test performance (e.g., Brébion, Smith, Amador, Malaspina, & Gorman, 1997; Holthausen, Wiersma, Knegtering, & Van den Bosch, 1999). In contrast to this finding, the severity of depressive symptoms was equivalent in this study between patients with generalized cognitive deficits (deteriorated or premorbidly impaired groups) and those with more limited cognitive impairments (preserved group). Ammari and colleagues (2014), the only study that has examined the symptom profiles of the proposed intellectual subtypes, also reported equivalent rates of general psychiatric symptoms including depression. The depression equivalence across the intellectual subtypes is important because it suggests that IQ profiles and cognitive impairments in schizophrenia are not reducible to the attenuating effects of depression. Overall, this study supports the view that IQ status/cognitive performance and psychopathology are independent in schizophrenia.

Implications

The study of intellectually preserved patients with schizophrenia offers a unique window into the intricacies of the illness and may impart valuable information on both the worth and limits of improved cognitive function in the schizophrenia patient population. Indeed, one of the main incentives for understanding the signature of cognitive impairment in schizophrenia is the relationship between cognitive performance, functional skills, and functional outcome (Bowie & Harvey, 2005). It has been suggested that enhancement in disease-related cognitive impairments (e.g., working memory and attention, learning, etc.) may produce a wide range of benefits in

real-world living for patients suffering from this disabling form of mental illness (Green et al., 2004). Intact social cognition has also been shown to be associated with better daily living skills and community adjustment in patients with schizophrenia (Brekke, Kay, Lee, & Green, 2005; Couture, Penn, & Roberts, 2006; Sergi et al., 2007). Correspondingly, the National Institute of Mental Health – Measurement and Treatment Research to Improve Cognition in Schizophrenia (NIMH-MATRICS) initiative is striving to produce an evaluative framework and instrument base that will endorse and encourage the introduction of a new class of cognitively-enhancing medications in schizophrenia. Indeed, cognitive impairments are now viewed as principal targets of both rehabilitative/remediation and psychopharmacological treatment (Gold, 2004; Marder, 2006a, 2006b, 2006c; Marder & Fenton, 2004; McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007; Reeder, Newton, Frangou, & Wykes, 2004; Stone & Seidman, 2008). The logic behind this initiative is that improving a patient's cognitive status should result in meaningful changes and enhancements in functional status and adjustment. In the present study, the abilities of intellectually preserved patients on tests of attention, working memory, and social cognition approximated those of healthy adults. Therefore, one may argue that these patients allow for the unique opportunity to view the upper limit of functionality that can potentially be acquired from these proposed medications.

In addition, subtyping based on neuropsychological data in schizophrenia has important practical implications since more refined behavioural profiles may be relevant to clinical management, cognitive enhancement, and rehabilitation, both for new intake and existing patients with schizophrenia. For example, in view of mounting evidence that IQ and cognitive performance are associated with enhanced ability to manage the responsibilities and stressors of daily living and better overall outcome (e.g., Leeson, Barnes, Hutton, Ron, & Joyce, 2009; Wells

et al., 2015), intellectual preservation may be viewed as a protective factor and may prove to be a positive prognostic marker for the long-term functional outcome status of schizophrenia patients. Although research has shown that intellectually preserved patients do not show complete normalization of real world adjustment, these patients are advantaged relative to intellectually impaired patients in both life skills and several key indicators of real-world functioning, including support utilized in the community (Ammari et al., 2010, 2014). Reducing the amount of support required by each patient with schizophrenia not only improves their ability to live independently in the community, but it also helps lessen the stigma and financial burden of the illness through decreased dependence on community supports. On the other hand, intellectual or cognitive impairment may be used as a vulnerability or negative prognostic marker for the functional outcome status of schizophrenia patients.

Overall, knowledge of the intellectual or cognitive status of patients would assist in developing individualized treatment plans that would maximize a patient's independent functioning potential and in tailoring enhancement medications to improve very specific aspects of cognition. For instance, it has been suggested that list learning and working memory are amenable to pharmacological and other interventions. Patients with deteriorated and premorbidly impaired intellectual patterns also have impairments in learning and working memory functioning. Hence, identifying these patients as distinct treatable groups is certainly worthwhile. Moreover, there is evidence that high premorbid intellectual ability may reduce the risk of developing schizophrenia-spectrum disorders (Reichenberg et al. 2006a, 2006b; Seidman, Bukka, Goldstein & Tsuang, 2006). Conversely, low intellectual functioning is a risk factor for schizophrenia and schizophrenia-spectrum disorders (Reichenberg et al., 2006a, 2006b; Seidman et al., 2006). Therefore, premorbid intellectual ability and individual strengths and weaknesses in

cognitive functioning should be assessed in the context of prevention efforts for high risk individuals and in developing or selecting appropriate treatment and rehabilitation services for schizophrenia patients.

Limitations

There are several limitations to the present study. First, the numbers of patients in the deteriorated and premorbidly impaired subtypes were relatively small, resulting in low power for the statistical analyses as only medium-to-large group effects were most likely to reach statistical significance. Consequently, it is possible that there were significant group differences that were not exposed as detecting small-to-medium effect sizes will require larger sample sizes. Future studies would benefit from recruiting more patient and comparison control participants (e.g., minimum of n = 200, 100, respectively), which would hopefully result in twice the number of patients in each of the subtypes, and allow investigators to determine more precisely the nature of the clinical, cognitive, and neurobiological validity of the subtypes.

Second, premorbid IQ scores were not obtained directly as the design of this study was cross-sectional rather than longitudinal. Although the WRAT is a validated measure of premorbid IQ, an actual premorbid IQ measure may more accurately classify patients, especially cases of extreme in scores. Undoubtedly, the most convincing argument for intellectual decline following the onset of schizophrenia would include the use of retrospective premorbid IQ estimates such as scores from school-, recruit-, or clinic-based testing. In addition, it is possible that the current IQ score obtained using the two-subtest WASI does not provide an adequate measure of current general intellectual ability. The results may be different if a more comprehensive measure of general intellectual ability was utilized.

Third, although the MCCB taps a number of cognitive domains deemed relevant in the study of cognition in schizophrenia, the possibility remains that intellectually preserved patients may have more impairments of cognitive abilities not assessed by the battery utilized in this study. It is also possible that intellectually preserved patients would show cognitive deficits on measures more sensitive to specific cognitive impairments. Other investigators have used the complete Wechsler Adult Intelligence Scale (WAIS) as well as the Wechsler Memory Scale (WMS) among other standard measures and test batteries (Allen et al., 2003; Kremen et al., 2000; Palmer et al., 1997; Wilk et al., 2005). Further study is needed to determine the specific components of cognitive processing that are abnormal in these patients. Fourth, it is unclear to what extent the proposed intellectual patterns also occur in healthy populations, possibly indicating natural psychometric score differences and ability profiles that are not unvaryingly pathological in nature. Indeed, some investigators have identified approximately equal proportions of participants meeting the 'deteriorated' pattern in both their schizophrenia and healthy control samples (Ammari et al., 2014; O'Conner et al., 2012).

A final limitation concerns the dimensionality vs. categorical view of mental illness. Several arguments for and against schizophrenia being a homogeneous single disease with varying levels of impairment have been put forth. Advocates for heterogeneity argue that genetic findings reject the parsimonious hypothesis that all schizophrenia is caused by the same pattern of genetic mutations, birth complications and viral infections (Jablensky, 2006). In addition, they cite evidence for several subtypes of schizophrenia linked to identifiable chromosome abnormalities (e.g., Chiu et al., 2002; Horowitz, Shifman, Rivlin, Pisanté, & Darvasi, 2005; Kendler et al. 2000; Liu et al., 2002a, 2002b). Therefore, patients with distinct intellectual abilities differ in their cognitive capabilities because they have fundamentally distinct illnesses

with differing underlying pathophysiologies and correspondingly distinct effects on brain structure and function. On the other hand, advocates for homogeneity argue that there are no disease entities in psychiatry; only continua of variation (Crow, 1995). Even when the etiology of a disorder is known and is unitary, the manifestation and outcome may be surprisingly varied (Jablensky, 2006). Therefore, phenotypic variation in schizophrenia is compatible with etiological homogeneity in that it reflects a continuum of severity in which patients vary along clinical, cognitive, and neurobiological dimensions (Cardno & Farmer, 1995; Goldberg & Weinberger, 1995). Accordingly, the differing cognitive abilities in those patients who are intellectually preserved compared with those with deteriorated or premorbidly impaired intellect could stem from variation in the severity of a single disease process. In other words, the disparity between these patient subtypes could be an artificial differentiation on a severity continuum. This would suggest that patients with preserved intellect are less severely affected but still exhibit markers of cognitive impairment in some domains or even exhibit these at a subclinical level. The possibility that the intellectual subtype distinctions are in actuality a question of the relative extent of impairment in diverse processes influencing distinct neural mechanisms rather than pure and biologically distinct subtypes cannot be completely excluded based on the available data. Therefore, the intellectually preserved subtype may not constitute a distinct subgroup, but rather it may represent a group of patients with less severe cognitive impairments and potentially less marked neurobiological manifestations compared with the deteriorated and premorbidly impaired subtypes.

Conclusions

The data of the present investigation bring back to center stage the fundamental question of phenotypic and etiological heterogeneity in schizophrenia. The heterogeneity vs. homogeneity

debate and the likely existence of etiologically diverse subtypes in schizophrenia dates back to the inception of the diagnostic concept and is far from over. Collectively, the results of the present investigation provide additional evidence that patients with schizophrenia can be meaningfully categorized into subtypes based on the intellectual profiles they exhibit. In other words, neurocognitive subtyping may be effective in organizing and reducing the heterogeneity of schizophrenia. More specifically, there are pronounced differences between the intellectually preserved and intellectually impaired patients, the latter including both the deteriorated and premorbidly impaired groups combined. This suggests that groups defined by intellectual preservation versus impairment may represent two neurobiologically distinct subgroups. The findings of this study have implications for addressing the heterogeneity of schizophrenia, which remains a major barrier to significant scientific progress in this field. Some patients may have impairment of a primary process which results in extensive deficits in multiple domains of cognitive performance, while others may have impairment of a specific process which results in selective performance deficits. Individual differences in intellectual or cognitive performance may thus be extremely valuable in classifying patients into distinct subtypes with more homogeneous pathophysiologies.

Further investigation of the classification scheme used in this study is warranted in order to help elucidate the relationship between cognitive and neurobiological features in schizophrenia, and facilitate the investigation of disease heterogeneity. These distinctions could be an essential step leading to more valid intermediate phenotypes for genetic and neurobiological studies. Although some differences in cortical thickness were found in the proposed subtypes, larger group sizes may lead to further evidence that these subtypes represent neurobiologically distinct subpopulations within schizophrenia. The promise of this approach in

the study of illness heterogeneity in schizophrenia would be strengthened by evidence that these intellectual subgroups differ biologically from the rest of the patient population. Such distinctions could be an essential first step leading to a much more informed search for specific pathogenetic pathways and genetic mechanisms that underlie the illness. Clearly, this is an area that warrants further investigation using larger samples and the application of other neuroimaging and histochemical techniques along with longitudinal research designs. Importantly, the longitudinal stability of these cognitive subtypes across months and years and different treatment regimens is unknown and thus requires future study. Nonetheless, the findings of the present investigation are encouraging and must be replicated and complemented with additional cognitive, clinical, and neurobiological data. The mapping of a clinical syndrome onto distinct neuropsychological subtypes corresponding to distinct brain pathophysiologies is becoming possible and the ensuing discoveries may in the future significantly transform the present nosology.

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Table 1.

Demographic Characteristics of Schizophrenia and Healthy Participant Groups

Variable	PP (n = 29)	DP (n = 14)	IP (n = 14)	PC (n = 36)	Statistic	*p*
Age, years (*M, SD*)	39.6 (10.3)	41.4 (9.8)	42.9 (10.6)	40.3 (13.8)	$F_{3, 89} = 0.27$	n.s.
Sex (males)	18 (62%)	6 (43%)	10 (71%)	21 (58%)	$\chi^2 = 2.52$	n.s.
Education, years (*M, SD*)	13.5 (2.2)	12.8 (2.5)	11.8 (1.9)	13.5 (2.0)	$F_{3, 88} = 2.54$	n.s.
Birth Country (Canada)	25 (86%)	13 (93%)	11 (79%)	33 (92%)	$\chi^2 = 2.06$	n.s.
First language English	26 (90%)	13 (93%)	12 (86%)	36 (100%)	$\chi^2 = 4.65$	n.s.

Note: PP = Preserved Patients; DP = Deteriorated Patients; IP = Premorbidly Impaired Patients; PC = Preserved Controls; Post-hoc comparisons were Bonferroni-corrected.

Table 2.

Clinical Characteristics of Patients

Variable	PP (n = 29)	DP (n = 14)	IP (n = 14)	F	*p*	Contrasts
PANSS General†	40.7 (9.1)	41.1 (5.5)	44.6 (6.8)	$F_{2, 54} = 1.25$	n.s.	
PANSS Positive†	41.7 (8.5)	40.9 (4.8)	43.8 (8.1)	$F_{2, 54} = 3.67$	n.s.	
PANSS Negative†	37.5 (7.5)	40.2 (7.6)	39.4 (4.5)	$F_{2, 54} = 0.87$	n.s.	
Anergia†	42.6 (9.7)	46.1 (11.6)	43.8 (8.9)	$F_{2, 54} = 0.60$	n.s.	
Thought Disturbance†	41.7 (7.9)	40.3 (6.7)	45.9 (8.9)	$F_{2, 54} = 2.02$	n.s.	
Activation†	43.3 (8.2)	44.2 (7.5)	45.1 (6.9)	$F_{2, 54} = 0.25$	n.s.	
Paranoid†	43.9 (7.5)	44.2 (5.6)	45.8 (7.2)	$F_{2, 54} = 0.36$	n.s.	
Depression†	50.7 (11.8)	50.5 (12.6)	54.2 (11.9)	$F_{2, 54} = 0.47$	n.s.	
Schizoaffective	15 (52%)	6 (43%)	4 (29%)	$\chi^2 = 2.06$	n.s.	
Inpatients	3 (10%)	3 (21%)	2 (14%)	$\chi^2 = 0.96$	n.s.	
Duration of Illness	14.9 (10.5)	17.0 (8.5)	21.1 (13.4)	$F_{2, 70} = 3.28$	n.s.	

Atypical Meds	27 (93%)	11 (79%)	11 (79%)	$\chi^2 = 6.97$	n.s.
Antidepressants	14 (48%)	4 (29%)	2 (14%)	$\chi^2 = 6.97$	n.s.
Anxiolytics	8 (28%)	5 (36%)	3 (21%)	$\chi^2 = 0.71$	n.s.
Lithium	5 (17%)	0	2 (14%)	$\chi^2 = 2.68$	n.s.
Anti-Parkinson	4 (14%)	2 (14%)	2 (14%)	$\chi^2 = 0.00$	n.s.

Note: PP = Preserved Patients; DP = Deteriorated Patients; IP = Premorbidly Impaired Patients; PC = Preserved Controls; PANSS = Positive and Negative Syndrome Scale; † = T-scores; Post-hoc comparisons were Bonferroni-corrected

Table 3.

Cognitive Characteristics of Schizophrenia and Healthy Participant Groups

Variable	PP (n = 29)	DP (n = 14)	IP (n = 14)	PC (n = 36)	$F_{3, 89}$	*p*	Contrasts
Reading IQ	100.5 (5.8)	89.2 (10.6)	79.6 (7.6)	103.3 (6.9)	42.14	<.001	DP, IP < PP, PC; IP < DP
WASI IQ	117.1 (5.7)	71.2 (10.2)	77.9 (5.7)	116.9 (9.3)	184.27	<.001	DP, IP < PP, PC
MCCB†							
PS	39.9 (8.6)	27.4 (11.1)	28.7 (11.8)	51.1 (10.0)	27.88	<.001	PP, DP, IP < PC; DP, IP < PP
Att./Vig.	43.5 (9.7)	26.1 (12.9)	28.5 (11.0)	50.1 (9.7)	25.96	<.001	DP, IP < PP, PC
WM	47.1 (8.0)	27.6 (11.3)	29.4 (8.6)	50.1 (8.2)	35.90	<.001	DP, IP < PP, PC;
Verbal	43.9 (8.2)	31.2 (6.4)	31.1 (4.2)	50.0 (9.0)	30.82	<.001	PP, DP, IP < PC; DP, IP < PP
Visual	41.8 (9.7)	27.4 (10.5)	25.4 (7.5)	45.5 (7.4)	27.07	<.001	DP, IP < PP, PC
Reason/PS	44.0 (9.4)	36.7 (7.6)	37.4 (7.6)	54.3 (8.5)	22.05	<.001	PP, DP, IP < PC
Social	45.7 (10.0)	32.8 (11.3)	36.0 (11.8)	49.7 (11.3)	10.78	<.001	DP, IP < PP, PC
Composite	39.9 (8.6)	17.9 (11.2)	19.5 (7.5)	49.9 (7.8)	70.31	<.001	PP, DP, IP < PC; DP, IP < PP
Beads Test	10.0 (4.0)	5.9 (5.2)	7.0 (5.4)	9.6 (3.7)	4.15	.008	DP < PP, PC

IPSAQ	6.7 (3.8)	4.3 (2.9)	6.4 (3.7)	6.2 (2.9)	1.75	n.s.	
Faux Pas	46.7 (5.8)	28.6 (14.4)	33.9 (13.9)	49.9 (8.6)	20.90	<.001	DP, IP < PP, PC
Reading the Mind	25.5 (3.3)	18.8 (5.1)	18.2 (3.6)	28.1 (3.0)	39.26	<.001	PP, DP, IP < PC; DP, IP < PP

Note: PP = Preserved Patients; DP = Deteriorated Patients; IP = Premorbidly Impaired Patients; PC = Preserved Controls; WRAT3 = Wide Range Achievement Test 3rd edition; WASI= Wechsler Abbreviated Scale of Intelligence; MCCB= MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery; PS = Processing Speed; Att./Vig. = Attention/Vigilance; WM = Working Memory; Verbal = Verbal Learning; Visual = Visual Learning; Reason/PS = Reasoning/Problem Solving; Social = Social Cognition; IPSAQ = Internal, Personal and Situational Attributions Questionnaire, number of external personal attributions to negative social situations; Faux Pas = Faux Pas Recognition Test; Reading the Mind = Reading the Mind in the Eyes Test; † = T-scores; Post-hoc comparisons were Bonferroni-corrected

Table 4. *Cortical Thickness in Schizophrenia and Healthy Participant Groups*

Variable	PP (n = 29)	DP (n = 14)	IP (n = 14)	PC (n = 36)	$F_{3, 87}$	*p*	Contrasts
RH superior temporal sulcus	2.43 (0.22)	2.55 (0.20)	2.38 (0.20)	2.60 (0.21)	5.67	.001	PP, IP < PC
LH fusiform gyrus	2.58 (0.14)	2.65 (0.19)	2.54 (0.20)	2.73 (0.16)	6.38	.001	PP, IP < PC
RH fusiform gyrus	2.60 (0.19)	2.65 (0.18)	2.54 (0.16)	2.71 (0.19)	3.39	.022	IP < PC
LH middle temporal gyrus	2.70 (0.20)	2.84 (0.24)	2.76 (0.14)	2.88 (0.17)	5.09	.003	PP < PC
RH middle temporal gyrus	2.75 (0.18)	2.86 (0.21)	2.75 (0.14)	2.91 (0.17)	5.76	.001	PP, IP < PC
LH inferior parietal lobule	2.42 (0.14)	2.47 (0.19)	2.43 (0.15)	2.53 (0.16)	3.25	.026	PP < PC
RH inferior parietal lobule	2.47 (0.13)	2.50 (0.20)	2.44 (0.20)	2.58 (0.15)	4.04	.010	PP, IP < PC
LH supramarginal gyrus	2.48 (0.14)	2.55 (0.18)	2.48 (0.15)	2.58 (0.14)	3.28	.025	PP < PC
RH supramarginal gyrus	2.50 (0.14)	2.59 (0.15)	2.53 (0.16)	2.64 (0.16)	4.99	.003	PP < PC
RH precuneus	2.33 (0.14)	2.37 (0.17)	2.29 (0.15)	2.43 (0.18)	3.32	.024	IP < PC
RH frontal pole	2.56 (0.29)	2.65 (0.36)	2.58 (0.24)	2.80 (0.31)	3.93	.011	PP < PC
LH lateral orbitofrontal cortex	2.53 (0.12)	2.67 (0.16)	2.54 (0.14)	2.58 (0.15)	3.59	.017	DP < PP
LH pars triangularis	2.35 (0.19)	2.52 (0.19)	2.33 (0.11)	2.45 (0.16)	4.63	.005	DP < PP; IP < DP

Note: PP = Preserved Patients; DP = Deteriorated Patients; IP = Premorbidly Impaired Patients; PC = Preserved Controls; Post-hoc comparisons were Bonferroni-corrected

Figure 1. *T-score profiles for patient and control groups on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) domains*

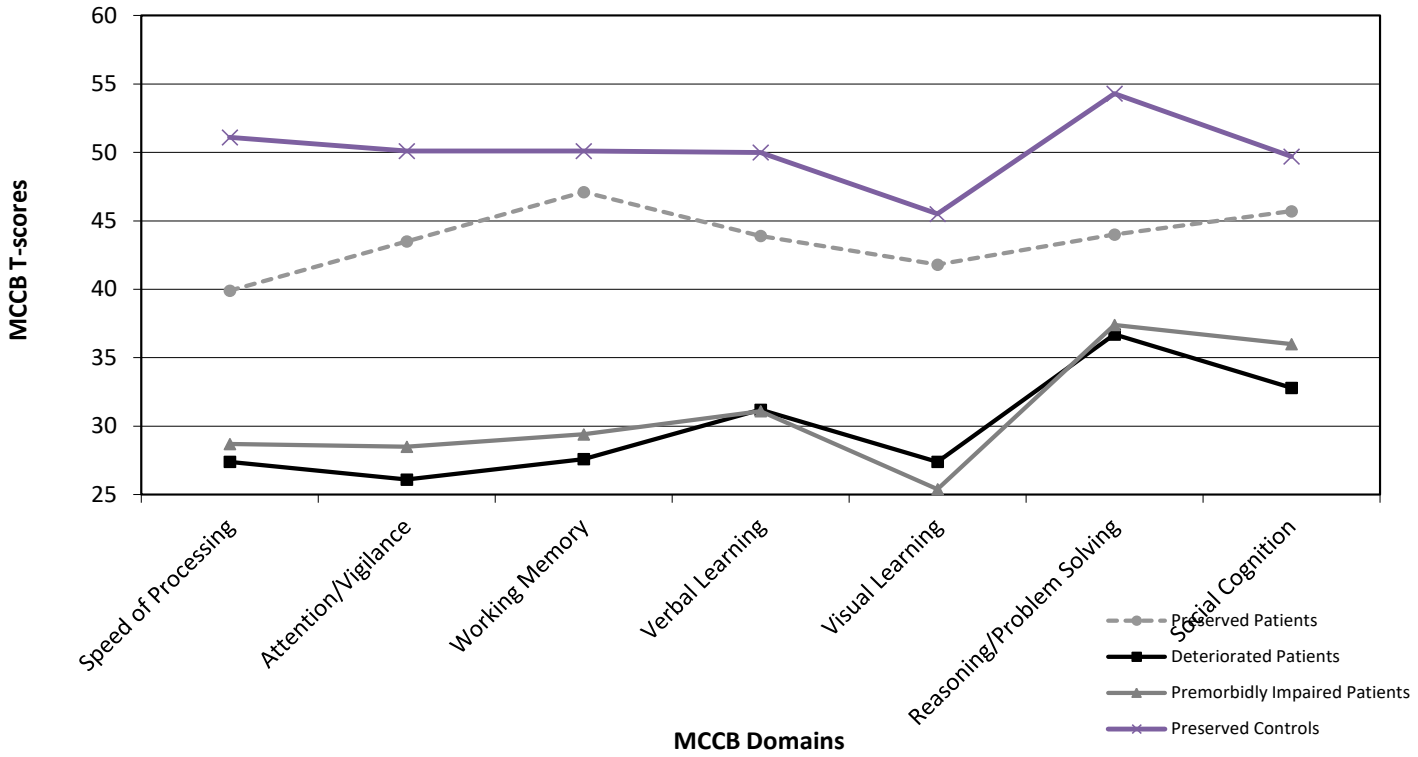

Figure 2.
Cortical thickness difference maps between control and schizophrenia groups (*p* values are calculated as $-\log_{10}p$)

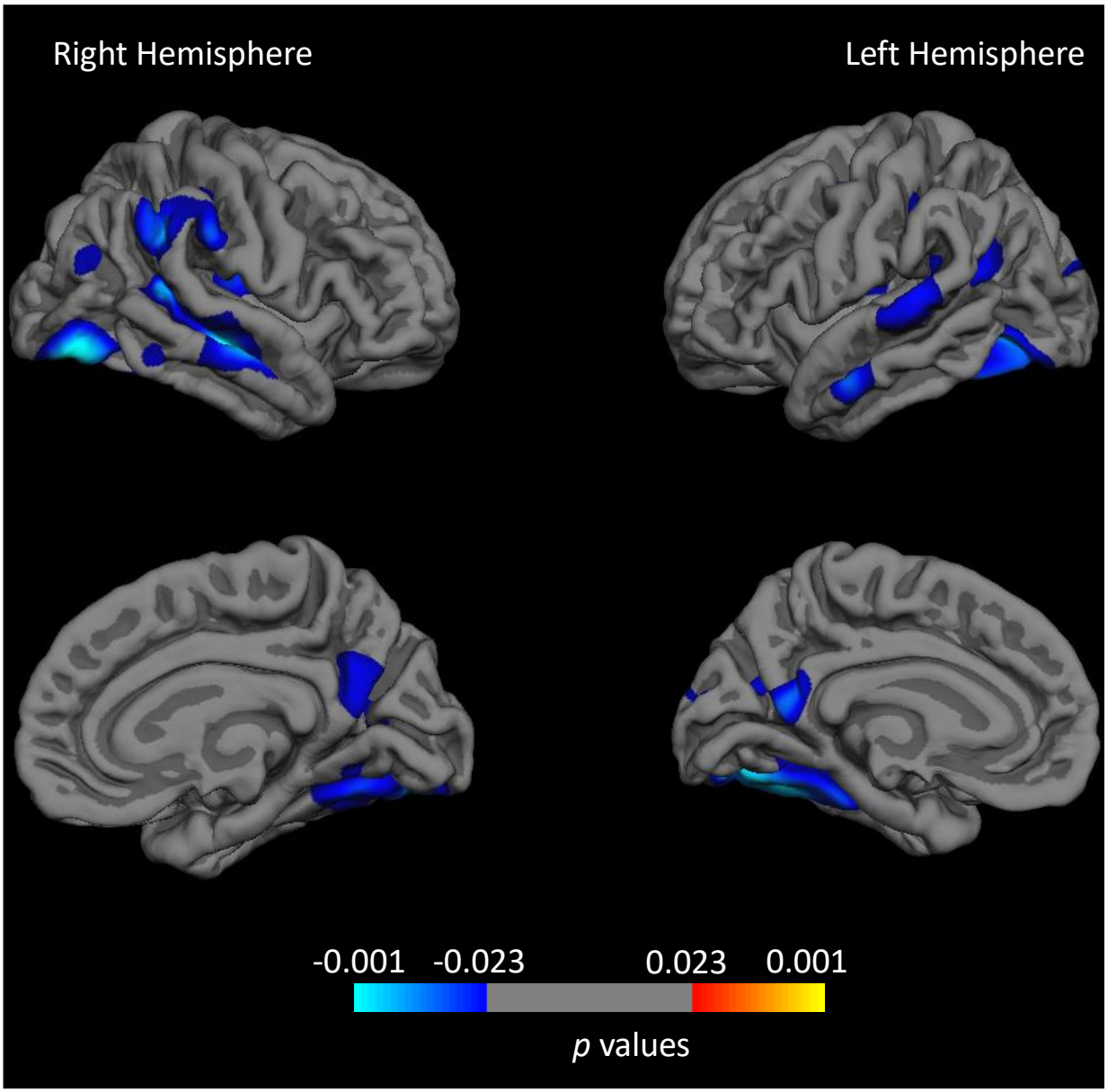

Figure 3.
Cortical thickness difference maps between control participants and preserved schizophrenia patients (*p* values are calculated as $-\log_{10}p$)

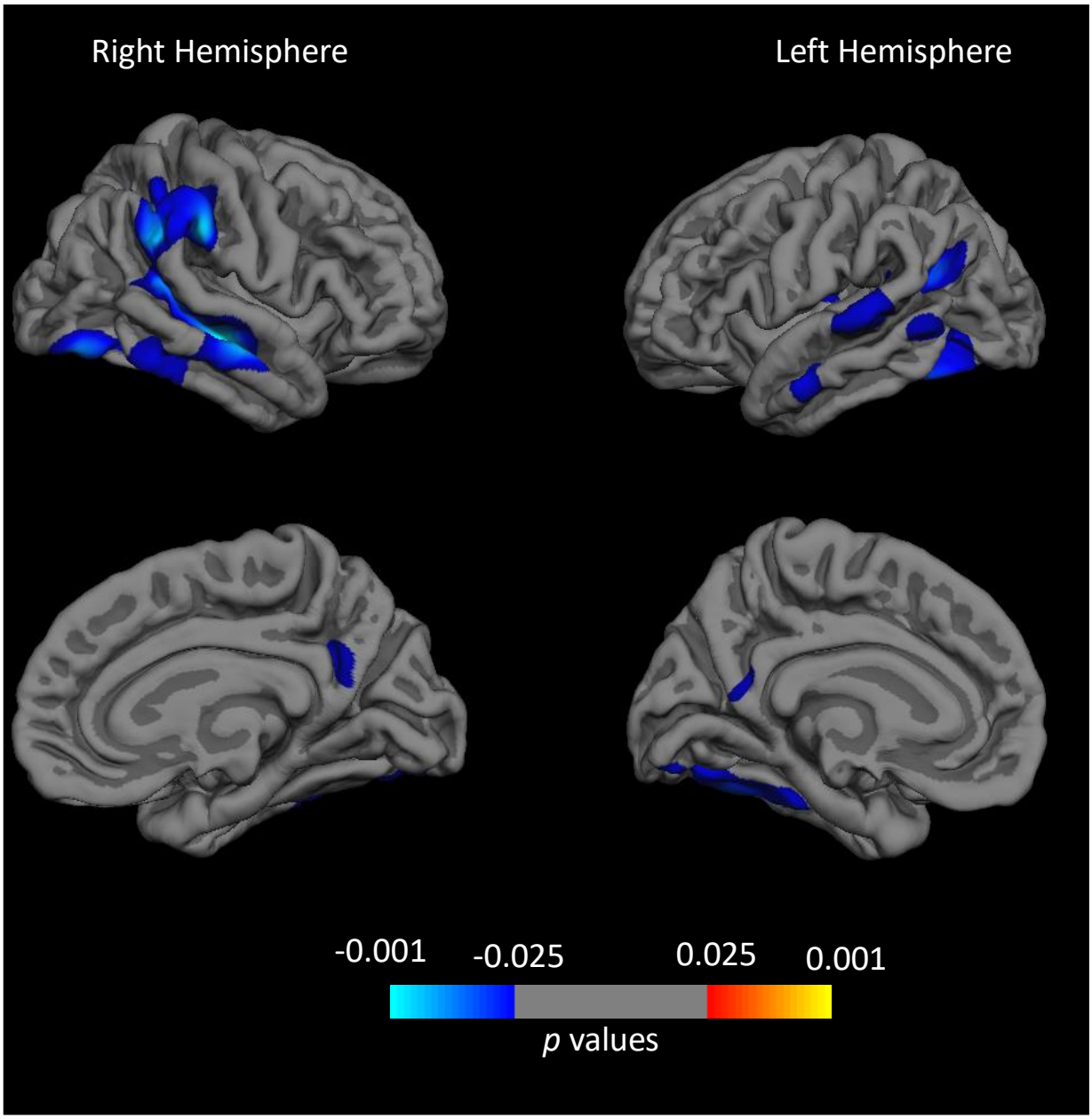

Figure 4.
Cortical thickness difference maps between controls and premorbidly impaired schizophrenia patients (*p* values are calculated as $-\log_{10}p$ and set at an uncorrected threshold of $p=0.05$)

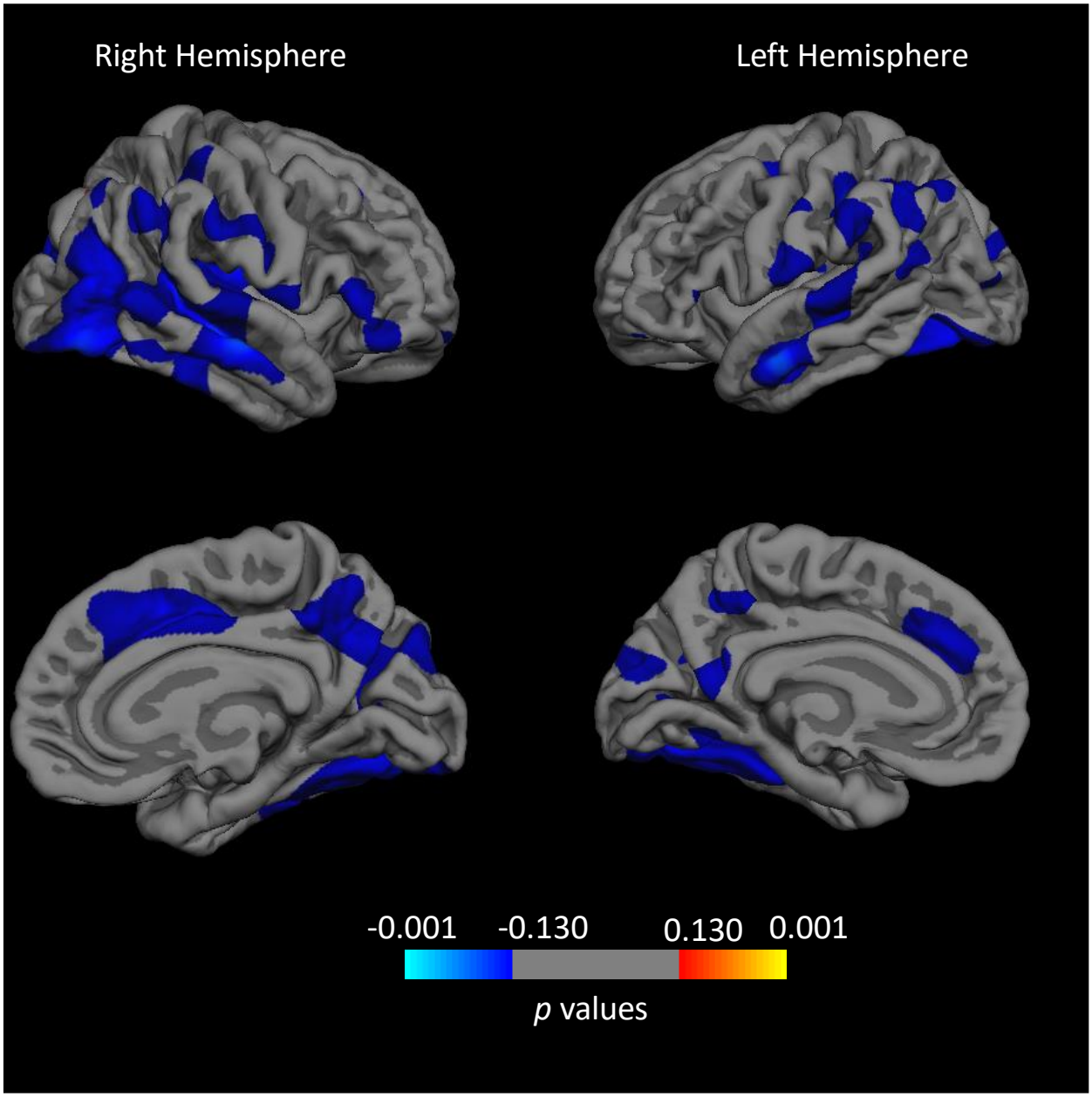

Figure 5.
Cortical thickness difference maps between deteriorated and premorbidly impaired schizophrenia patients (*p* values are calculated as $-\log_{10}p$ and set at an uncorrected threshold of $p=0.05$)